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Review

Glycopolymers as a Tool for Specific Surface Modification of Polymeric Biomaterials

Joachim Storsberg [1,2,3,*], Sophia Rosencrantz [1,4] and Ruben R. Rosencrantz [1,5]

[1] Division of Life Science & Bioprocesses, Fraunhofer-Institute for Applied Polymer Research IAP, Geiselbergstrasse 69, 14476 Potsdam, Germany
[2] Division of Pharma- and Chemical Engineering, University of Applied Sciences Berlin (BHT), Luxemburger Strasse 10, 13353 Berlin, Germany
[3] Faculty of Medicine, Private University in the Principality of Liechtenstein (UFL), Dorfstrasse 24, 9495 Triesen, Liechtenstein
[4] Fraunhofer Cluster of Excellence Immune-Mediated Diseases CIMD, 60258 Frankfurt am Main, Germany
[5] Biofunctional Polymer Materials, Brandenburg University of Technology Cottbus-Senftenberg (BTU), Universitätsplatz 1, 01968 Senftenberg, Germany
* Correspondence: joachim.storsberg@iap.fraunhofer.de

Abstract

The interface between biomaterials and biological systems is crucial for medical implants and tissue engineering. Surface modifications are a key strategy for controlling interactions. Synthetic glycopolymers offer a versatile toolbox, mimicking the structure and function of natural glycoconjugates like mucins. This review highlights the significance of glycopolymers for targeted surface modifications of established biomaterials, such as silicones and poly(meth)acrylates. Controlled polymerization techniques, like the reversible-addition-fragmentation chain-transfer (RAFT) polymerization, enable the synthesis of well-defined glycopolymer architectures. Glycopolymeric surface functionalization creates tailored interfaces for different biological responses, from preventing protein and cell adhesion to promoting specific cell-type binding. The focus lies on using single, well-characterized polymeric base materials and tuning their surface properties through glycopolymer coatings to achieve various and specific functions. This approach opens new dimensions in the development of advanced biomaterials for applications like contact lenses, drug delivery systems, and biosensors and also possesses potential regulatory advantages by leveraging the safety profiles of existing materials.

Keywords: glycopolymers; polymer biomaterials; surface modification; biointerface; contact lenses; ophthalmic implants; cell adhesion; cell material interaction

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1. Introduction

The performance and lifetime of medical devices, from contact lenses to implantable constructs, depends on the interactions occurring at the material–tissue interface [1,2]. Uncontrolled biological responses, such as protein-caused fouling, bacterial adhesion, and inflammatory reactions, can lead to implant failure, adverse side effects and negative patient outcomes. Surface modification of biomaterials has become a growing research field in materials science, aiming to create interfaces that can actively and predictably control biological interactions [3,4]. A promising strategy in this field is the use of synthetic glycopolymers, a class of polymers designed to mimic the structure and function of naturally occurring glycoconjugates [5].

In nature, cells are embedded in a dense layer of carbohydrates, named glycocalyx, which mediates and is responsible for a variety of biological recognition processes [6,7]. Nanoparticles with different organ and cell specificity for targeted delivery could be developed by mimicking the glycocalyx [8].

This complex network of glycans regulates a wide range of biological events, from cell protection and adhesion to signaling and differentiation. The specific arrangement and density of glycans on the cell surface determines the high-avidity interactions required to trigger cellular responses. An example of such a natural glycoconjugate are mucins, high-molecular-weight glycoproteins that are the primary components of mucus, a protective and lubricating layer on epithelial surfaces (Figure 1) [9,10]. Native mucins consist of a protein backbone densely decorated with oligosaccharide side chains (glycans), forming a highly hydrated, lubricating, and protective barrier [11]. This architecture provides lubrication via attraction of water, protects underlying tissues from mechanical stress, and prevents, e.g., the adhesion of pathogens.

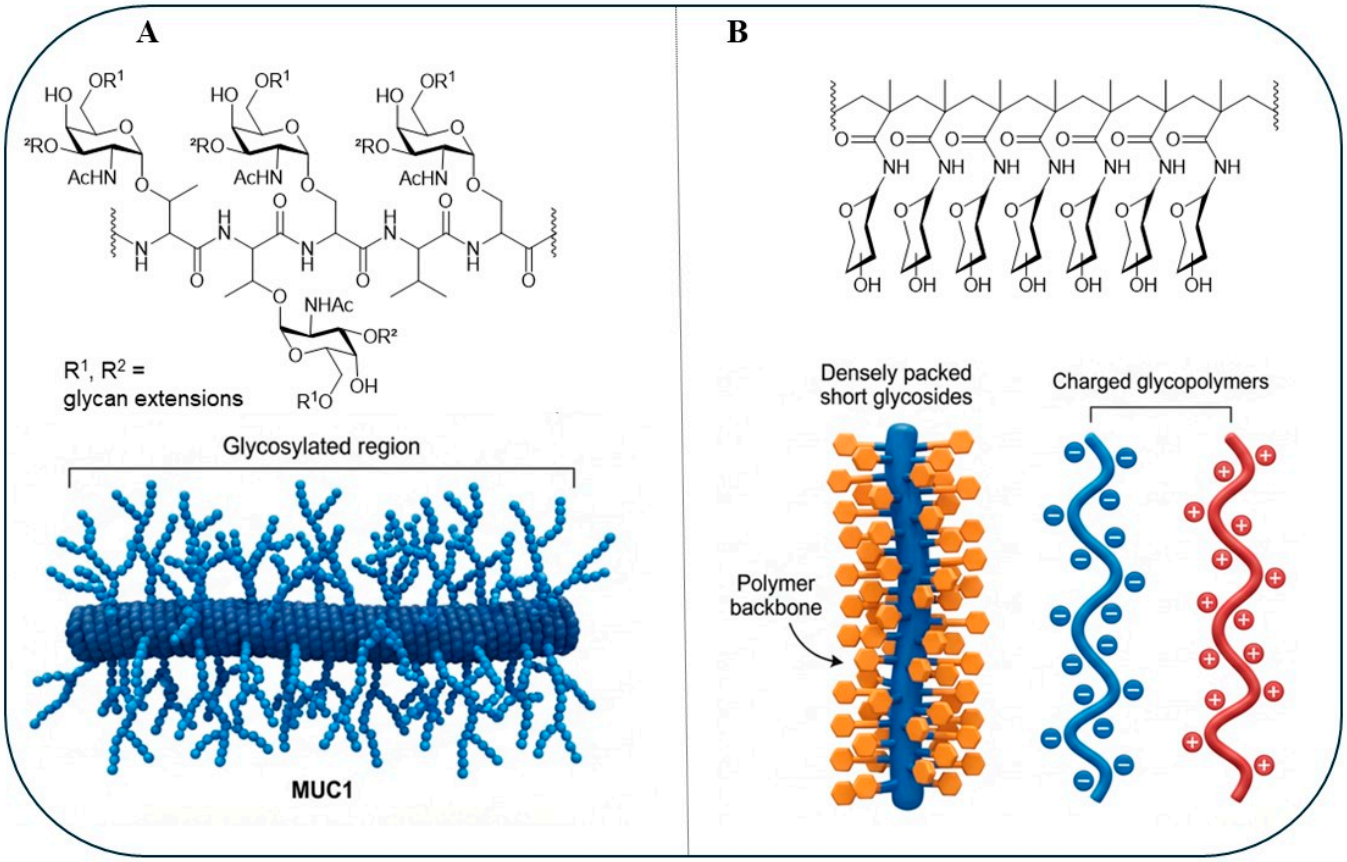


Figure 1. Illustration of natural mucin and synthetic glycopolymer mimics. (**A**): Representative structure of a native mucin (e.g., MUC1) with a protein backbone and glycosylated regions. (**B**): Synthetic artificial mucin mimics, including densely packed short glycosides on a (synthetic) polymer backbone and charged glycopolymers.

Full functional equivalence to natural mucins has not been established. The current literature supports the mimicking/matching of selected structural, physicochemical, and biointerfacial properties. However, a complete functional analogue of natural mucins is not given [12–15].

Inspired by this natural design, synthetic glycopolymers have been developed to replicate and even enhance these functionalities [16]. These polymers consist of a synthetic backbone to which carbohydrate moieties are attached as pendant groups [17].

Glycopolymers are recognized for their potential in various biomedical applications due to their ability to interact with biological systems in a manner similar to natural glycoconjugates. Unlike the complex and often heterogeneous structures of native glycoproteins, synthetic glycopolymers can be engineered, e.g., by using controlled polymerization techniques. This allows the fine-tuning of parameters such as molecular weight, polymer architecture (e.g., linear, brush, star-shaped), carbohydrate ("sugar") density, and charge distribution [18–22]. This control is important for a systematic investigation of structure–property relationships and for designing materials with tailored specific biological activities.

This review focuses on the role of glycopolymers as a versatile tool for the specific surface modification of well-established biomaterials, particularly those widely used in ophthalmology and other medical applications, such as silicones (polysiloxanes) and poly(meth)acrylates. We describe the current state of research on how glycopolymer coatings can modify and transform a single base material into a multifunctional materials platform. This opens a promising and capable way of creating different and even opposing functions (even on one and the same implant/base material surface). This concept has significant future potential, not only for developing novel, high-performance biomaterials but also for optimizing medical device regulatory processes. By modifying "only" the surface of a material with an already established safety and medical product approval record, the way to clinical translation can be accelerated. The central point is the precise tuning of cell–material interface by designing appropriate glycopolymer structures. The broad spectrum from bio-inert, cell-repellent surfaces to highly specific, cell-adhesive substrates, opens new possibilities in the development of tailor-made biomaterials (Figure 2). The development of glycopolymer-based strategies for the prevention and the treatment of infections by pathogens has been summarized and indicates their potential as antimicrobial agents [23].

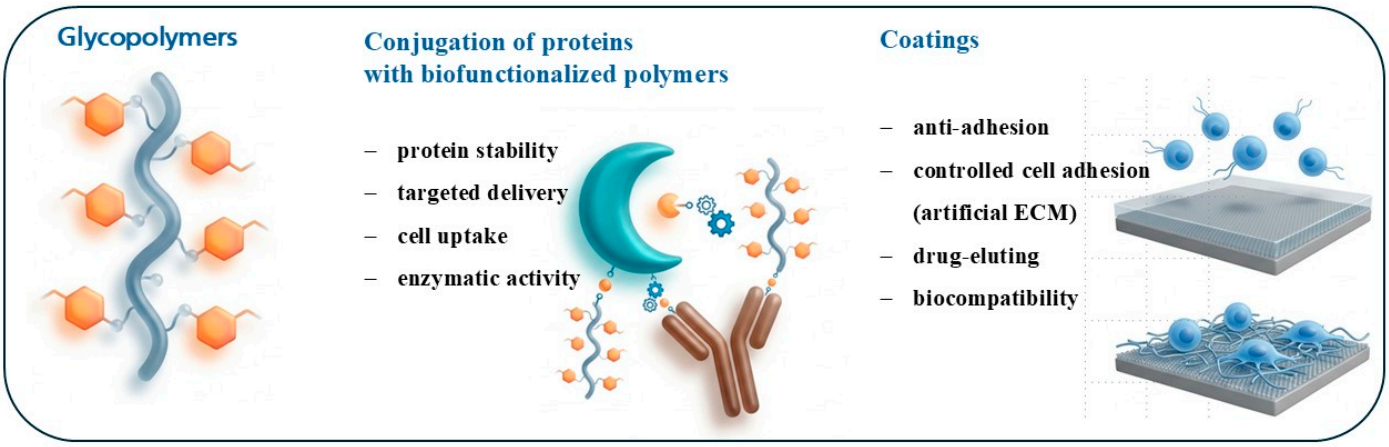


Figure 2. Glycopolymers for conjugations and coating. Conjugation of proteins with glycopolymers can enhance protein stability, enable targeted delivery, cell uptake, or maintain enzymatic activity. Glycopolymers as coatings on material surfaces can achieve various properties such as, e.g., anti-adhesion, controlled adhesion, controlled drug-release and improve biocompatibility.

An overview of some experimental support is summarized in Table 1.

Table 1. Experimental overview of glycopolymer functions in bioconjugation and as surface coatings (as presented in Figure 2).

Application Field	Comparison	Outcome	Ref.
Protein stabilization	Glycopolymer vs. no additive, glycopolymer vs. trehalose	Protein activities were significantly higher in the presence of trehalose glycopolymers compared to no additive or free trehalose. Monomeric trehalose decreased activity.	[24]
Protein stabilization/retained bioactivity	Glycopolymer system vs. native insulin vs. PEG conjugate	Glycopolymer prevented aggregation caused by shaking. Conjugate remained bioactive after thermal stress and showed longer circulation.	[25]
Targeted delivery	Glycopolymer-coated NPs vs. PEGylated NPs	Glycopolymer-coated NPs displayed better cellular uptake in tumor cells, increased circulation time and higher liver-tumor selectivity compared to PEGylated NPs.	[26]
Cell uptake	Glycopolymer-coated NPs vs. PEGylated NPs	Glycopolymer-coated NPs showed improved uptake in tumor cells with simultaneously reduced phagocytic elimination and/or reduced macrophage uptake.	[26]
Enzymatic activity	Glycopolymer vs. no additive/free trehalose	Formulations containing glycopolymer kept higher enzymatic activity after stress inducing compared to no-additive/free trehalose control.	[24]
Coatings: anti fouling/anti adhesion	Glycopolymer-coated surface vs. control surface	High-density poly(GAMA) displayed resistance to non-specific protein adsorption.	[27]

Challenges in Biomaterial Design

The challenge in biomaterial design often lies in the opposite requirements for bulk and surface properties. A material may provide ideal mechanical strength, elasticity, and oxygen permeability for its intended application, but its surface might be inherently thrombogenic or susceptible to biofouling, or cell-repellent where cell adhesion is needed (and vice versa). The interaction between a biomaterial and cells at the interface is crucial for cellular functions like adhesion, growth, and differentiation [28]. Therefore, understanding and controlling the surface chemistry at the interface between the material and the biological environment is critical for the success of medical implants and devices [29]. Surface modification offers an elegant solution by de-linking these properties, allowing the bulk material to be optimized for mechanical performance while the surface is engineered for biological compatibility. Glycopolymers are particularly advantageous in this context because the vast diversity of natural carbohydrate structures provides a huge chemical library to encode specific biological information onto a synthetic surface. By grafting these sugar-containing polymers onto a material's surface, properties like hydrophilicity and hemocompatibility can be significantly improved [27].

Carbohydrates play a central role in a wide range of biological recognition events, and their specific structures determine their interactions with proteins like lectins [30]. Even subtle changes in a carbohydrate's structure can dramatically alter its binding affinity and specificity [31]. This high degree of specificity allows for the design of "biomimetic" surfaces that can elicit precise cellular responses [32]. Selecting and arranging specific

sugar molecules on a synthetic polymer offer a level of specificity and control not easily achievable with other surface modification agents.

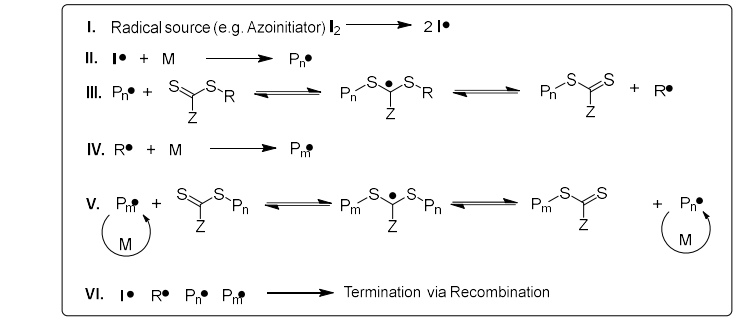
2. Controlled Synthesis of Glycopolymers

A current review systematically compares the synthesis and biomedical applications of glycopolymers, which are derived either from carbohydrate- or from vinyl monomer-based polymer backbones [33].

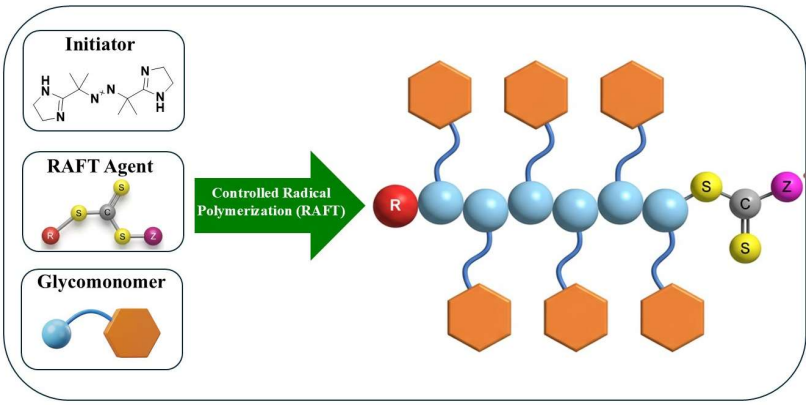
2.1. The RAFT Polymerization Route

The ability to tailor the biological function of a glycopolymer-modified surface is fundamentally dependent on the precise control over the polymer's molecular structure. Early methods for glycopolymer synthesis often resulted in polymers with broad molecular weight distributions and limited architectural control, which made it difficult to establish clear structure–activity relationships [34]. The development of controlled/living radical polymerization (CLRP) techniques has revolutionized the field, providing new synthetic routes towards well-defined glycopolymers with predictable molecular weights, low polydispersity, and complex polymer architectures [18,35].

Among the most powerful and versatile CLRP methods is reversible-addition-fragmentation chain-transfer (RAFT) polymerization [36–39], described for the very first in 1998 [38]. RAFT uses a chain transfer agent (CTA) (Figure 3a,b) to mediate polymerization, allowing for precise control over molecular weight and narrow molecular weight distributions. The technique is tolerant of functional groups present in glycomonomers, often permitting polymerization without complex protecting group chemistry, which is advantageous for biomedical applications [18,35,36,40,41]. The CTA can also serve as an anchor for direct surface immobilization, providing a straightforward route to well-defined, surface-grafted glycopolymers [42–46].



(**a**)



(**b**)

Figure 3. (**a**). Proposed mechanism of the RAFT polymerization (adopted from [47]). I_2: initiator; M: monomer; Z: stabilizing group; R: radical leaving group; P_n, P_m: growing or "dormant" polymer chain.

The mechanism can be divided into 6 key steps. (**I**): Initiator decomposition of a radical initiator (e.g., an azoinitiator) into initiator radicals; (**II**): chain initiation; (**III**): pre-equilibrium, addition to the RAFT agent, followed by fragmentation; (**IV**): reinitiation; (**V**): main equilibrium, exchange between active growing and dormant chains by repeated addition-fragmentation; (**VI**): irreversible termination by recombination; (**b**). RAFT polymerization of glycomonomers towards well-defined glycopolymers (simplified illustration). The R-group initiates chain growth, the Z-group stabilizes the intermediates thiocarbonylthio-species. The glycomonomer contains, e.g., a radical-polymerizable vinyl group. CTA ("RAFT Agent") structure influences RAFT kinetics and brush architecture [48,49]; direct stability comparisons on glycopolymer-coated biomaterial surfaces, however, are limited.

This level of control is critical for creating functional biomaterials. By precisely defining the polymer architecture, parameters can be systematically varied.

The ability to synthesize a library of well-defined glycopolymers, where only a single structural parameter is varied at a time, is essential for deconvoluting the complex interactions at the biointerface. This synthetic technique, like RAFT, is a possible route upon which the targeted surface modification of biomaterials can be designed.

2.2. Surface Modification Strategies: Anchoring Glycopolymers to Biomaterials

A well-defined glycopolymer in solution is only the first step; its utility as a surface modifier depends on the ability to bind effective and stable (immobilization) onto the targeted surface of the biomaterial. The choice of immobilization strategy is essential as it influences the density, conformation, and the stability of the formed glycopolymer layer, which is the key factor for its biological performance [46,50–53]. Several techniques have been developed for this purpose, the most common being "grafting-to," "grafting-from," and layer-by-layer (LbL) assembly (Figure 4).

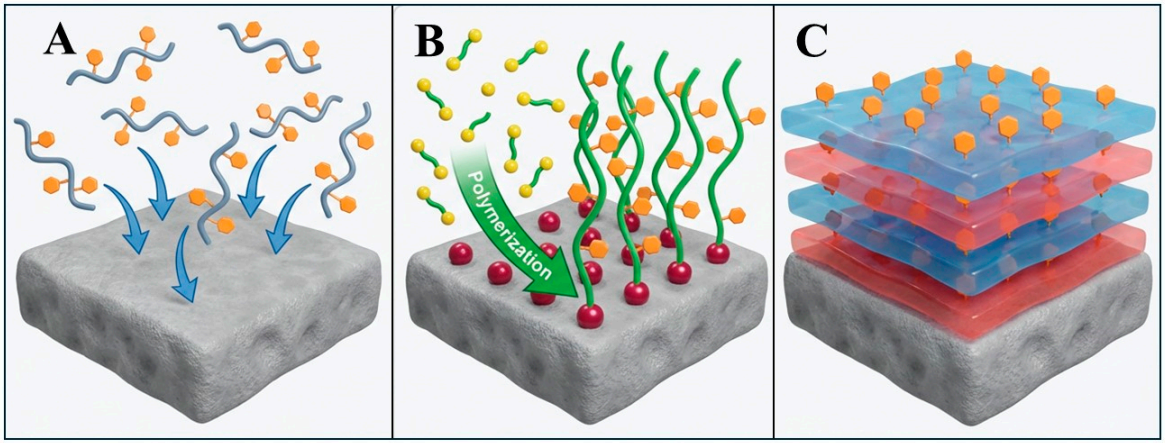


Figure 4. Surface modification strategies with glycopolymers: (**A**): "Grafting-to": pre-formed glycopolymers with functional groups are covalently (chemically) attached to reactive sites on the substrate surface. (**B**): "Grafting-from": glycomonomers are polymerized directly from initiator molecules (e.g., RAFT reagent) immobilized on the substrate surface. (**C**): Layer-by-layer (LB) technique: polyelectrolytes with opposite charge (polyanions, polycations, red and blue layers, containing sugar moieties) are alternately deposited onto the substrate building a multilayer film.

2.2.1. Grafting-To and Grafting-From Approaches

The "grafting-to" method involves the synthesis of the complete glycopolymer chain before attaching it to a reactive surface [54]. This approach is advantageous because the polymer can be fully characterized before attachment. However, a significant limitation is that as polymer chains begin to occupy the surface, they create steric hindrance, which makes it difficult for additional chains to attach [55–57]. This effect often leads to a lower grafting density compared to other methods.

Conversely, the "grafting-from" approach involves immobilizing a polymerization initiator or CTA on the biomaterial surface and then growing the glycopolymer chains directly from it [58]. This method can achieve much higher grafting densities, leading to the formation of dense polymer "brushes." These brush-like structures, where the polymer chains are stretched away from the surface, are particularly effective at preventing non-specific protein adsorption due to the high entropic penalty for protein penetration into the brush [59]. They also present a high concentration of carbohydrate ligands in a sterically accessible manner for specific binding events [43,59]. In particular, RAFT polymerization is the typical choice to the "grafting-from" technique, as RAFT agents can be readily attached to surfaces through various surface chemistry techniques (e.g., silanization on glass or silicon, or thiol chemistry on gold) to initiate controlled surface-initiated polymerization (SI-RAFT) [60,61].

2.2.2. Layer-by-Layer (LbL) Assembly

Layer-by-layer (LbL) assembly is another common and "easy-to-apply" technique for creating functional coatings. This method relies on the alternating adsorption of polymers with complementary interactions, most common oppositely charged polyelectrolytes (polyanions, polycations). As demonstrated, charged glycopolymers can be used to build multilayered thin films on a substrate [62–64]. For example, a positively charged glycopolymer can be alternated with a negatively charged glycopolymer (or another polyanion like heparin) to create a stable, stratified coating. A key advantage of the LbL technique is the ability to incorporate other functional components within the multilayered structure [65]. For instance, drug-loaded liposomes can be embedded within the glycopolymer matrix, creating a dual-function surface that is both biocompatible and capable of sustained drug release [62,66–68]. This is particularly relevant for applications like therapeutic contact lenses and other ophthalmic biomaterials, such as, e.g., IOLs.

3. Application to Common Biomaterials

These modification strategies are directly applicable to the biomaterials of interest for this review. Silicones, which are widely used for their excellent mechanical properties and oxygen permeability (e.g., in contact lenses), are inherently hydrophobic. This hydrophobicity can lead to reduced surface wettability and deposition of proteins and lipids from the tear film, causing discomfort [69,70]. Glycopolymer coatings can render the silicone surface highly hydrophilic, mimicking the natural mucin layer of the tear film and significantly improving biocompatibility and lubricity [1,71]. Bioinspired polymer layers create a highly wettable surface that resists the deposition of lipids and proteins, reduces bacterial adhesion, and may improve lubrication against the ocular tissue [72,73]. Directly attaching mucin macromolecules to hydrophobic contact lenses has also been shown to create hydrophilic surfaces that prevent lipid adsorption and reduce wear on corneal tissue during friction [74].

Polyacrylates and polymethacrylates (PMAs, Figure 5) represent another important class of polymers which are used in biomaterials, especially in contact and intraocular lenses. Their physicochemical properties are very strongly dependent on the chemical structure of the m(meth)acrylates pendant side groups and by the copolymer composition. This determines their characteristics such as hydrophilicity, transparency, mechanical performance, and swelling (hydrophilicity) behavior [75]. For example, materials such as poly(methyl methacrylate) are valued for their optical clarity and mechanical stability, whereas hydrophilic methacrylate-based polymers such as poly(2-hydroxyethyl methacrylate (PolyHEMA) can form water-swollen networks, called hydrogel, that have been widely used in various ophthalmic applications [76]. They also can benefit from glycopolymer

modification. The surfaces of these materials can be readily functionalized with initiator groups for "grafting-from" polymerization or chemically modified to allow for "grafting-to" attachment. This allows the inert bulk material to be endowed with a highly specific, biologically active surface, expanding its range of potential applications. The application of surface modification is not limited to the before-mentioned classes of polymers; it can be applied almost to any biomaterial by choosing the appropriate attachment method.

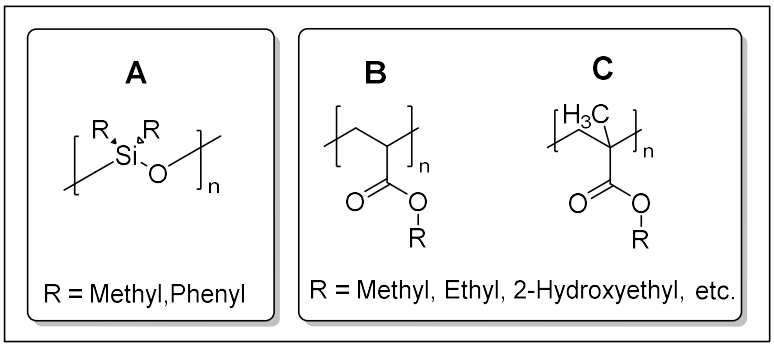


Figure 5. Polymer structures of silicones (polysiloxanes) (**A**) and PMAs: polyacrylates (**B**) and polymethacrylates (**C**). There exist a broad variety of acrylates and methacrylates, depending on the desired physical properties and application. Variation of the side group R and the comonomer composition enables the tuning of the physical properties and application profile of these biomaterials in a broad spectrum. In many biomaterials, e.g., implants, these polymers are crosslinked copolymers synthesized from different monomer units.

By selecting the appropriate combination of base material and surface modification strategy, it becomes possible to create a vast library of functional materials from a limited set of starting components.

3.1. Tailoring the Biointerface: From Bio-Inert to Bio-Specific

The true power of glycopolymer surface modification lies in the ability to rationally design the biointerface to elicit a specific, desired biological response. By carefully selecting the glycan structure, polymer architecture, and grafting density, a single base biomaterial can be endowed with a wide spectrum of functionalities, ranging from completely passive (bio-inert) to highly active and specific (bio-specific) (Figure 6). This method provides new possibilities for the application of well-established materials such as silicones and poly(meth)acrylates.

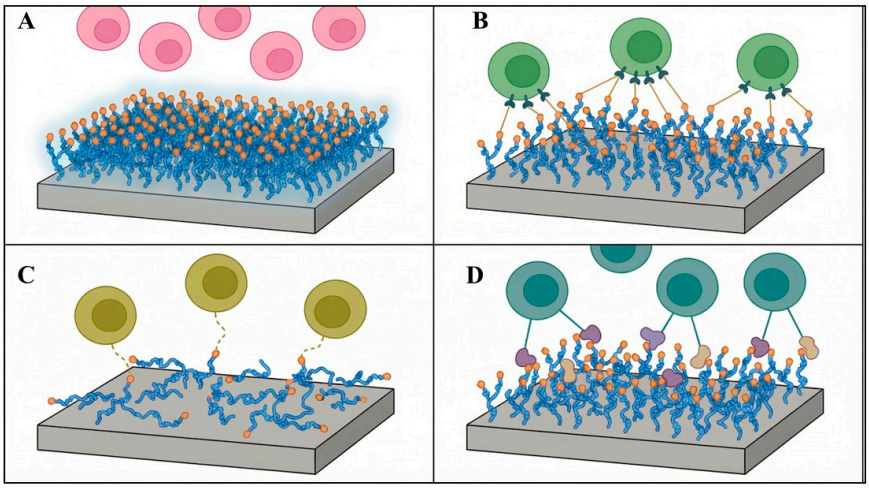


Figure 6. Schematic illustration of different kinds of cell responses to glycopolymer-coated biomaterial surfaces. The specific function depends on which glycan is used, its density, accessibility, and interfacial

recognition. (**A**): a dense, hydrated glycopolymer brush without receptor recognition. This prevents cell approach (cell-repellent). (**B**): Glycans are recognized by complementary lectins or other glycan-binding receptors. This enables multivalent interactions and direct cell attachment. (**C**): Low ligand density or incomplete receptor–glycan matching results in weak interactions and only partial cell adhesion. (**D**): Cell adhesion occurs through adsorbed proteins and not via glycan-receptor binding.

3.2. Creating Bio-Inert, Cell-Repellent Surfaces

For many medical devices, the primary goal is to prevent interactions with the biological environment, a property known as being "non-fouling" or "bio-inert" [77]. Non-specific protein adsorption is often the first event that occurs when a foreign material is introduced into the body, which can trigger a cascade of subsequent adverse reactions, including blood coagulation, inflammation, and bacterial colonization. Glycopolymers, particularly those with high densities of hydrophilic, neutral sugars, can create a tightly bound hydration layer on the material surface. That layer acts as a physical and energetic barrier, effectively repelling proteins and preventing their adhesion—a property often referred to as creating a "stealth" or "non-fouling" surface [30,78–81].

This principle is directly applicable to contact lenses. A silicone hydrogel lens coated with a dense brush of mucin-mimicking glycopolymers can resist the deposition of proteins and lipids from the tear film, leading to improved comfort, reduced risk of infection, and better visual acuity over the wearing period [15,71,74]. The ability to prevent cell adhesion is also critical. Certain glycopolymer coatings can effectively prevent the adhesion of human lens epithelial cells (HLEpiCs) [82,83]. This is a crucial property for intraocular lenses, where the prevention of posterior capsule opacification, caused by the migration and proliferation of HLEpiCs, is a major clinical goal.

3.3. Designing Bio-Specific, Cell-Adhesive Surfaces

In contrast to creating inert surfaces, glycopolymers can also be designed to promote highly specific interactions. This is achieved by leveraging the "glycocluster effect," where the multivalent presentation of specific carbohydrate ligands leads to strong and selective binding to complementary lectins on a cell's surface [84–86]. While a single carbohydrate–lectin interaction is typically weak, the simultaneous binding of multiple ligands on a polymer chain to multiple receptors on a cell membrane results in a dramatic increase in binding avidity and specificity. The principles of design of multivalent glycosystems and their specific interactions with various human lectins have been intensively studied. These findings provide a base for the future development of targeted drug delivery and therapeutics [87].

This multivalent presentation allows for the creation of surfaces to which specific cell types can selectively bind or adhere. The density of the carbohydrate binding sites on the polymer has been shown to strongly influence the rate of receptor clustering and the proximity between bound receptors [88]. This principle is crucial for designing materials for applications like tissue engineering, where guiding specific cell types is essential. For example, a surface functionalized with a glycopolymer presenting galactose or N-acetylgalactosamine moieties can be used to target hepatocytes [78,89–93]. Hepatocytes uniquely express the asialoglycoprotein receptor (ASGPR), which specifically recognizes and binds to ligands with terminal galactose or GalNAc residues [94,95]. This has deep implications for tissue engineering, where the goal is to guide the organization of specific cell types to create functional tissue constructs.

4. Glycopolymers as Platform Technology

The ability to switch the function of a surface from cell-repellent to cell-specific simply by changing the glycopolymer coating represents a paradigm shift in biomaterial design. Studies have shown that a base material coated with one type of glycopolymer can repel certain cell types, while the same base material coated with another glycopolymer can promote the adhesion of different cell types [46,96]. This differential cell response is governed by the specific carbohydrate structures presented on the surface and their interactions with cell surface receptors. Even subtle changes in the glycopolymer's architecture can fine-tune the cellular response. For example, varying the length of the "spacer" that connects the sugar molecule to the polymer backbone has been shown to affect the adhesion, viability, and proliferation of osteoblast cells [97]. This demonstrates a high degree of control over the biological outcome.

This highlights a significant advantage: a manufacturer could use a single, well-characterized, and regulatory-approved base material (e.g., a specific silicone or poly(meth)acrylate) and create a whole portfolio of medical devices with distinct functions simply by applying different glycopolymer coatings. This approach could potentially streamline the regulatory approval process [98]. The bulk of the safety and biocompatibility data would pertain to the base material, which remains unchanged. The regulatory focus would then shift to the surface coating, which is present in minute quantities but dictates the device's function. This strategy could significantly reduce the time and cost associated with bringing new, advanced medical devices to market [99]. The lack of harmonization in regulatory requirements across different countries makes such strategies particularly attractive [100].

4.1. Applications of Glycopolymer-Modified Biomaterials

The versatility of glycopolymer coatings has led to their exploration in a wide array of biomedical applications. By tailoring the surface properties of materials, researchers can address specific challenges in different biological contexts, from the ocular environment to systemic drug delivery (Figure 7).

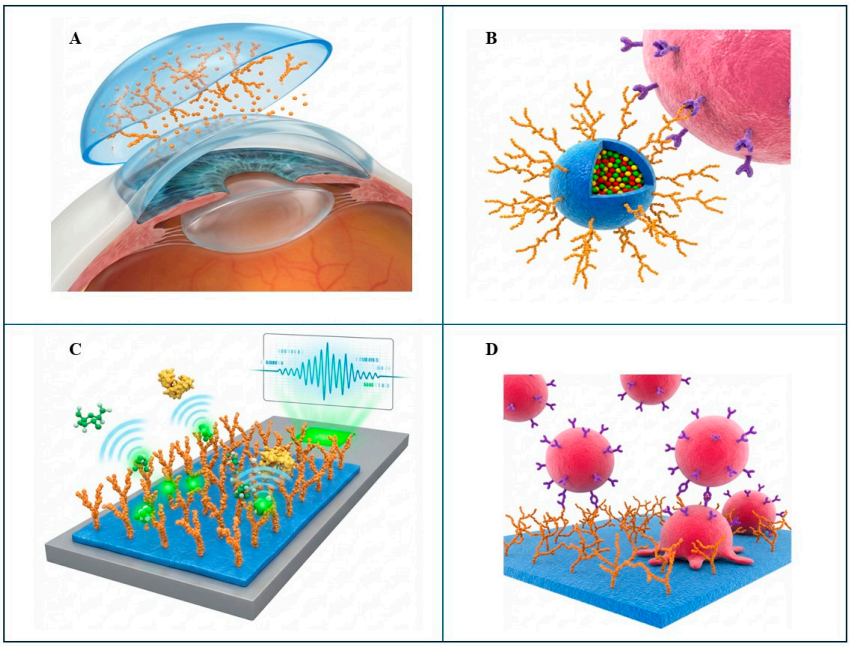


Figure 7. Applications of glycopolymer-modified biomaterials. (**A**): Contact lenses, e.g., therapeutic CLs, drug eluting CLs, higher wearing comfort. (**B**): Targeted drug delivery: higher selectivity. (**C**): Biosensors: sugar polymer coating distinguishes structurally similar subtypes and enhances the ability to determine detection specificity. (**D**): Tissue engineering and implants: cell attraction.

4.1.1. Advanced Contact Lenses

The contact lens market is a prime example of where glycopolymer technology can have a significant impact. The primary challenges in contact lens wear are discomfort, often arising from dryness and friction, and the risk of microbial infections [101]. Glycopolymer coatings directly address these issues. By creating a highly hydrophilic, mucin-mimetic surface on silicone hydrogel lenses, these coatings can dramatically improve on-eye wettability and lubricity, mimicking the natural tear film and reducing friction during blinking [15,71,74]. This leads to enhanced wearer comfort and reduced symptoms of dry eye.

Furthermore, these coatings can be designed to prevent the adhesion of bacteria. *Pseudomonas aeruginosa*, a common cause of contact lens-related keratitis, adheres to surfaces through specific interactions between its cellular lectins and carbohydrates on a surface [46]. The dense, hydrated polymer layer acts as a barrier to bacterial attachment, offering a non-biocidal approach to reducing the risk of infection [102,103]. The LbL assembly technique allows for the creation of advanced, multifunctional coatings, transforming a contact lens into a therapeutic device [104]. LbL have been successfully used to create glycopolymer thin films that act as scaffolds for embedding antimicrobial agents or drug-loaded liposomes [62,66]. This approach allows for the creation of a biocompatible surface that is also capable of sustained and controlled drug release.

4.1.2. Targeted Drug and Gene Delivery

The ability to target specific cells or tissues is a very important goal of drug delivery. In order to minimize negative side effects and to increase specificity and selectivity, glycopolymers have the potential to achieve this by mimicking nature's biological recognition system. That perspective highlights the opportunities and challenges in the use of glycopolymer-based nanoparticles for targeted drug delivery and emphasizes the need for a deeper understanding of the bio–nano interface [105]. Nanoparticles or liposomes, shell-decorated with specific glycopolymers, can act as "smart" delivery vehicles. For example, nanoparticles coated with mannose-containing glycopolymers can target mannose receptors on macrophages and dendritic cells, which is a promising strategy for delivering vaccines or immunomodulatory agents [106]. Star-shaped glycopolymeric photosensitizers have been developed for targeted photodynamic cancer therapy to improve selectivity and effectiveness [107]. Similarly, galactose-functionalized carriers can target liver cells for the treatment of liver diseases [106].

In gene therapy, cationic glycopolymers have been developed as non-viral vectors for DNA and siRNA delivery. The positively charged backbone of a cationic glycopolymer electrostatically interacts with negatively charged nucleic acids (like plasmid DNA or siRNA), condensing them into compact nanoparticles called "polyplexes" [108,109]. This complexation protects the genetic material from degradation by enzymes in the body [110]. The carbohydrate portion of the glycopolymer provides several advantages. It can form a hydrophilic shell around the polyplex, which promotes colloidal stability and prevents aggregation [108]. More importantly, specific sugar ligands (like galactose) can be used for the polyplex to target specific cells via receptor-mediated endocytosis, which can improve transfection efficiency and reduce off-target effects [111,112].

4.1.3. Biosensing and Diagnostics

The highly specific nature of carbohydrate-lectin binding makes glycopolymers ideal recognition elements in biosensors. Surfaces functionalized with a specific glycopolymer can be used to detect the presence of complementary lectins, which can be biomarkers for diseases. For instance, changes in the expression of certain galectins, like Galectin-3, are associated with cancer progression and metastasis [113,114]. Its involvement in

tumor development makes it a promising target for early cancer diagnosis [115]. An SPR sensor chip coated with a glycopolymer that specifically binds Galectin-3 can be used to detect and quantify this biomarker in patient samples, offering a potential diagnostic tool [42]. Thus, glycopolymers presenting specific tetrasaccharides could be demonstrated as potent inhibitors of Galectin-3, thereby suppressing the apoptosis of T-lymphocytes and inhibiting the migration of tumor cells [116]. Functional glycopolymer nanoparticles based on naphthalimide have recently been used for targeted bioimaging of tumor cells [117].

The use of glycopolymer brushes, which present multiple sugar ligands, enhances the binding strength and specificity for lectins, making them a very promising tool for developing diagnostic arrays [43].

These glycopolymer-based sensors can be highly sensitive and selective. They can be designed to differentiate between lectins with very similar binding preferences, a task that is challenging for other sensor types. This technology is being explored for a range of diagnostic applications, from detecting viral pathogens (which often use cell-surface glycans for entry) to monitoring biomarkers for inflammatory diseases in bodily fluids like tears or blood [23,118–120]. For example, heparan sulfate-mimetic glycopolymers were developed that bind to the spike protein of SARS-CoV-2 in a length- and sulfation-dependent manner and can thus function as antiviral agents [121]. Recent advances in fluorescent glycoconjugate probes for biosensing, bioimaging, and targeted photodynamic therapy were described in a comprehensive review [122].

4.1.4. Tissue Engineering and Regenerative Medicine

In tissue engineering, scaffolds provide a three-dimensional framework to support and guide cell growth and organization to form functional tissue [123]. Glycopolymer-modified surfaces of these scaffolds can be used to control cell behavior in a sophisticated manner. A scaffold could be designed with defined patterns of different glycopolymers to spatially control where different cell types adhere and grow [124]. For example, a surface could be patterned with a cell-adhesive glycopolymer in specific regions to promote the formation of a blood vessel network, while the surrounding area is coated with a cell-repellent glycopolymer to prevent unwanted tissue growth [125]. This strategy leverages the natural role of carbohydrates in mediating cell–matrix interactions to create more effective scaffolds for tissue regeneration [5].

Glycopolymer coatings can tune surfaces from repellent to adhesive and allow for dynamic control over cell adhesion. For example, using a thermoresponsive glycopolymer, cell sheets could be grown on a surface at 37 °C and then detached non-enzymatically by simply lowering the temperature, preserving the cell–cell junctions and the extracellular matrix for transplantation [126]. This kind of cell sheet engineering is a promising technique in regenerative medicine by using glycopolymers as a layer of desired biological specificity. A recent example is the development of a multifunctional, antibacterial hydrogel, based on glycopolymers, that accelerates wound healing by regulating inflammation and promoting collagen deposition [127].

4.2. Soluble Glycopolymers as Therapeutics

Beyond their role as surface coatings, glycopolymers can be formulated into soluble nanogels that function as “pathoblockers”. These nanoparticles are composed of glycopolymer chains and act as high-avidity decoys, designed to intercept bacteria before they can adhere to surfaces or to each other. This approach represents a promising alternative to classical antibiotics by targeting the bacterial adhesion mechanisms—and not the bacterial metabolism—thus preventing the development of resistance [23,128]. Glycopolymer-based nanogels, presenting melibiose (α-galactose) and fucose, effectively inhibited bacteria-to-

bacteria lectin binding and reduced *Pseudomonas aeruginosa* biofilm formation by up to 75% when applied as pre-treatment [129]. Glycopolymer nanogels can be loaded into the porous matrix of the scaffold [130]. As the scaffold resides in the body, it slowly releases these nanogels into the surrounding tissue. This creates a localized "cloud" of pathoblockers that competitively bind to bacterial lectins, preventing bacteria in the vicinity from adhering to the scaffold or to each other [131].

5. Conclusions and Future Perspective

Synthetic glycopolymers have been established as an important tool in the field of biomaterial surface engineering. Their ability to mimic natural glycoconjugates, combined with modern controlled polymerization techniques like RAFT, provides a platform for tailoring the interface between synthetic materials and biological systems. Glycopolymers can transform a single, well-characterized base biomaterial into a multifunctional platform. By altering the functional structure of the glycopolymer coating, the surface can be switched from being passive, anti-adhesive and cell-repellent to actively promoting the adhesion of specific cell types. This versatile tool represents a useful advantage in the development of next-generation medical devices.

Experimental studies have demonstrated that different glycopolymer coatings can selectively prevent or promote the adhesion of specific cell types on the same underlying base material, as well as the inhibition of biofilm formation caused by pathogenic bacteria. Such findings open new ways for advanced medical devices such as intraocular lenses (IOL; the worldwide most used implant) that resist "biofouling" or post-cataract complications while providing high compatibility with the surrounding tissue. Contact lenses can be made that offer enhanced comfort combined with therapeutic potential (therapeutic contact lenses). The potential to use the existing regulatory approval of base materials by focusing "only" on the functional surface modification for better performance could significantly de-risk and accelerate the innovation cycle (by saving time and cost) for medical devices such as implants.

A central point for future clinical transfer and use, particularly with biomaterials, is the long-term stability and degradation behavior of the lectin coating under physiological conditions. Here, the stability of a lectin coating is of crucial importance. It determines the maintenance of the desired functionality over the intended duration of use of the implant. An essential factor in this is the type of attachment to the surface—chemically covalent versus physically adsorbed. A covalent attachment of lectins to the biomaterial surface leads to higher stability compared to pure physisorption (e.g., LbL). A review on protein-based bioactive coatings confirmed that covalent attachment was crucial in delaying desorption under physiological conditions and in increasing the long-term stability of the coating [127]. In contrast, for physically adsorbed layers, desorption is one of the main problems. This limits their effectiveness in vivo [132].

A promising long-term stability in vitro (4 months, buffer, 4 °C) through a specific but non-covalent bioaffinity-based immobilization was described for the binding between the lectin Concanavalin A (Con A) and the glycosylation of the protein BMP-2 [133]. This type of coating retained its functionality over a period of 4 months.

For use in the body, resistance to proteases is another essential factor. Lectins are thus, in principle, also exposed to degradation by proteases. Covalent binding can increase proteolytic stability. A study showed that a wheat germ agglutinin (WGA) coating on a silk fibroin-based biomaterial exhibited increased resistance to proteolytic degradation by trypsin [134]. Long-term studies that explicitly investigate the degradation of lectin coatings on implants over months or years in humans are currently rare. Most current studies describe periods of days to a few weeks in cell culture (in vitro) or animal models. A study

that examined the coating of titanium dioxide nanotubes (for orthopedic implants) with the lectin Oni showed improved adhesion and proliferation of osteoblast-like cells [135]. Even though no long-term degradation data were presented, this suggests good biocompatibility and a potential improvement in osseointegration.

For future developments, several key areas need further investigation: as mentioned before, the long-term stability of these glycopolymer coatings in vivo remains a crucial and critical question that requires additional studies under physiologically relevant conditions, including biocompatibility tests such as enzymatic degradation, mechanical wear, stability and functionality under different sterilization methods (thermal, gamma, EO, or new methods that need to be validated such as UV or CO_2). Furthermore, the development of scalable, reproducible, and cost-effective manufacturing processes for applying these coatings to commercial products will be essential for future clinical translation. The exploration of a wider and more complex library of glycan structures, including those that mimic specific O- and N-linked glycans found on cell surfaces, will open even more specific and fine-tuned control over biological cell responses. The development of sequence-controlled glycopolymers, where different sugar units are arranged in a specific order along the polymer backbone, could lead to materials that can engage in even more complex biological conversations. The integration of glycopolymers with other stimuli-responsive materials could lead to surfaces that can change their properties on demand, for example, releasing a drug or switching from cell-repellent to cell-adhesive in response to a specific biological signal or external trigger (e.g., light, temperature or pH).

The interdisciplinary synergy between polymer chemistry, surface science, cell biology and medical needs, coupled with advanced characterization techniques and a deeper understanding of the glycocode, will forward the research towards smart biomaterials. Polymer-based materials will not just coexist with the body (tissue) but will actively direct biological specificity and functions, leading to safer, effective, and more personalized medical devices and therapies.

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