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# Hydrophilic Modification Strategies to Enhance the Surface Biocompatibility of Poly(dimethylsiloxane)-Based Biomaterials for Medical Applications

*Chanutchamon Sutthiwanjampa, Seungpyo Hong, Woo Ju Kim, Shin Hyuk Kang,* and Hansoo Park**

**Poly(dimethylsiloxane) (PDMS) has been widely employed in biomedical disciplines due to its several advantages, including biocompatibility, nontoxicity, and low-cost preparation. However, the intrinsic hydrophobicity of this material encourages biofouling and reduces cell regulation capacity, thereby limiting its biomedical applicability. The purpose of this study is to explore the surface modification and functionalization of PDMS and PDMS-based biomaterials to improve their properties for biomedical applications. The content of this review is organized based on physical and chemical surface modification strategies to improve surface hydrophilicity to enhance antibiofouling and the regulation of immunomodulation and cell modulation on the surface of PDMS and PDMS-based biomaterials. Future developments in this area are also discussed.**

## 1. Introduction

Poly(dimethylsiloxane) (PDMS) (also well-known as silicone) has been widely employed for decades in biomedical applications, including contact lenses, microfluidics, pacemakers, catheters, artificial skin, and numerous medical/surgical implants.[1–4] It has been used in drug delivery systems, analytical chemistry, medical diagnostics, DNA sequencing, biosensors, and biological production and analysis.[5–10] PDMS has gained popularity and has become widely used because of its low toxicity, optical transparency, hyperelasticity, good oxidative, and thermal stability, high fluidic resistance, physiological inertness, ease of fabrication, and low production cost.[2–4,11–13] However, its applicability in its native condition is limited, and its limitations are discussed in detail in Section 2. It has poor wettability due to the hydrophobicity of the surface induced by methyl ($-CH_3$) groups, resulting in low biocompatibility.[14] For example, the hydrophobicity of the PDMS surface is an issue when attempting to fill a microchannel in a microfluidic device using capillary force.[15] Thus, introducing hydrophilicity to and enhancing the biocompatibility of the PDMS surface would be advantageous.

PDMS-based biomedical devices are typically deliberately implanted in the body to fulfill a particular function.[16] Furthermore, leaving these materials in the body for an extended period of time can result in complications with the immune system. The body's immune system responds to the implant by encasing it in a dense collagen capsule because it perceives it as a foreign object. Because PDMS-based implants are impervious to most molecules in the surrounding microenvironment, this encapsulation, which occurs on every implant, limits functionality and can cause tissue contracture and pain.[17] Several researchers have noticed that enhancing the surface of PDMS using both physical and chemical approaches can help to overcome these shortcomings.

The study of the structure and function of natural systems as inspiration for (sustainable) technological design and engineering is known as biomimetics.[18] Biomimetic mechanisms, which have been exploited in many strategies developed over

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The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/admi.202202333.



**DOI: 10.1002/admi.202202333**

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the last century, have recently gained extensive attention in polymer science. Natural materials from nature (e.g., shell, wood, and scales), including from humans (e.g., ligaments, tissue, and bone), have enormous potential for meeting various complex functional needs.[19] Biomaterials have recently been produced with an emphasis on the construction of biomimetic materials capable of evoking specific cellular responses and directing new tissue formation via bioactive molecular recognition that can be modulated by changing the material design parameters.[20] For example, combining osteoinductive biomolecules including growth factors, hormones, enzymes, and DNA with osteoconductive calcium phosphates can help regulate and improve osteogenesis and bone production.[21] Simple ways for creating biomimetic materials include mimicking the natural surface topography and modifying the material surface with bioactive chemicals;[22] the techniques for the latter include biomimetic integration,[23] chemical bonding,[24] and physical adsorption.[24]

In this review article, we go into great length on such issues in biomedical applications as well as ways for surface modification and functionalization of PDMS and PDMS-based medical materials to overcome their limitations for biomedical applications by focusing on hydrophilic surface modification including biomimicking approaches. This review is divided into various sections based on the modification strategies and the properties to be modified. Applications are mentioned where relevant in the discussion of specific modification techniques.

## 2. Problems with PDMS in Biomedical Implants

As stated in Section 1, although PDMS is often used in biomedical devices, it has several serious flaws that limit its widespread use. Understanding the causes of the difficulties is critical for overcoming them. The challenges of using PDMS in biomedical applications are covered in Subsections 2.1–2.4.

### 2.1. Nonspecific Protein Adsorption

One of the primary drawbacks of PDMS in biomedical applications is its hydrophobic nature, which causes considerable nonspecific protein adsorption from the surrounding environment. This is a critical issue that must be solved because it leads to unfavorable bioreactions in the future.[25] Plasma proteins such as globulin, fibronectin, fibrinogen, vitronectin, and albumin can quickly bind to the surface of PDMS, and the "Vroman effect"—a dynamic protein adsorption process in which proteins compete for adsorption on a surface—leads to difficulty in controlling layer instability by dynamically altering the composition of the adsorbed proteins.[26] Because of the uneven protein composition or loss of the target or biologically relevant proteins due to nonspecific protein adsorption, the interaction between any protein-containing solution and the PDMS surface is of concern. As a result, modification and/or functionalization of the PDMS surface to minimize nonspecific protein adsorption has become a widely researched topic. In this context, oxygen ($O_2$) plasma treatment is arguably the simplest and most widely used method for changing the surface hydrophobicity of PDMS, thereby removing the associated disadvantages. Unfortunately, a hydrophilic $O_2$-plasma treated-PDMS surface usually recovers its hydrophobicity within 4 days after treatment,[27,28] thereby limiting both the shelf life and long-term use of the as-manufactured devices. Strategies for improving the biocompatibility of PDMS-based biomaterials and tactics for preventing nonspecific protein adsorption and boosting the antibiofouling properties of PDMS surfaces for use in biomedical applications are covered in Section 3.

### 2.2. Bacterial Infection and Biofilm Formation

The first and most crucial step in implant infection is the hydrophobically adherence of bacterial, resulting in biofilm formation on the hydrophobic implant surface. If the bacteria become resistant to the host defense mechanisms and/or subscribed medication (e.g., antibiotics), this can lead to severe complications, such as microbial contamination and consequential persistent and chronic diseases.[29,30]

Microorganisms are categorized into two forms: the biofilm-embedded type known as the "sessile form" and the free-floating type that can disperse across the implant surface known as the "planktonic form."[31] The sessile form can survive antibiotic therapy, resulting in chronic indolent infection, whereas the planktonic form can cause systemic infection in the host.[31] As microbes in the sessile form are substantially more resistant to antibiotics and the host defenses than the same species in the planktonic form, biofilm formation, and persistence are major limitations of implantable PDMS devices.[32] Thus, it has been reported that ≈60–70% of nosocomial infections are caused by implantable medical devices.[32]

Bacterial adhesion to implant surfaces involves several biological processes and physical interactions.[33–35] The following steps characterize biofilm formation: reversible and irreversible bacterial adhesion and biofilm formation, maturation, and dispersion.[36,37] The irreversible adhesion phase is the most important of these steps and plays a critical role. Bacterial surface mechanosensing (the ability of bacteria to mechanically sense physical contact with a surface)[38] and the inherent physicochemical features of the surface (such as charge, hydrophobicity, roughness, topography, chemistry, and material stiffness) influence bacterial adhesion and the initial biofilm formation process.[39–49] The mechanical and physicochemical features of the material surface, the bacterial strain and its glycoprotein sequence, and the experimental conditions (such as the incubation duration or flow versus static assays) all have an impact on bacterial adhesion to the material surface.

Some researchers have reported that adherence of *Staphylococcus aureus*, *Escherichia coli*, *Bacillus* sp., and *Pseudoalteromonas* sp. on a hydrophilic surface and the surface stiffness are positively associated,[44,50,51] whereas others have reported the opposite.[52,53] *E. coli* and *Pseudomonas aeruginosa* have been found in higher densities on a soft hydrophobic PDMS surface rather than a stiff one.[53] Moreover, bacterial cells cling tightly to a hydrophobic surface due to the low free surface energy.[54,55] It has been revealed that *E. coli* attachment to the PDMS surface is the result of mechanosensing through its flagella.[56] In addition, a high level of cyclic-di-GMP (a crucial initiator that

regulates biofilm development) was found in *P. aeruginosa* during bacterial adhesion, resulting in more adherent cells and a larger biofilm formation.[57] On the other hand, Straub and co-workers[58] hypothesized that rather than bacterial surface mechanosensing and particular interactions, the intrinsic nonspecific physicochemical features of the PDMS surface had a more significant impact on the early stages of bacterial adherence.

Nonspecific protein adhesion and bacterial adherence are the fundamental issues with PDMS-based biomaterials. Furthermore, nosocomial infections related to implanted materials are the most common and severe due to biofilm formation.[32] Surfaces with antibiofouling properties can hinder the adsorption of nonspecific proteins and/or hydrophobic compounds as well as bacterial adhesion. To reduce biofilm formation, preventing bacterial adhesion should help to alleviate the infection problem.[59,60] Oral or intravenously administered broad-spectrum antibiotics are the most often utilized and successful clinical technique for bacterial infection control.[61] Unfortunately, the widespread and excessive use of antibiotics has increased the number of resistant microorganisms. In addition, the absence of a biofilm-specific indicator is a significant diagnostic issue when trying to identify infections involving biofilm formation. In these situations, antibiotics and the host defense system cannot effectively treat implant infections, which typically linger until the recommended course of action of removing the implant is undertaken.[31] Hence, new antibacterial strategies along with controlling the surface chemistry and topography of the implants are necessary to restrict nonspecific protein adhesion and bacterial colonization. Related strategies for improving the antibiofouling property of the surface of PDMS-based biomaterials are described in detail in Section 3.

### 2.3. The Foreign Body Reaction

Implanting biomaterials in the body frequently provokes an unfavorable immune response that can eventually lead to the complete isolation of the implant via a process known as the foreign body reaction.[62] The nature of the body's induced foreign body reaction to a biomaterial depends on the physical, chemical, and biological aspects of the material surface. Surface roughness and texture, and surface free energy are examples of physical features while functional groups, surface charge, and wettability are examples of chemical features. Biological features include the cellular immune response caused by epitopes that are either intrinsic to the material surface or a result of protein adsorption and denaturation thereon. During the initial stage of the foreign body reaction, nonspecific proteins are adsorbed onto the foreign surface and form a layer of extrapolymeric substance,[62] thereby fouling the implant surface. Nonspecific protein adsorption on the biomaterial surfaces triggers the foreign body reaction, which initiates a cascade of immunological pathways as well as various cell–cell interactions via cytokines such as tumor necrosis factor-alpha (TNF-$\alpha$) and the interleukin (IL) family.[63] Subsequently, when attempting to phagocytize the foreign material, macrophages become aggravated and release cytokines. During this process, macrophages stimulate the surrounding immune cells, thereby inducing them to release additional growth factors and cytokines that stimulate fibroblasts to differentiate into myofibroblasts and form a tight collagenous sheath around the foreign material called a capsular contracture (**Figure 1**). Because the capsule contains a dense avascular layer of collagen, it is impermeable to most molecules in the surrounding environment and isolates the implant from the local tissue environment, which limits proper healing by the body and assimilation of the implant.[64] As the

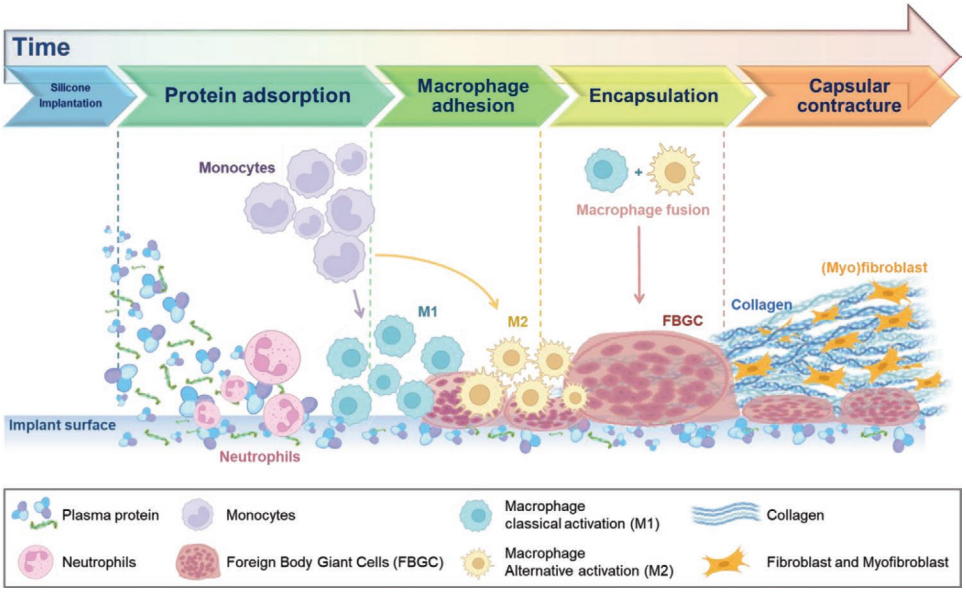


**Figure 1.** The five stages of the foreign body reaction. After implantation of the poly(dimethylsiloxane) device, plasma proteins become nonspecifically absorbed on the implant surface, subsequently inducing an inflammatory reaction and the rapid infiltration of neutrophils. The circulating monocytes gradually congregate in the surrounding tissue and undergo macrophage differentiation. The aggregated macrophages then fuse to form giant foreign body cells that release cytokines. These make the fibroblasts create a fibrous capsule to separate the foreign body from the surrounding tissues, which is called capsular contracture.

surface is effectively walled-off by the collagen sheath, the combination of the inflammatory foreign body reaction and thick collagen encapsulation enhances the susceptibility to infection while reducing the ability of the immune system to effectively resist infection.[65,66] Consequentially, several studies have been conducted to explore viable strategies for improving the surface of biomaterials to mitigate this problem. Modulating the innate immune response to PDMS-based biomaterials is a prospective therapeutic route for alleviating this problem.[67] A cascade of actions is triggered by generating a local anti-inflammatory milieu around the implant via communication between the innate immune system cells and other cell types. The long-term effects of the immune response on an implant need to be mitigated by modifying the initial innate immune response in the immediate proximity of the device. Strategies to overcome this issue are described in detail in Section 3.

### 2.4. The Limitations of Target Cell Adhesion

As mentioned previously, the majority of an implant surface's beneficial characteristics are related to its physicochemical properties influencing the immunological and inflammatory responses of the host, including cell adhesion and integration. Over the past 10 years, the demand for advanced stem cell technology has risen dramatically as a result of the importance of stem cells for medical therapeutics, drug development, and a variety of healthcare applications including toxicological studies, disease modeling, and cell replacement therapy.[68–70] Accumulating target stem cells on the PDMS surface is an important approach for delivering their therapeutic effect. However, the hydrophobic surface of PDMS limits cell adhesion and proliferation, thereby making it difficult to exploit it in biomedical applications. Its intrinsic surface hydrophobicity has been reported by several researchers to be a key contributor to poor cell adhesion and uneven spreading (i.e., cell aggregation and thrombus).[71–73] Cell adhesion significantly influences cellular regulation and communication. Cells can adhere to each other as well as the extracellular matrix (ECM).[74,75] Adhesion-inducing molecules, such as integrin connect the ECM to the cytoskeleton inside the cells, thereby enabling cells to communicate with each other and with the ECM. The physical and mechanical features of the culture microenvironment also regulate cellular activity.[76] Changes in the interactions between the cells and the ECM depend on the type of cell, the properties and characteristics of which are influenced by their tissue origin, shape, and disease condition.[77,78] The growth rates, proliferation, viability, differentiation, and migration of cells on the same culturing surface vary depending on the cell type.[79,80] Cell-substratum interactions are critical for a variety of biological processes, while both the physical features (such as roughness) and chemical features (such as charge and hydrophilicity) of the substrate surface influence cell adhesion and growth.[81–84] Modification of the PDMS surface can potentially improve cell adhesion and long-term culturing. According to Grinnell et al.,[85,86] nonspecific protein adsorption on the PDMS surface inhibits cell adhesion, thereby preventing cell attachment. Thus, numerous techniques have been designed to overcome nonspecific protein adsorption and thereby improve cell adherence to the PDMS surface. These approaches along with physical and chemical modification of the PDMS surface are discussed in Section 3.

## 3. Strategies to Enhance the Surface Biocompatibility of PDMS and PDMS-Based Biomaterials for Biomedical Applications

As described in Section 2, the intrinsic low surface energy of PDMS[87] causes its surface to be hydrophobic, which leads to several limitations for biological applications. The basic principle to reduce these is to enhance its surface biocompatibility. Strategies to improve this involve both surface hydrophilic[88] and superhydrophobic[89,90] modification. Surfaces with a contact angle of less than 90°, between 90° and 150°, and greater than 150° are classified as hydrophilic, hydrophobic, and superhydrophobic, respectively.[91] However, the contact angle is measured based on a water droplet that interfaces with air, so superhydrophobic surfaces may not be effective at fouling control when fully submerged in a liquid (such as in the human body),[92] especially when the scale of its topographic features is comparable to the size of a bacterial cell. As a result, an optimal method for changing the surface properties of PDMS to ease these complications while maintaining its benefits is required.

In this review, we focus on hydrophilic modification strategies for modifying and functionalizing the surfaces of PDMS and/or PDMS-based materials to make them more suitable for biomedical applications. As well as physical and chemical modification, strategies involving antibiofouling and modulating cell adhesion, including regulation of the immune response, on the PDMS surface are separately discussed below.

### 3.1. Surface Physical Modification

#### *3.1.1. Antibiofouling Strategies*

Antifouling strategies for the surfaces of medical implants by matching the properties of the surrounding tissue are greatly desirable. The wettability of a surface can be affected by changes in its topography,[93–95] which has a significant impact on bacterial adherence. Bacterial adhesion can be reduced by either creating a superhydrophobic surface or via micropatterning of a hydrophilic surface.[96] Several researches have examined the effect of plateau diameter, form, and height, as well as the distance between the plateaus, on biofouling.[97–99] Interestingly, a square-shaped topographic pattern with a side length of 20, 50, or 100 μm and an interpattern distance equal to or more than 10 μm enhanced *E. coli* biofilm production and adhesion.[100] Meanwhile, in another investigation of *E. coli* adhesion behavior on a PDMS surface with 5 μm tall line patterns of various widths, narrower lines with lower interpattern spacing were more effective at suppressing bacterial adherence.[101]

Various topographic features, such as cylindrical wells, ridges, irregular micropits, line patterns, honeycombs, and pillars of varying forms, have been shown to inhibit bacterial biofilm development.[61,96,102–106] Bacterial adhesion typically

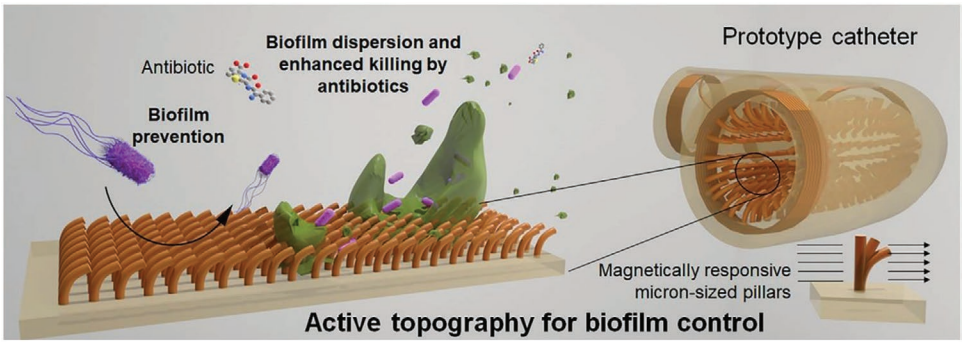


**Figure 2.** Long-term biofilm control via active topography. The programmed beating of micrometer-sized pillars propelled by a magnetic field can be adjusted to provide antifouling.[114,116] Reproduced with permission.[116] Copyright 2021, Elsevier.

decreases with decreasing topographic pattern size, even when the bacterial strains, substrate type, and the size and layout of the pattern are different.[96,106] Lu and colleagues[96] reported that micropatterned PDMS films of squares, ridges, or a four-way grid with groove diameters ranging from 0.5 to 4 µm all inhibited the adhesion of *E. coli*, *S. aureus*, and *P. aeruginosa*.[96] Specifically, the micropatterned film was more effective at preventing bacterial adhesion when the bacteria were larger than the pattern. In general, micrometer-scale topography can hinder bacterial adherence by affecting interactions between the bacteria and the PDMS surface. Although several nanometer-scale topographic modifications of other surfaces have exhibited bactericidal activity by damaging the bacterial membrane,[107–109] bactericidal activity of the PDMS surface, even after nanoscale topographic modification, has not previously been reported.[110,111]

The surface stiffness is not involved in bacterial adhesion and biofilm formation. Arias et al.[112] found that complex micrometer- and submicrometer-scale wavy (wrinkled) topographic modification of the PDMS surface decreased *E. coli* adhesion and biofilm mass independently of the surface stiffness. Furthermore, a nanotextured PDMS implant limits the in vitro protein adsorption and adhesion of *S. aureus*, *S. epidermidis*, and *P. aeruginosa* to the surface, which subsequently attenuates capsular contracture.[113] These findings prove that inhibition of the initial step of bacterial adhesion and biofilm formation can reduce the risk of further complications with an implanted medical device.

Controlling long-term biofilm formation is a favorable approach for reducing infection-related bacterial adhesion. Accordingly, advanced surface topographic cues involving programmable and stimuli-responsive techniques have been established. Gu et al.[114] developed a long-term antifouling PDMS-based prototype catheter by modifying the surface with micrometer-scale pillars followed by loading super-paramagnetic nanoparticles onto the pillar tips. This topography mimics the cilia protruding from human lung epithelial cells, which provides a natural antibiofouling topography that repels microorganisms,[115] thereby preventing bacterial infection (**Figure 2**). The prototype catheter successfully prevented biofilm development and removed established biofilms of uropathogenic *E. coli* (UPEC), *P. aeruginosa*, and *S. aureus* on human urinary bladder T24 cells without causing toxicity. Furthermore, the prototype stayed clean for up to 30 days in artificial urine whereas the control catheter was blocked by UPEC biofilms after 5 days. In addition, real-time monitoring and a threshold-activated bactericidal device (generating an electric field) were used in an electrode/probe microfluidic chip applied in a wirelessly monitored catheter. This is a fascinating approach that merits development and additional research and could be used for other liquid-handling devices.

### *3.1.2. Strategies for Modulating Cell Adhesion Including Regulation of the Immune Response on the PDMS Surface*

It has been reported that the topographical structure of a biomaterial surface is a key mediator for the cellular response through mechanosensing and mechanotransduction.[117–119] Surface modification using micro/nanopatterns has attracted a great deal of interest as a way of imitating the distinct components of the human extracellular environment toward controlling cell proliferation and regulation. At the macro- (100 µm to 1 mm), micro- (100 nm to 100 µm), and nano- (1–100 nm) scales, adding topographical characteristics such as nodes, wells, pores, steps, ridges, and grooves to the surface of the target biomaterial can mediate the cell response.[120–122] Both the nano- and microtopographies of the ECM have a role in cell contact and signaling.[123] As cells respond naturally to surrounding structures, the nano- and microtopographical surfaces naturally influence cell attachment, adhesion, morphology, alignment, proliferation, polarization, and migration at the nano- and microscale.[124]

So far, microcontact printing, photolithography, nanoimprint lithography, replica modeling, and other topographical cues have been used to modify the PDMS surface to imitate the microenvironment suitable for cell growth and modulation. Gao et al.[125] found that laser-cut microchannels on the PDMS surface combined with suitable stiffness increased the proliferation of human mesenchymal stem cells (MSCs). Escutia-Guadarrama et al.[126] printed stable and durable micropatterns of COL I (a natural ECM protein necessary for hepatic cell adhesion) on PDMS to provide a surface that mimics real hepatic tissue; HepG2 and primary rat hepatocytes were confined and organized using simple thin lines that mimic hepatic cord patterns. Marx-Blumel et al.[127] mimicked the natural stem cell environment in vivo by optimizing a hematopoietic stem cell (HSC) medium composition with a panel of cytokines and

valproic acid and then used an artificial 3D bone marrow-like scaffold built of PDMS based on a human long-bone cross-section. This 3D scaffold was a good fit for amplifying the production of human HSCs in vitro, while also supporting their survival, multipotency, and ability to self-renew, which could help to improve the outcomes of HSC transplantation by enabling effective HSC growth in vitro prior to clinical use.

The shape of cells or tissues has been exploited to create negative molding substrates on PDMS-based biomaterial substrates.[128–131] Imprinting the cellular or tissue morphology on PDMS at the micro- or nanometer-scale is the basis for this technology, while cell concentration and separation, tissue engineering, drug delivery, imaging, and sensing are some of the applications of this approach.[132] To achieve this, a cell imprinting approach has been applied to induce differentiation in MSCs and modify trans-differentiation.[131,133] For example, the ability of an osteoblast-imprinted substrate to drive stem cell development toward osteogenic phenotypes has been reported.[134]

Using cell imprinting on the PDMS surface to provide excellent cell detection and isolation can be employed as a biomarker for early cancer diagnosis, and thus better prognosis. A cell-imprinted biomimetic interface comprising PDMS has been created by utilizing a soft lithography technique to capture circulating tumor cells (CTCs) by recreating their morphology on PDMS after functionalization with natural anti-EpCAM antibodies (**Figure 3**).[135] The modified interface displayed precise identification and selective capture of targeted MCF-7 cells by replicating the unique immune affinity for the antigen by successfully combining "plastic" and "natural" antibodies. In an artificial blood sample, the imprinted surface performed well in CTC detection, with a capture efficiency of more than 55%.[135] To stimulate the tenogenic development in MSCs, Haramshahi et al.[136] employed the tenocyte shape as a positive mold to generate a tenocyte-imprinted PDMS substrate. This could stimulate the expression of tenocyte markers (scleraxis and tenomodulin) in adipose-derived stem cells (ADSCs) both in vitro and in vivo, indicating that it is a promising method for differentiating stem cells without the use of growth factors.[136] As another example, an inorganic hard matrix of bone rich in hyaluronic acid mimicked by using a PDMS/hydroxyapatite nanocomposite substrate imprinted with osteoblasts was produced to encourage and enhance stem cell osteogenic growth.[21] The findings indicate that the surface patterns and viscoelastic properties of the substrate can influence stem cell growth and lead to the osteogenic phenotype. Furthermore, osteoinductive hydroxyapatite nanoparticles embedded in nanocomposite substrates can accelerate and optimize stem cell osteogenic differentiation via chemical signaling. Recently, bone surface-mimicking PDMS membranes have been shown to strongly increase osteoblast cell differentiation and maturation markers, cell adhesion, and proliferation.[137]

Anisotropic topography on the PDMS surface provided by, for instance, aligned fibers, gratings, grooves, wrinkles, and so on, is widely used to regulate the cellular response.[138–141] In particular, wrinkled structures have been shown to

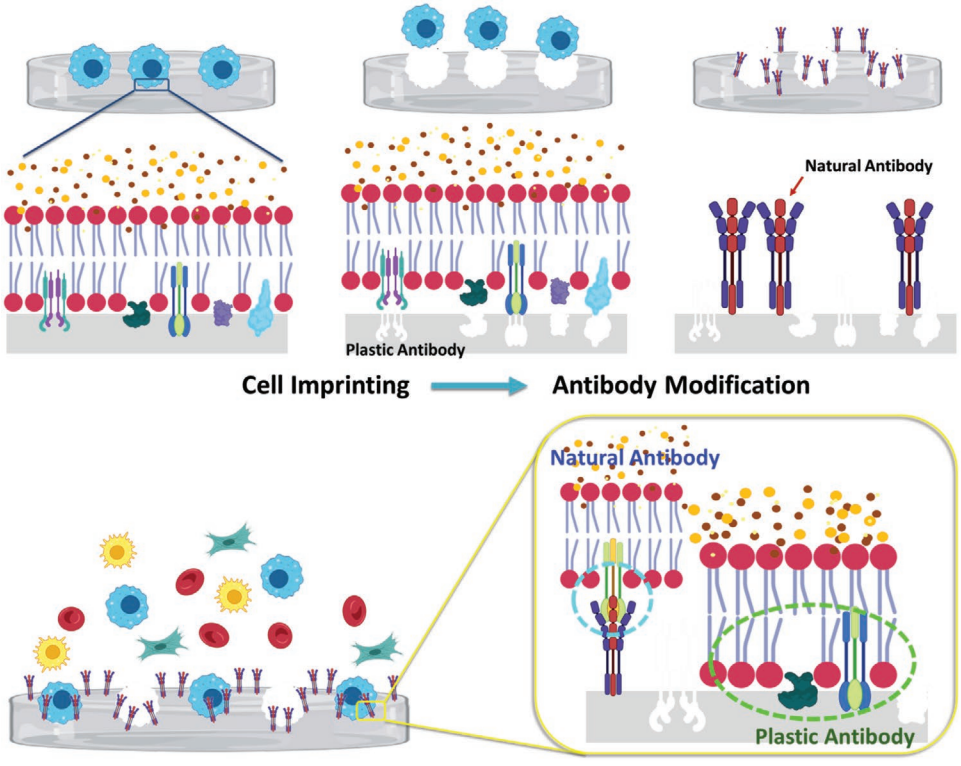


**Figure 3.** A schematic representation of substrates imprinted with cells for tumor cell capture. The template cells were eliminated before creating plastic antibodies. Naturally occurring anti-EpCAM antibodies were attached to the cell-imprinted surface for intelligent recognition of target circulating tumor cells attributable to the synergism between natural and synthetic antibodies. Adapted with permission.[135] Copyright 2019, Royal Society of Chemistry.

significantly mediate cellular attachment, elongation, alignment, and functionalization.[139] For example, to mimic the nerve nano/microstructure, the nano- and microtopography of PDMS-based hierarchical structures have been shown to promote the neural differentiation of human bone marrow-derived MSCs.[142] This approach can be applied to design biomaterials for neural tissue engineering and to help understand how topography affects neuronal differentiation. Similarly, providing anisotropic topography on the PDMS surface by coating it with an ECM-mimicking cell-derived matrix dramatically promotes osteogenesis,[143] which could be a potent method for producing osteogenesis-promoting materials.

Mobasseri et al.[144] discovered that the angle of the slope on an undulating collagen-coated PDMS substrate rather than the tips or bases influences cell patterning at the epidermal-dermal interface of healthy and young skin cells. Variations in the slope are thought to play a role in the breakdown of epidermal homeostasis found in psoriatic lesions, which could help to promote wound healing and reduce scarring. In addition, a wrinkled topography affects cell alignment depending on the cell type. Han et al.[138] found that PDMS with a wrinkled surface promoted the proliferation but not the orientation or elongation of vascular smooth muscle cells (VSMCs). This approach could be applied to reduce the risk of VSMC dysfunction, which is a stent-related disease. In contrast, Liguori and colleagues[141] demonstrated that a micrometer-sized wrinkled PDMS surface promotes the adhesion, alignment, and TGF-1-induced generation of smooth muscle cells from ADSCs, whereas nanometer-sized topography blocked the differentiation of ADSCs without affecting their adhesion. As smooth muscle cells and fibrosis are related, these findings imply a potential role for nanotopography as a cutting-edge fibrotic inhibitor. Moreover, wrinkled topography on the PDMS surface can modulate cellular hepatic fibrosis both in vitro and in vivo.[133] These findings suggest that the alignment and orientation of cells on the PDMS surface can subsequently modulate the host immune response and fibrotic encapsulation.

The foreign body response involves various immune cells such as macrophages, fibroblasts, T-cells, and dendritic cells.[145–148] Thus, modulating them can help to reduce implant-associated complications. During a PDMS-induced adverse response, macrophages and fibroblasts play a role in mediating the foreign body reaction, and the spreading of these cells can lead to fibrosis. Thus, controlling their response can lead to blocking the first biological recognition steps in the signaling process for the development of fibrous tissue. Microscale topography has been reported to affect macrophage and fibroblast modulation. Baker et al.[149] investigated the effects of PDMS micropillar arrays on fibroblast and macrophage responses both in vitro and in vivo. The greatest pillar height and spacing were found to induce the highest fibrotic response due to cell accumulation and collagen production. In addition, Robotti et al.[150] discovered that micropits significantly minimize fibroblast spreading and hinder their differentiation into myofibroblasts, which in turn inhibits the attachment and proliferation of fibroblasts and thus plays a critical role in fibrosis suppression. Chen et al.[151] imprinted a wide range of micro- and nanoscale parallel frameworks on polymer surfaces (including PDMS) to investigate their effect on macrophage activity during the foreign body reaction. Even though the various-sized frameworks did not have a unique pattern, they discovered that when compared to planar controls, changing the framework topography affected the macrophage behavior on the polymer surface regardless of the surface chemistry. Inflammation-related activity and macrophage activation occurred on the larger-sized framework (500 nm to 2 μm), with a topography-induced sensitivity limit at 500 nm. In contrast, planar controls and a smaller-sized framework (250–300 nm) provided the same adhesion and motility kinetics seen in conventional macrophage adhesion, spreading, and fusion during the foreign body response. In addition, the shape and orientation of the macrophage cells were found to be influenced by the micro- and nanopattern topography of a polymer surface. Chen et al.[152] found that changing the pore size of the PDMS scaffolds was helpful for maturing immunological dendritic cells: scaffolds with smaller hole diameters improved dendritic cell maturation in vitro and higher dendritic cell recruitment and sustained activation in vivo.[152] These findings advance the knowledge of how the immune response interacts with the architecture of biomaterial scaffolds, which might have broader ramifications for vaccine delivery and immunotherapy.

According to the outcomes of clinical studies, the immune response is different depending on the material surface architecture.[153,154] Doloff et al.[155] recently investigated the foreign body reaction toward PDMS implants with various surface topographies (average roughness: 0–90 μm) in the mammary fat pads of mice and rabbits for up to 1 year, as well as in human breast implants retrieved after revision procedures. Among the implants, those with a surface roughness of 4 μm caused the lowest levels of inflammation and the foreign body reaction. In particular, the one with the most positive skewness and contact points per unit surface area (indicating fibrosis suppression) also showed the potential involvement of T-cells in the surface-mediated immune response. From the findings, surface topography and roughness are key factors in modulating the host immune response and fibrotic encapsulation of PDMS implants.

Enhancing the roughness of the PDMS surface via modification with electrospun fibers is another physical modification strategy that has received much attention over the last few decades. Due to the variety of biocompatible materials that can be electrospun as well as the numerous methods for incorporating agents with different physicochemical properties, electrospun fibers are useful in a wide range of biological applications, including tissue engineering and drug delivery.[156–158] Micro- and nanosized electrospun fiber networks offer a promising environment for improving cell adhesion and proliferation because their design closely resembles that of the ECM found in human tissues.[159–161] An electrospun nanofiber membrane-coated PDMS surface provides a mechanically stable surface that minimizes blood coagulation with well-spread adhesion and proliferation of fibroblast cells,[162] as well as the keratinocyte HaCaT cell line.[163]

Indeed, not only surface modification but also material geometry are important physical property modification techniques. Some researchers have looked into the effect of material geometry (such as size and shape) in regulating the foreign body reaction. Matlaga et al.[164] investigated the in vivo

 

biocompatibility of rods extruded from a variety of medical-grade materials (including silicone rubber) with varying cross-sectional shapes. In comparison to triangular and pentagonal cross-sections, rods with a circular cross-section had the least severe foreign body reaction. These findings suggest that the shape of the implant can have a major impact on macrophage behavior. Veiseh et al.[165] reported that sharp features, corners, and acute angles in an implant cause more acute reactions than smooth, well-contoured surfaces.[165] Colaris et al.[122] suggested that the morphology of the PDMS implant surface (such as texture, size, and shape) and the manufacturing process must be taken into account when looking for potential triggers for pathological effects, particularly in cases where an inflammatory or immune response is known to have occurred. Furthermore, stiffness also influences the capability of a material to modulate the immune response. Noskovicova et al.[166] found that a soft PDMS surface (elastic modulus = 2 kPa) reduced the fibrotic encapsulation of subcutaneous PDMS implants in mice compared to stiff conventional PDMS (elastic modulus = 2 MPa).

### 3.2. Surface Chemical Modification

Functionalization via chemical bonding, surface coating, and physicochemical approaches have all been employed to enhance the biocompatibility of the PDMS surface. PDMS surface modification from its inherent hydrophobicity to hydrophilicity could minimize the level of protein adsorption, thereby enhancing cell adhesion via the innate immune response on the PDMS surface. Introducing hydroxyl (−OH) groups via $O_2$ plasma or UV/ozone treatment is a simple chemical technique to improve the surface wettability of PDMS.[167–170] However, as mentioned in Section 2, the disadvantage of this technique is that it reduces not only the hydrophobic recovery coefficient but also the oxygen permeability coefficient by 40–80%.[171] This is because undesirable cracks develop as a result of improper treatment,[28,172] which leads to instability and thus limits the use of PDMS in biomedical applications. Although placing the modified PDMS surface in bacterial broth or water can maintain the surface hydrophilicity,[173–175] this approach has limited clinical utility. Surfaces that have been chemically modified can potentially promote long-term biocompatibility.

Surface modification via chemical techniques involves chemical reactions with a suitable agent (noncovalent bonding) or direct covalent bonding of a polymer or bioactive compound to the surface (grafting), both of which, independently or together, are widely used techniques in PDMS surface modification. Although surface biofunctionalization via noncovalent bonding is a straightforward and gentle process that causes minimal damage to the biomaterial substrate and the bound molecules, the bonds formed thereby are not stable. Even though the surface of the material has been changed to become hydrophilic, the hydrophobic properties of the PDMS can still be recovered because very erratic polymer chains presenting Si−OH bonds rearrange themselves in the bulk state, while untreated PDMS oligomers from the bulk state migrate to the surface.[28,168,176] This is a flaw that makes it difficult to maintain the long-term surface biocompatibility of the PDMS. As a result, modifying the hydrophilic surface of PDMS permanently to improve its long-term stability for antibiofouling and modulating cell attachment as well as regulating immune response is desirable.[177]

Incorporating bioactive molecules on the PDMS surface improves not only the surface hydrophilicity but also the hydrophilicity stability. To create biomimetic materials that are sustainable over the long-term, stable immobilization of biomolecules on the substrate surface is required to maintain bioactivity and, eventually, proper functionality. Protein grafting, enzyme immobilization, and cell preseeding are among the biomimetic approaches that mimic some of the structural and/or functional aspects of the extracellular microenvironment.[178] Approaches for mimicking the natural ECM involving coating of the PDMS surface with natural polymers (e.g., collagen, gelatin, and hyaluronic acid) are being continually developed. Although biodegradable natural polymers have moieties that allow them to be recognized biologically and immunologically, they are mechanically weak.[179] On the other hand, synthetic polymers have stronger mechanical properties (which can be changed by hydrolysis) but weaker biocompatibility.[180,181] Although these chemical approaches can be conducted directly if the substrate surface is chemically reactive, surface preactivation is required for strong hydrophobic and/or chemically inert polymers, such as PDMS prior to chemical immobilization or grafting. This can be accomplished by using a wet chemistry procedure to oxidize the surface, introducing surface amino- and/or other functional groups, or applying ionizing irradiation (plasma, laser, or ion-beam).[182] In this section, modifying PDMS via the chemical functionalization of biomolecules (both natural and synthetic) to improve the long-term stability in biomedical applications is reviewed.

#### *3.2.1. Antibiofouling Strategies*

A common method to achieve this is grafting bioactive substances or polymers onto the surface of the material. A variety of antibiofouling polymers that can successfully inhibit the adherence of bacteria and proteins have been created. They typically exhibit high hydrophilicity, resulting in the formation of a wettable layer on the material surface that decreases surface-foulant interaction and attachment. Antibiofouling polymers are promising because they can mitigate the use of antimicrobial drugs, thereby avoiding the risk of bacterial resistance. However, their efficacy depends on both the polymer and the foulant species.[183] Tryptophan, arginine, and lysine are amino acids that make interesting antibiofouling polymer candidates due to their good antimicrobial activity against *E. coli*, *S. aureus*, and *C. albicans*.[184] An enzymatically degradable (hyaluronic acid/chitosan)n-(hyaluronic acid/polylysine)n composite multilayer film provides a modified surface that mimics host defense peptides has demonstrated a self-defense bacterial adhesion effect against *S. aureus* and *E. coli*, as well as wound healing without cytotoxicity to human lens epithelial cells, both in vitro and in vivo.[185] Other polymers such as polyethylene glycol (PEG), poly(2-hydroxyethyl methacrylate) (PHEMA), polyacrylic acid (PAA), and poly(2-methacryloyloxyethyl phosphorylcholine) (MPC), as well as zwitterionic polymers, have been employed to improve the surface antibiofouling ability of PDMS.[65,186–191]

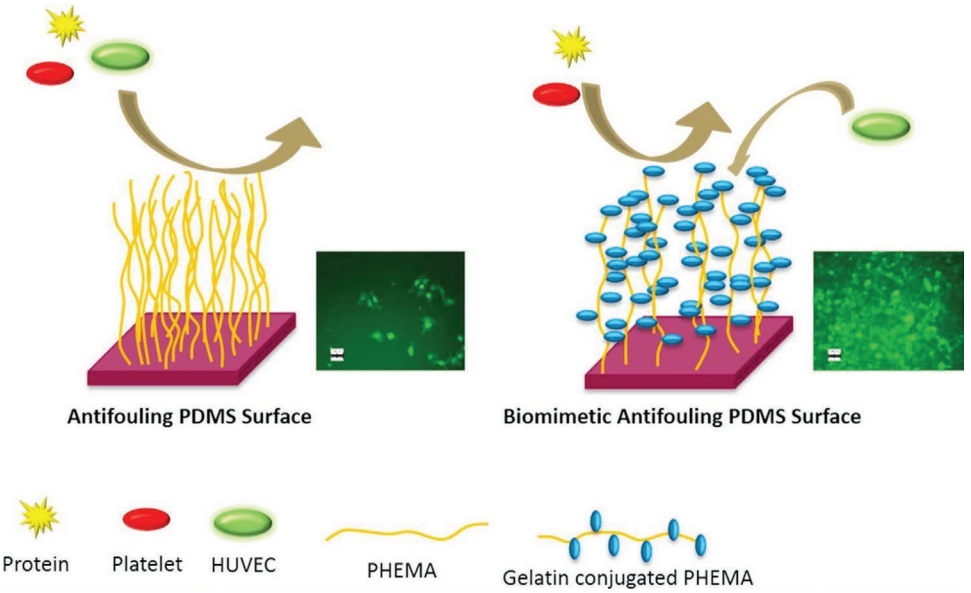


**Figure 4.** A schematic of high-density poly(2-hydroxyethyl methacrylate) (PHEMA) brushes attached to a poly(dimethylsiloxane) (PDMS) surface limiting cell adhesion and growth while displaying excellent platelet and protein resistance. The promotion of endothelialization is the result of gelatin conjugation to PDMS-g-caPHEMA.[186] Reproduced with permission.[186] Copyright 2018, Elsevier.

Among the hydrophilic polymers, PEG-based ones have been the most studied for biomedical applications as they are nonimmunogenic, antithrombogenic, and resistant to protein adsorption.[192] Their antibiofouling action is caused by both steric hindrance and hydration effects depending on the size, branching, and surface-packing density of the polymer.[183] PEG derivatives have been used to improve the surface properties of PDMS for a variety of applications. Protein adhesion was significantly reduced for more than 30 days by anchoring PEG to a silanized-PDMS substrate.[193] Furthermore, due to the elasticity of PDMS, PEG-grafted PDMS can be used to either promote or prevent protein adhesion. For example, the greater the stretching force, the more space between two PEG molecules, which in turn, increases the accessibility of protein molecules to the surface.[194] Coating the PDMS surface with a ring-opening metal-free organocatalytic ring-diblock copolymer that contains PEG and cationic polycarbonate provided better antifouling and antimicrobial activities compared to PEG-grafted PDMS.[195,196] This approach might apply to overcome the formation of biofilms as a result of microbial adhesion and intravascular catheter-associated infections.

Hydrophilic polymers such as PAA are commonly used to improve the antibiofouling properties of a material. Hussain et al.[65] created an antibacterial PDMS surface against *E. coli*, *S. aureus*, and *P. aeruginosa* by modifying the surface via plasma treatment and activation, then grafting a co-PAA/acrylamide (AAm) hydrogel to it, and finally mobilizing it with a bioactive collagen surface before impregnating with gentamicin. As another polymer-grafting example, excellent protein and platelet resistance were displayed by a PDMS surface coated with well-defined high-density PHEMA brushes.[186] Ghaleh et al.[186] developed a PDMS surface covered with well-defined high-density PHEMA brushes conjugated with gelatin that demonstrated outstanding protein and platelet resistance capabilities (**Figure 4**). The biomimetic PHEMA brushes provide antifouling due to their hydrophilic nature with bioactive properties due to a high density of -OH groups that can be conjugated with biomolecules. In comparison to an uncured PDMS substrate, grafting PHEMA chains on the PDMS surface increased surface wettability, which reduced nonspecific protein adsorption and platelet adherence. Moreover, the adhered platelets on the modified surface retained their typical round shape. In another study, a decrease in *E. coli* adhesion has been observed on a PHEMA-grafted PDMS surface.[197]

Inspired by polymers that mimic cell membranes and prevent fouling, phosphorylcholine (PC)-containing polymers, which imitate the lipid components in cell biomembranes, have been employed as antifouling agents. Qin et al.[187] created a modified PDMS surface with long-term antifouling and antibacterial properties through the covalent grafting of MPC onto PDMS (**Figure 5**). Mammalian cells were unaffected by the MPC gel-coated PDMS, and it effectively inhibited bacterial adhesion as well as, in particular, macrophage attachment; the latter was accomplished by inhibiting the expression of proinflammatory markers, which reduces the activation of M1-like macrophages and increases the polarization of M2-like macrophages.[187] Zwitterionic PC-containing polymethacrylate copolymer chains have been reported to improve the hydrophilicity, coating stability, and antifouling capabilities of a PDMS surface.[188] They also prevented the adhesion of nonspecific proteins (fibrinogen and bovine serum albumin) as well as bacteria (*E.* coil, *P.* aeruginosa, and *S.* aureus). Furthermore, platelet spreading and pseudopodium deformation were significantly reduced, resulting in decreased platelet activation and enhanced hemocompatibility.[188]

Natural polymers such as hyaluronic acid have also been grafted to the PDMS surface to overcome the biofouling issue. It is a key component in the gel-like part of the ECM

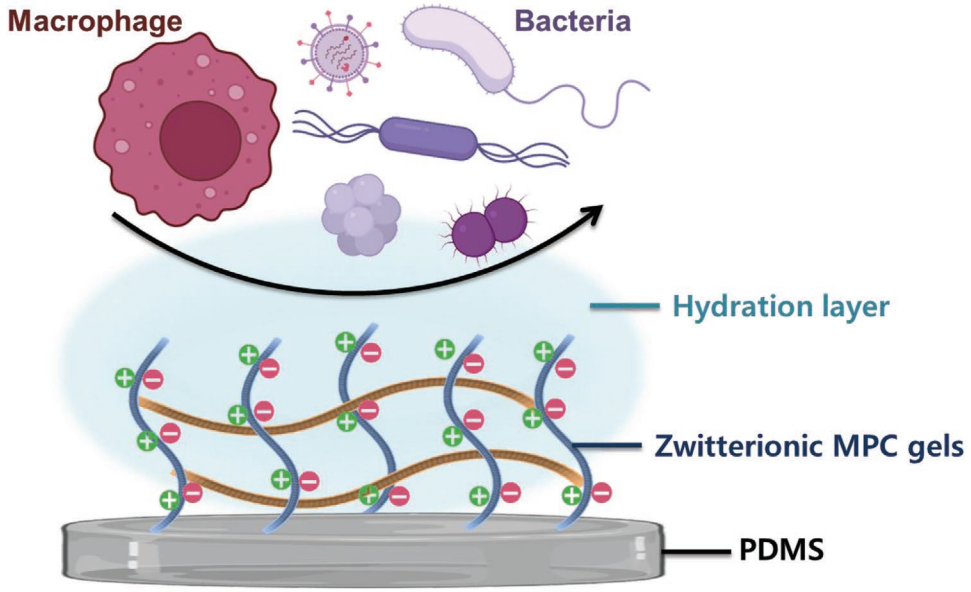


**Figure 5.** Covalent grafting of a cell-membrane-inspired zwitterionic gel layer consisting of 2-methacryolyl phosphorylcholine (MPC) to PDMS to bestow antifouling and antibacterial properties. Adapted with permission.[187] Copyright 2018, American Chemical Society. This is an unofficial adaptation of an article that appeared in an ACS publication. ACS has not endorsed the content of this adaptation or the context of its use.

in connective tissues. A nondegradable and stable hydrophilic PDMS surface has been constructed by grafting a PDMS surface with hyaluronic acid to limit protein adsorption and promote cell adhesion.[198] This modified surface had high resistance to fibrinogen and albumin adherence, and according to a long-term study, it was very durable and stable for up to one year without losing its qualities. Similarly, conjugating itaconic acid (a mammalian metabolite) to the PDMS surface resulted in an increase in surface hydrophilicity that inhibited protein adsorption and infection-related cellular adhesion by *S. epidermidis*, *E. coli*, and *P. aeruginosa*.[72]

### *3.2.2. Strategies for Modulating Cell Adhesion Including Regulation of the Immune Response on the PDMS Surface*

*Strategies for Modulating Cell Adhesion*: Cell adhesion to the substrate surface is critical for determining cell survival, proliferation, and differentiation,[73] while surface chemical characteristics have a major impact on cell growth.[199] Modifying the surface chemistry of PDMS is a simple technique for controlling protein adsorption and cell activity. Surface chemical modification has the potential to promote cell adherence and long-term culturing ability. Various studies have been focused on modifying the PDMS surface to reduce its hydrophobicity because surface wettability is a key factor in cell adhesion to the substrate. Although several attempts to improve cell survival on PDMS-based substrates via plasma treatment, silanization, and polymer functionalization have resulted in improved cellular behavior, the impact has not been satisfactory due to short-term stability.

Hydrophilic polymers that convert the PDMS surface from being hydrophobic to hydrophilic are known to facilitate cell attachment and development, reduce nonspecific or hydrophobic protein adsorption, and hence, improve cell adhesion. Covalent grafting of hydrophilic molecules provides a viable alternative strategy for overcoming the limitation of short-term stability outlined above by enhancing the stability and prolonged bioactivity of functionalized biomolecules toward target cells. Despite being more advanced, covalent grafting strategies can boost the availability of biomolecules more than noncovalent ones.[71,200]

Although specific protein adsorption has been reported to influence initial cell adhesion,[201] inconsistencies in protein dissociation and stacking can promote cell-sheet aggregation and separation during long-term culturing.[202] To overcome this problem, covalent bonding of matrix protein enables the protein to establish a homogeneous layer on the surface, thereby enhancing long-term and stable cell adhesion.[200,203] Natural polymers have cell-interactive domains on their backbones that make them inherently bioactive. As a result, surface functionalization using them promotes better cell adhesion, proliferation, and differentiation than when using synthetic polymers. In particular, it should be noted that the breakdown products from natural polymers are chemically benign and only cause a minimal immune reaction.[204] The PDMS surface modified with hyaluronic acid is biocompatible with human retinal pigment epithelial cells and significantly improves cell contact over time without degrading the cellular properties for up to 12 months.[198]

Combining ECM proteins such as collagen and hyaluronic acid with polymers to modify the PDMS surface can improve cell adhesion and modulation. For example, covalently binding collagen mixed with glutaraldehyde to the PDMS surface significantly improved the uniformity of the collagen I layer distribution on it, which increased MSC adhesion and proliferation due to improved roughness and reliable collagen I binding sites.[200,203] Collagen combined with dopamine incorporated onto the PDMS surface improved the surface wettability, which promoted the adhesion and proliferation of fibroblasts,[205] tendon stem cells,[205] bone marrow stromal cells,[206] and

ADSCs,[207] as well as multipotential activities such as osteogenesis and adipogenesis. Similarly, a composite with an appropriate ratio of polydopamine to hyaluronic acid used to modify the PDMS surface provided low cytotoxicity and high adhesion and proliferation of human umbilical vein endothelial cells and macrophages.[208] Furthermore, gelatin combined with PHEMA tethered to the PDMS surface provided antifouling, which promoted cell attachment and growth via ligand-receptor interaction, and so could be used in cardiovascular tissue engineering devices.[186]

Regarding functionalization with bioactive molecules, the use of intermediary molecules that can bind both to the biomaterial surface and the bioactive molecules is an alternative strategy for solving limitations such as the inactivation or denaturation of covalently grafted immobilized biomolecules and weak noncovalent cues. Glycosaminoglycans, ECM proteins, tiny oligopeptides resembling ECM proteins, streptavidin–biotin compounds, aptamers, and antibodies have all been used as intermediate molecules.[209–213] These biomolecules can physically or chemically modify the surface of the biomaterial as well as provide immobilized areas for biomolecules. For example, Lin et al.[210] developed a dual-function biomimetic material by coating laminin and liposome-loaded dexamethasone on plasma-modified PDMS to fabricate a slow-release angiogenesis inhibitor. Retinal pigment epithelial (RPE) cells derived from human-induced pluripotent stem cells (hiPSC) were cultured on the top of a PDMS structure modified by covalently grafting laminin while the unmodified bottom side was loaded with liposomes containing dexamethasone via biotin-streptavidin linkage (**Figure 6**). The hiPSC-RPE cells could proliferate, express normal RPE-specific genes, and maintain their phenotype, which included phagocytosis and the release of antiangiogenic PEDF (pigment epithelium-derived factor) on the laminin-modified surface. The use of this PDMS membrane with modified and unmodified surfaces decreased oxidative stress-induced angiogenesis, as evidenced by decreased VEGF (vascular endothelial growth factor) release by the RPE cells and suppression of vascularization.[210] As another example, TGF-1-impregnated collagen grafted to a PDMS substrate showed a synergistic effect on the chondrogenesis of ADSCs in vitro.[213] This approach formed strong and stable covalent connections between the biomaterial surface and the intermediate molecules (collagen) while preventing the bioactive molecules (TGF-1) from being exposed to the surrounding hostile microenvironment. The binding domains on the intermediate molecules on the biomaterial surface provide hydrophilicity, which favors bioactive compound immobilization.[214] Thus, long incubation times are not required and a wider range of buffer systems can be used instead of chemical bonding.[215] The major drawback of this technique is that it necessitates extra preparation steps.

*Strategies for Regulating the Immune Response on the PDMS Surface*: Since the properties of the biomaterial can influence surrounding immunomodulation and biomaterial-mediated inflammation is a complicated issue that affects patient health in general and limits the functionality of implanted devices, the development of active mechanistic methods for the delivery of anti-inflammatory agents as well as passive nonfouling surface treatments to prevent nonspecific protein adsorption and modulate cell adhesion has received a lot of attention.[216,217] The biological behavior of immune factors is directly influenced by changes in the surface characteristics and surface chemistry of the substrate. Immune-isolating materials for covering implant surfaces have been developed in an effort to reduce the host's inflammatory reaction to an implant.[218] Using a variety of surface modification techniques, the foreign body reaction can be reduced and biomaterial-tissue integration can be improved. The inclusion of functional groups to alter the surface properties of a polymer, such as ionic charge and wettability,[173] as well as coating with other polymers or bioactive moieties to imitate the natural tissue environment,[71,218] are examples of these modification strategies. For example, an IL-4-coated biofunctionalized implant was recently shown to be able to regulate macrophage polarization, decrease fibrous capsular contracture

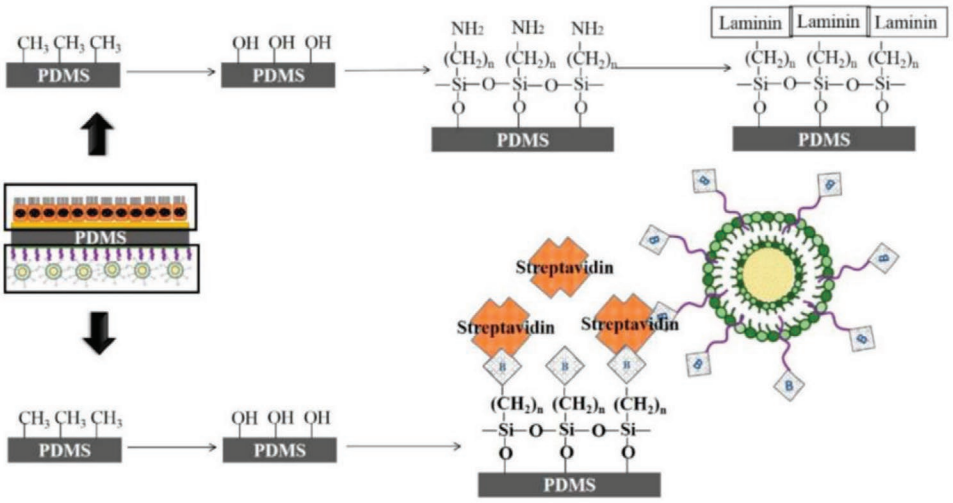


**Figure 6.** A schematic of a poly(dimethylsiloxane) (PDMS) membrane with attached dexamethasone-loaded liposomes. The liposomes were attached to the bottom surface via hydroxylation, silane-biotinylation, and noncovalent streptavidin bridges. The top surface was covered with laminin through silanization, hydroxylation, and laminin crosslinking.[210] Reproduced under the terms and conditions of the Creative Commons Attribution (CC BY) license 4.0.[210] Copyright 2019, The Authors, published by MDPI.

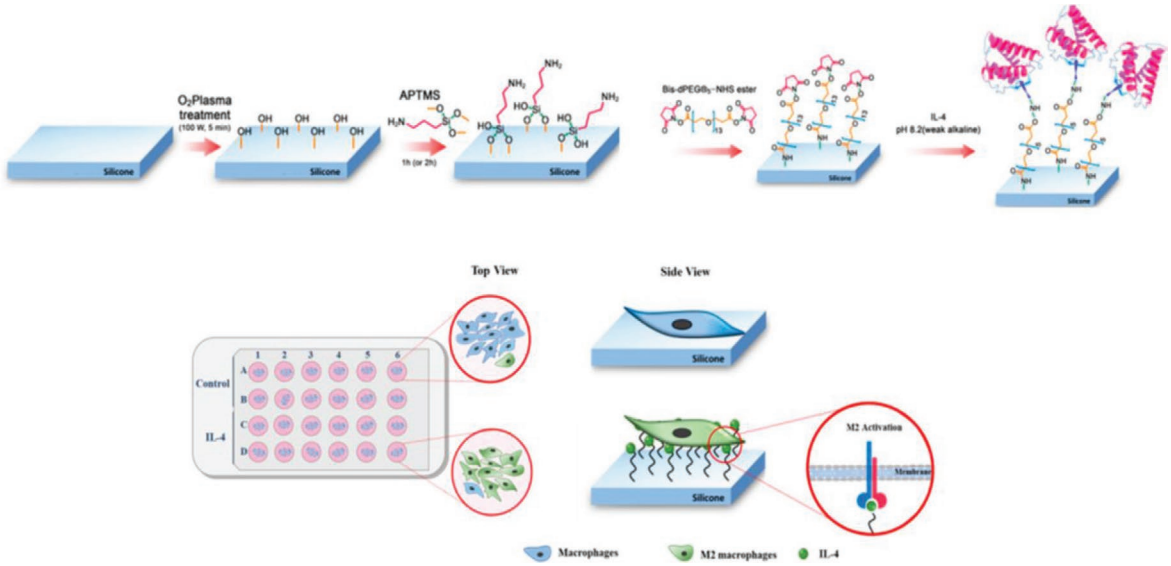


**Figure 7.** A schematic representation of manufacturing poly(dimethylsiloxane) implants with an interleukin (IL-4) coating and cell culturing on its surface in vitro.[219] Reproduced under the terms and conditions of the Creative Commons Attribution (CC BY) license 4.0.[219] Copyright 2021, The Authors, published by MDPI.

and the adverse immunological response, and promote tissue regeneration (**Figure 7**).[219] Coating the surface with an itaconic acid-conjugated gelatin polymer provided evenly attached fibroblast for up to 8 weeks in vitro and alleviated the foreign body reaction in vivo, thereby minimizing fibrosis on the PDMS surface.[71] Our recent study revealed that itaconic acid-conjugated PDMS surface also improved ADSC adhesion and orientation.[220] Interestingly, coating the stem cells on both the unmodified and modified PDMS surfaces lessened the fibrotic response of the foreign body reaction compared to the unmodified control PDMS by up-regulating macrophage polarization (**Figure 8**),[220] thereby indicating the potential of ADSCs to alleviate the immune response. Thus, this strategy could be used to develop biomaterials for utilizing MSCs (and the other cell types) for stem cell therapy.

ECM-inspired structures or those comprising ECM components can help to generate a microenvironment for the innate immune system and promote normal wound healing and repair. Thus, ECM proteins and synthetic ECMs can be used as implant coatings to reduce the amount of inflammation, regulate protein adhesion and subsequent cytokine release, and control immunomodulation.[221–223] Recently, MPC, a zwitterionic polymer, was used to create an artificial ECM to mimic the components that give structure and support to cells and tissues. Subsequently, it has garnered much interest for use as a coating material, mainly for implants and devices in the biomedical field.[187,221,222,224–227] Over the long-term, covalently attaching MPC to the surface of PDMS diminishes the immune response along with the thickness of the fibrous capsule and levels of inflammatory indicators.[225,226,228] Researchers have reported that based on the inflammatory and fibrosis scores, MPC zwitterion-coated PDMS microfillers reduced the immunological response in a rat model.[221,222]

Semipermeable hydrogels have been intensively investigated as antifouling implant coverings due to their unique properties, such as high water content, ease of solute transport, and the capacity for numerous active groups for future chemical modification.[221,229] They can be used to encapsulate islets against attack from immune cells by preventing direct physical contact while allowing molecules such as reactive oxygen species, NO, and cytokines to pass freely across the hydrogel network. In addition to delivering anti-inflammatory capability, polymeric hydrogels can include traps for catching proinflammatory signals. After biomaterial implantation, small compounds can also affect monocyte recruitment and the phenotype, which is a deviation from the typical approach of alleviating the immune response toward a biomaterial. Hydrogels have been incorporated with ECM proteins or ECM-inspired structures. For example, Joo et al.[229] reported that coating PDMS with a hydrogel made from crosslinked hyaluronic acid and gelatin successfully reduced the immune response involving fibrosis and capsule formation in vivo.[229] Immunomodulatory cytokines contained in thin ECM-like hydrogels can be utilized to regulate the interaction of a nonbiodegradable material with the surrounding tissue.[230,231] Barthes et al.[231] demonstrated that to evenly heal a partial tracheal defect in rats, a gelatin-based hydrogel containing a cytokine cocktail comprising IL-10 and prostaglandin E2 on a PDMS tracheal patch surface suppressed the internal inflammatory response within the lumen of the endotracheal tube, which remained open and allowed the animal to breathe normally without the need for stents. By mitigating inflammation and fostering integration, this method could help to alleviate the currently poor outcomes associated with implantation.

Physicochemical strategies (a combination of physical and chemical techniques) have been reported to effectively lessen the foreign body reaction.[218,232] For instance, Yoo et al.[218] combined micropatterning and a multilayer coating of poly-*L*-lysine and hyaluronic acid on the PDMS surface that is cytocompatible and suppresses the expression of TGF-$\beta$ and $\alpha$-SMA (the

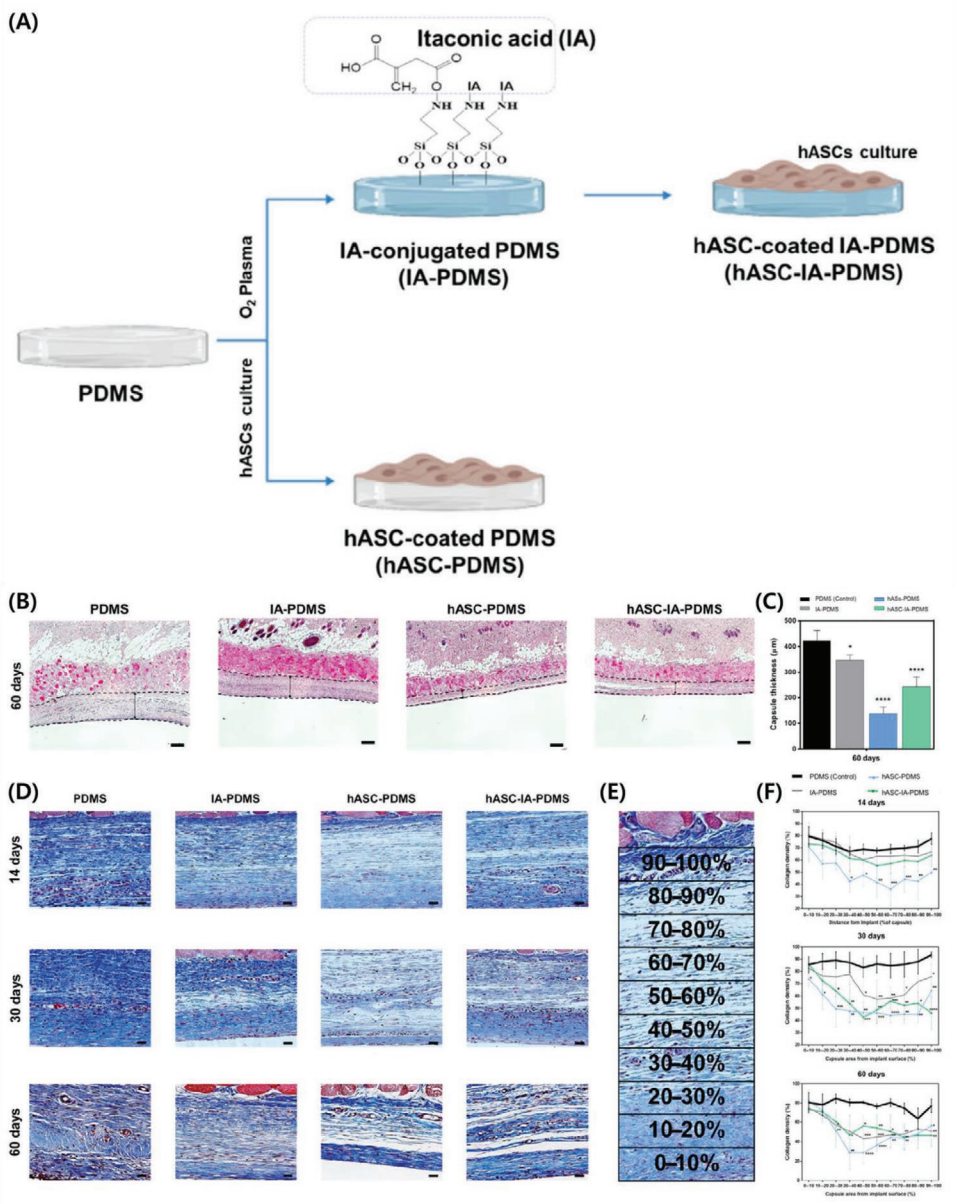


**Figure 8.** A) A poly(dimethylsiloxane) (PDMS) surface and a PDMS-conjugated itaconic acid (IA) (150 mM) surface coated with human adipose-derived stem cells (ADSCs) (hASCs). B) Images showing that the capsule thickness around implants at 60 days after PDMS, IA-PDMS, hASC-PDMS, or hASCs-IA-PDMS implantation had lessened around the hASC-coated PDMS surfaces compared to the PDMS surface without hASCs. Tissue stained with B) H&E and D) Masson's trichrome. E) Data gathered at 10% increments from the entire capsule area (100%) at the interface. F) The density of collagen deposition around the implants at 14, 30, and 60 days postimplantation. The results indicate that the collagen density around the hASC-coated PDMS surfaces was lower than that of the PDMS surface without hASCs.[220] Reproduced under the terms and conditions of the Creative Commons Attribution (CC BY) license 4.0.[220] Copyright 2022, The Authors, published by John Wiley & Sons, Inc.

major pro-fibrotic cytokine and myofibroblast markers, respectively). The outcomes of an in vivo study of implanting the modified PDMS in rats indicate that the strategy effectively lessened the foreign body reaction and reduced capsular contracture after 8 weeks. Similarly, generating microtextured PDMS surfaces using electrospun nanofibers has been shown to suppress foreign body reaction-related factors in vivo, while it contributed to macrophage polarization to the M2 phenotype in vitro and in vivo.[232] These surface modifications could be applied to implantable PDMS devices to alleviate the foreign body response and capsular contracture.

## 4. Future Directions

Novel approaches for developing PDMS implants that imitate natural surface features, such as pattern topography, surface chemical alteration, and bioactive component immobilization,

could improve implant biointegration and biocompatibility. Surface modification and functionalization using a biomimicked microenvironment to improve biocompatibility over time could be useful in biomedical applications. Moreover, manufacturing medical devices based on biomimetic alteration and functionalization approaches could alter the immune system response, limit bacterial adhesion and biofilm formation, improve functional treatment, and reduce complications. This could pave the way for the creation of long-term implantable biocompatible medical devices for various biomedical systems (e.g., bone and tissue regeneration). Furthermore, advanced biomimetic controllable electromechanical devices with multibiocompatibility functions, such as immune response suppression, wound healing, and post-treatment complication detection, could be developed in the future to detect or treat local and surrounding dysfunctions such as cancer or excessive inflammation. These will help people undergoing long-term treatment.

## 5. Conclusions

So far, a large number of studies on the design of biomaterials to improve their biocompatibility have been conducted. Because of its biocompatibility and lack of toxicity, PDMS is widely used in biomedical applications. However, PDMS-based biomaterials still have drawbacks that need to be addressed. There have been many attempts at reducing them. The development of PDMS surfaces that imitate natural surfaces such as animal skin and human tissues is of particular importance. Mimicking human tissue, cells, or the ECM when fabricating biomedical devices to reduce biofouling and foreign body reaction, as well as modulate the cellular and immune responses, is receiving much attention. Biomimetic materials, particularly those based on PDMS, have significant advantages, such as cell signaling, drug delivery, and wound healing capabilities, for biomedical applications. The development of PDMS-based materials (e.g., implants, prostheses, and catheters) can help with tissue engineering and regenerative medicine. Engineering of both the physical and chemical properties of the PDMS surface, such as modifying the surface hydrophilicity and micro- and nanotopography, have been shown to influence events critical for enhancing biomaterial biocompatibility. A novel approach utilizing various biomimetic techniques, particularly surface topography transformation and bioactive molecule immobilization, has been used recently. Topographical changes have the advantages of being safe and cost-effective while incorporating bioactive molecules or polymers on the PDMS surface has the advantages of stability and high efficiency. Combining both methods to produce physicochemical cues is a promising approach for long-term multifunctional applications. The use of these new cues in the development of PDMS-based medical devices enables more spontaneous interaction between the devices and the surrounding tissue, which improves cell modulation in the long term while reducing biofouling and the foreign body response, as well as mitigating chronic inflammation. Nevertheless, only a few biomimetic PDMS surface modifications in clinical studies have been documented so far. Clinical applications using generated biomimetic surfaces as well as research into biomimetic materials with multibiocompatible functionality are being actively pursued.

## Acknowledgements

This work was supported via a research grant from the Biomedical Research Institute, Chung-Ang University Hospital (2021), and the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2022R1A4A3026347) and the Ministry of Science and ICT, Republic of Korea (MSIT) (NRF-2021R1A2C2007189).

## Conflict of Interest

The authors declare no conflict of interest.

## Keywords

antifouling, biomimicry, cell modulation, immune response, poly(dimethylsiloxane), surface modifications

Received: November 9, 2022
Revised: January 10, 2023
Published online:

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