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SYMPOSIUM

Anti-Inflammatory Polymeric Coatings for Implantable Biomaterials and Devices

Amanda W. Bridges, Ph.D.[1,2] and Andrés J. García, Ph.D.[1,3]

Abstract

Synthetic polymer coatings are used extensively in modern medical devices and implants because of their material versatility and processability. These coatings are designed for specific applications by controlling composition and physical and chemical properties, and they can be formed into a variety of complex structures and shapes. However, implantation of these materials into the body elicits a strong inflammatory host response that significantly limits the integration and biological performance of devices. Biomaterial-mediated inflammation is a complex reaction involving protein adsorption, leukocyte recruitment and activation, secretion of inflammatory mediators, and fibrous encapsulation of the implant. Significant research efforts have focused on modifying material properties using various anti-inflammatory polymeric surface coatings to generate more biocompatible implants. This minireview provides a brief background on the events of biomaterial-mediated inflammation and highlights various approaches used for modifying material surfaces to modulate inflammatory responses. These include both passive and active strategies, such as nonfouling surface treatments and delivery of anti-inflammatory agents, respectively. Novel approaches will be needed to extend the *in vivo* lifetime and performance of devices and reduce the need for multiple implantation surgeries.

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Inflammation and Device Performance

Medical devices and biomaterial implants are clinically used in a variety of applications, and their performance is critical to a patient's overall health and quality of life. Surgical procedures injure microvasculature and tissue surrounding the implanted device, initiating a localized nonspecific inflammatory response (**Figure 1**).[1] Although inflammation recruits native cells for remodeling and regenerating the damaged tissue, persistent and inflammatory stimuli significantly interfere with implant function and often result in device failure. Adverse host responses to implanted biomedical devices include thrombogenic responses on vascular grafts,[2,3] degradation and stress cracking of pacemaker leads,[4,5] tissue fibrosis surrounding mammary prostheses,[6] osteolysis and loosening of orthopedic joint prostheses,[7,8] reactive gliosis around neural probes,[9] and degradation in biosensor function.[10]

Author Affiliations: [1]Parker H. Petit Institute of Bioengineering and Bioscience, Georgia Institute of Technology, Atlanta, Georgia, [2]Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology, Atlanta, Georgia, and [3]George W. Woodruff School of Mechanical Engineering, Georgia Institute of Technology, Atlanta, Georgia

Abbreviations: (α-MSH) alpha melanocyte-stimulating hormone, (DEX) dexamethasone, (DNA) deoxyribonucleic acid, (FBGC) foreign body giant cell, (FBR) foreign body reaction, (IL) interleukin, (PEG) polyethylene glycol, (SAM) self-assembled monolayer, (TNF) tumor necrosis factor

Keywords: biomaterial, polymer, coating, host response, implant, anti-inflammatory

Corresponding Author: Andrés J. García, Ph.D., Parker H. Petit Institute for Bioengineering and Bioscience, Georgia Institute of Technology, 315 Ferst Drive, 2314 IBB, Atlanta, GA 30332-0363; email address *andres.garcia@me.gatech.edu*

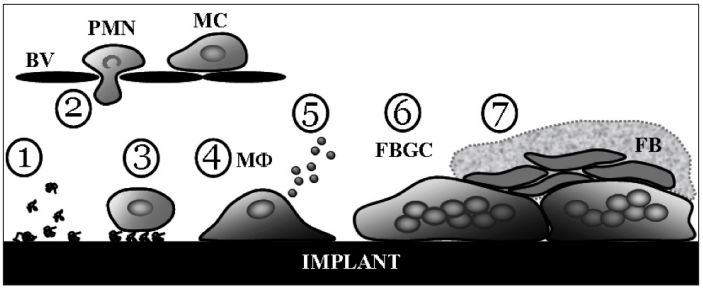

Figure 1. Events of host foreign body response to implanted materials. Neutrophils and monocytes recruited by stimulatory cues emigrate from the vasculature and adhere to the layer of adsorbed proteins on the implant surface (**Phases 1–3**). Differentiated macrophages become activated, secreting a variety of inflammatory mediators, and often fuse into multinucleated foreign body giant cells (**Phases 4-6**). Fibroblasts infiltrate the site and generate a collagenous fibrous capsule around the implant (**Phase 7**). BV, blood vessel; PMN, polymorphonuclear leukocyte; MC, immature monocyte; MΦ, differentiated macrophage; FBGC, foreign body giant cell; FB, fibroblast.

Host Foreign Body Response

Immediately following implantation, proteins and other biomolecules present in the blood plasma and biological fluids rapidly adsorb onto the surface of biomaterials. Adsorption of biomolecules from these multicomponent solutions is a dynamic process involving competition, rearrangements, and displacement of adsorbed species (the Vroman effect).[11,12] Material surface chemistry often drives hydrated biomolecules to partially release bound water molecules, leading to structural changes and reversible, as well as irreversible, physisorption of biomolecules into the surface. This process occurs more rapidly than cell recruitment to the implantation site; therefore, the composition and configuration of this complex protein milieu dictates subsequent cellular responses.[13–15] In many instances, adsorbed fibrinogen, IgG, and complement fragments mediate leukocyte-biomaterial interactions and subsequent inflammatory reactions.[16–21]

During the acute phase of this foreign body reaction (FBR), circulating polymorphonuclear leukocytes (e.g., neutrophils) are stimulated in response to inflammatory signals released at the implant site. This results in integrin receptor-mediated leukocyte recruitment, adhesion, and activation.[22–24] Short-lived neutrophils are then replaced by inflammatory monocytes and macrophages. The layer of surface-adsorbed proteins modulates macrophage phenotype and subsequent functions, including phagocytosis, cytokine expression, and fusion into foreign body giant cells (FBGCs).[14,15] Macrophages are considered the key mediators of implant-associated inflammation due to their distribution and motility, and they generate a multitude of biologically active products.[25,26] They play central roles in directing both inflammatory and regenerative responses associated with implanted biomaterials.[27–29]

Persistent inflammatory stimuli lead to insufficient healing of local tissue at the device interface. The hallmark of a chronic response is fusion of monocyte-derived macrophages to form multinucleated FBGCs, a complex process involving myriad molecules.[30,31] Foreign body giant cells have been implicated in the biodegradation of polymeric implants through surface oxidation and enzymatic degradation.[32–34] Additionally, fibroblasts recruited to the implant site generate a thick collagenous fibrous capsule around the implant. For a detailed explanation of the cellular and molecular mediators of the host foreign body response to biomaterials, we refer the reader to an excellent review provided by Anderson *et al*.[31] These cellular and tissue responses often impair *in vivo* device performance. In the case of indwelling biosensors, including continuous glucose sensors, cell-mediated inflammatory responses and fibrous scarring adversely impact sensor performance, including fluctuations in biosensor sensitivity, decreased response time, and material degradation.[35–37]

Accurate performance of glucose biosensors is critical to monitoring patient health, because diabetes is among the leading causes of death in the United States.[38] Since the 1980s, a number of methods have been utilized to generate more biocompatible biosensors, including flow-based systems, Nafion membranes, and diamond-like carbon coatings.[37] However, many glucose sensors only function reliably for a few days *in vivo* before failing.[39] It has been suggested that these implants may require a stabilization period during fibrous capsule development, resulting in erroneous analyte measurements for weeks after implantation.[40,41] Current limitations on device performance necessitate a new generation of coatings that are applicable to a wide variety of implantable materials. Novel, probably multipronged, approaches are needed to abrogate long-term inflammatory responses and extend the *in vivo* lifetime of medical implants in order to avoid the need for multiple surgical procedures.

Anti-Inflammatory Coating Strategies

The severity and extent of the biological response to an implanted biomaterial or device influences the probability for its successful integration with surrounding tissue, as well as overall device performance. Initial stages of the FBR are dictated largely by the extent of injury and surgical technique, implantation site, implant shape and size, material chemical and physical properties, and local and systemic health of the recipient.[1,42–44] Significant

research efforts have focused on modifying material properties using various anti-inflammatory surface coatings to generate more biocompatible implants.

Passive Strategies: Nonfouling Surface Treatments

The initial stages of the FBR involve nonspecific protein and biomolecule adsorption and subsequent leukocyte adhesion onto the biomaterial surface, events termed "biofouling." It is generally believed that reducing biofouling can ameliorate subsequent adverse inflammatory responses such as leukocyte activation and tissue fibrosis. Several passive strategies have been explored to achieve this goal, including preadsorption of material surfaces with less inflammatory proteins or cells. Such passivation strategies are attractive, because they are relatively straightforward and simple.[45,46] However, these coatings suffer from a lack of stability as other proteins, such as fibrinogen, can passively displace preadsorbed proteins such as albumin. Even covalently-tethered nonadhesive proteins can be degraded by leukocytes, resulting in deposition of proinflammatory adhesive components. Approaches involving cell deposition onto surfaces prior to implantation offer a possible strategy to promote wound healing by encouraging mass transport and reducing fibrotic responses at the tissue–implant interface.[47] However, issues related to cell sourcing, host responses to the donor cells, and long-term stability limit these strategies.

Nonfouling (protein adsorption-resistant) thin-layer polymeric coatings offer more substantial routes to reduce acute inflammatory responses. The design requirements for implanted materials and devices vary considerably depending on the *in vivo* application and site of implantation. In particular, nonfouling polymeric surface coatings for implantable biosensors must ideally conform to the following considerations:

- use of nontoxic materials
- effectively prevent *in vivo* biofouling
- appropriate thickness and permeability to allow analyte detection
- techniques to deposit coating onto a variety of materials and architectures
- mechanical, chemical, and electrical stability to withstand surface deposition, sterilization methods, implantation procedures, and *in vivo* environment.

Despite considerable research efforts, surface coatings that *completely* eliminate protein adsorption over the *lifetime* of a device have not been attained. Nevertheless, significant progress has been made in understanding the mechanisms driving protein adsorption, and several chemical groups that resist protein adsorption have been identified. Polyethylene glycol (PEG, $[CH_2CH_2O]_n$) has proven to be the most protein-resistant functionality and remains the standard for comparison (**Figure 2**).[48] Polyethylene glycol chain density, length, and conformation strongly influence resistance to protein adsorption.[49–51] The mechanism of resistance to protein adsorption by PEG surfaces probably involves a combination of the ability of the polymer chain to retain interfacial water and the resistance of the polymer chain to compression due to its tendency to remain an extended coil conformation.[52–54] Other hydrophilic polymers, such as poly(2-hydroxyethyl methacrylate),[55] poly(N-isopropyl acrylamide),[56,57] poly(acrylamide), and phosphoryl choline-based polymers[58–61] also resist protein adsorption. In addition, mannitol, oligomaltose, and taurine groups have emerged as promising moieties to prevent protein adsorption.[62–64]

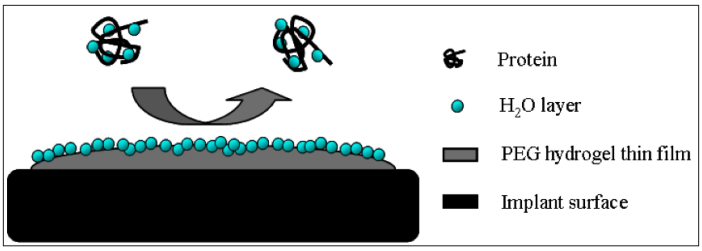

Figure 2. Passive anti-inflammatory surface coating for biomaterials. Hydrophilic polymeric coatings, such as PEG-based hydrogels, retain interfacial water molecules, rendering them highly resistant to protein adsorption.

These coatings have been applied as molecularly thin self-assembled monolayers (SAMs), polymer brushes, and thin or bulk hydrogels (**Table 1**) capable of reducing protein adsorption and leukocyte adhesion. Self-assembled monolayers are confined to inorganic planar surfaces and are only stable short-term in aqueous environments, limiting their use as coatings for *in vivo* biosensors.[65] Polymer brushes are more mechanically robust than SAMs and can be generated on nonplanar surfaces, including colloidal suspensions and polymeric substrates. Moreover, surface-initiated polymerizations allow control over functionality, grafting density, and thickness of the brushes.[66,67] Extensive research efforts have focused on hydrogel-based implant coatings. Hydrogels offer many advantages over traditional surface modification strategies, including a viscoelastic network structure, tunable material characteristics, incorporation of multiple chemical functionalities, nanoscale dimensions with complex architectures, and the ability to deposit onto a variety of material substrates.[68–72]

Table 1.
Examples of Nonfouling Ethylene Glycol-Based Surface Treatments

Coating Structure	Selected References
SAM	Prime and Whitesides[65] (1993)[a] Chapman *et al.*[77] (2001)[a] Zhang *et al.*[78] (2001)[a]
Polymer Brush or Surface Graft	Espadas-Torre and Meyerhoff[79] (1995)[a] Lee *et al.*[80] (1997)[a] Du *et al.*[81] (1997)[a] Zhang *et al.*[82] (1998)[a] Jenney and Anderson[83] (1999)[a] Shen *et al.*[84] (2001)[a] Otsuka *et al.*[85] (2001)[a] Boulmedais *et al.*[86] (2004)[a] Ma *et al.*[87] (2004)[a] Ma *et al.*[88] (2006)[a] Zhou *et al.*[89] (2007)[a] Waku *et al.*[90] (2007)[a] Cao *et al.*[91] (2007)[a]
Hydrogel	West and Hubbell[92] (1995) Quinn *et al.*[73] (1995) Quinn *et al.*[93] (1997) Collier *et al.*[94] (2004)[a] Nolan *et al.*[56] (2005)[a] Singh *et al.*[57] (2007)[a] Bridges *et al.*[95] (2008) Yu *et al.*[96] (2008)

[a] Materials were tested only *in vitro*.

Although many of these coatings exhibit reduced protein adsorption and leukocyte adhesion *in vitro*, inconsistent results have been obtained regarding the ability of these polymeric coatings to reduce *in vivo* acute and chronic inflammatory responses.[73–76] Possible explanations for the mixed *in vivo* results with these coatings include insufficient nonfouling behavior, coating degradation, and inflammatory mechanism(s) independent from protein adsorption. These results have motivated the development of active anti-inflammatory strategies.

Active Strategies: Delivery of Anti-Inflammatory Agents

In contrast to passive nonfouling surface treatments, coatings presenting or delivering anti-inflammatory agents offer a more interactive and directed approach to modulate cell behavior. Broad-spectrum drugs have typically been used to control chronic tissue inflammation. However, orally administered drugs may not achieve adequate local concentrations, and their long-term systemic use can cause major side effects. Therefore it is desirable to deliver therapeutics locally in a controlled, site-specific manner to improve the tissue–material response.

Various immunomodulatory agents can be immobilized onto nonfouling polymeric coatings or delivered in soluble form from the coating (**Figure 3**). Possible strategies for the controlled release of agents include passive diffusion from coatings or polyelectrolyte layers,[97,98] bioerodible/degradable coatings to release drugs by passive dissolution,[99] swelling coatings that release drugs by passive mechanisms, and hydrolysable or enzyme-degradable linkages to release the agent.[100–103] These delivery systems offer several advantages over passive methods, including highly controlled presentation of immunomodulatory agents, control over reaction kinetics, and versatility through hybrid designs. In addition to the basic requirements for passive coatings, designs for these bioactive coatings must consider the following properties:

- retain bioactivity of anti-inflammatory molecules for the intended lifetime
- optimal tethering distance for recognition of immobilized agents
- appropriate release profiles in terms of amounts, rates, total dosage, and release time (acute versus chronic release)
- drug character (e.g., hydrophobicity), residence times, and stability
- safety issues related to drug release (designed or accidental)
- agent–matrix (coating) interactions
- effects of material sterilization.

Examples of anti-inflammatory factors delivered from surface coatings are summarized in **Table 2**. Dexamethasone (DEX) is a synthetic glucocorticoid hormone with many applications in biomedical research, including treatment of inflammatory responses.[104] Dexamethasone modulates macrophage behavior and reduces the levels of numerous proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and interferon-γ.[105,106] Dexamethasone-releasing coatings have reduced tissue inflammation and

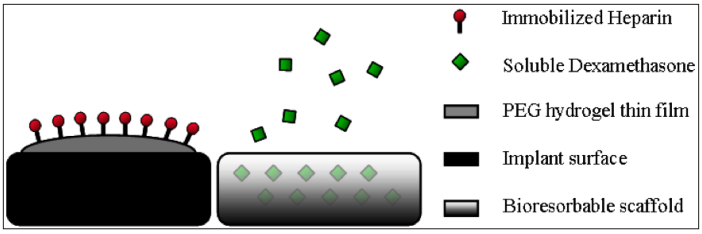

Figure 3. Bioactive implant coatings to deliver anti-inflammatory molecules. Representative schemes depict mechanisms for the active delivery of various immunomodulatory agents to reduce leukocyte adhesion and activation.

cell activation surrounding implanted glucose biosensors and neural implants.[107–110] In addition, polypyrrole-based electrode coatings designed to electrically control delivery of DEX lowered the amount of reactive astrocytes *in vitro*.[111]

Heparin is a highly sulfated glycosaminoglycan with strong anticoagulant activity, and it also exhibits anti-inflammatory properties. It is synthesized and secreted by mast cells at sites of infection and inhibits endotoxin-induced monocyte activation.[112] Heparin pretreatment significantly attenuates leukocyte transmigration through its actions on P- and L-selectin and the leukocyte-specific $\alpha_M\beta_2$ integrin, and it also binds cytokines and suppresses superoxide generation by neutrophils.[112,113] Heparin-based coatings have reduced protein adsorption and leukocyte recruitment.[114–117]

Alpha melanocyte-stimulating hormone (α-MSH) is an endogenous linear peptide with potent anti-inflammatory properties. *In vitro*, α-MSH reduced levels of pro-inflammatory TNF-α while increasing levels of anti-inflammatory IL-10 in stimulated human monocytes.[97] It stimulated production of the anti-inflammatory cytokine IL-10 and revealed a less obstructive cell layer on coatings for tracheal prostheses.[98] In addition, α-MSH inhibited nitric oxide production by stimulated microglia and reduced the magnitude of electrical impedance of neural implants.[118]

Superoxide anions are potent cytotoxic oxidants secreted during macrophage phagocytosis. Superoxide dismutase is an endogenous scavenger enzyme that catalyzes its breakdown into less reactive hydrogen peroxide and oxygen. Superoxide dismutase mimetics were developed as an anti-inflammatory mechanism. When covalently attached to ultrahigh molecular weight polyethylene, neutrophil recruitment was significantly reduced.[119]

Receptor antagonists, antibodies, and soluble receptors are endogenous molecules that competitively inhibit binding to the corresponding agonist, effectively acting as a molecular trap. Decoy antagonists have been developed against proinflammatory cytokines, such as IL-1, as a strategy to regulate inflammation.[130,131] In one interesting study, a fusion protein of recombinant human IL-1 receptor antagonist and elastin-like polypeptide was covalently immobilized onto SAMs.[125] This fusion protein was able to prevent endotoxin-stimulated human monocytes from differentiating and reduced the

Table 2.
Active Surface Treatments for Biomaterial Coatings

Agent	Delivery Mechanism	Selected References
DEX	electrochemical release	Wadhwa *et al.*[111] (2006)[a]
	passive release	Kim and Martin[109] (2006)
	passive release	Norton *et al.*[107] (2007)
	passive release	Zhong and Bellamkonda[108] (2007)
	passive release	Patil *et al.*[110] (2007)
α-MSH	passive release	Benkirane-Jessel *et al.*[97] (2004)[a]
	passive release	Schultz *et al.*[98] (2005)
	passive release	Zhong and Bellamkonda[118] (2005)[a]
	surface immobilization	He *et al.*[120] (2007)
Heparin	surface immobilization	Gerritsen *et al.*[121] (2000)
	surface immobilization	Wang *et al.*[122] (2003)[a]
	surface immobilization	van Bilsen *et al.*[115] (2004)
	surface immobilization	Sung *et al.*[123] (2004)[a]
	surface immobilization	Fu *et al.*[124] (2005)[a]
	surface immobilization	Rele *et al.*[116] (2005)
	surface immobilization	Tseng *et al.*[117] (2006)[a]
	surface immobilization	Du *et al.*[114] (2007)[a]
IL-1Ra	immobilized or soluble	Kim *et al.*[125] (2007)[a]
Superoxide dismutase mimetics	surface immobilization	Udipi *et al.*[119] (2000)
Curcumin	passive release	Nguyen *et al.*[126] (2004)[a]
	passive release	Su *et al.*[127] (2005)[a]
	passive release	Pan *et al.*[128] (2006)[a]
Vitamin E	passive release	Hahn *et al.*[129] (2004)[a]

[a] Materials were tested only *in vitro*.

expression of proinflammatory cytokines while increasing the production of anti-inflammatory and pro-wound-healing cytokines. Additional therapeutic strategies include inhibition of intracellular signaling cascades that result in cytokine production and the application of anti-inflammatory cytokines such as IL-10.[132] It is highly desirable to develop methods for targeting delivery of anti-inflammatory factors in order to limit systemic adverse effects and concentrate therapeutic molecules at sites of inflammation.

Novel approaches for controlled delivery of immuno-modulatory proteins have been enabled by the development of micro- and nanoparticles of biodegradable polymers.[133,134] Biodegradable polymeric microspheres have been utilized for sustained delivery of IL-1Ra, which effectively inhibited production of pro-inflammatory cytokines.[135] Synthetic thrombin receptor (PAR1) agonist peptide encapsulated in biodegradable microspheres shortened the inflammatory phase and accelerated tissue healing in a rat ulcer model.[136] Short half-lives and requirements for high dosing frequencies limit the use of therapeutic proteins; however, PEGylation strategies have been investigated as a potential approach to extend the therapeutic lifetime of molecules such as IL-1Ra.[137] Using layer-by-layer deposition techniques, Pierstorff *et al*. have developed a copolymer nanofilm system as a multifunctional platform to release a variety of anti-inflammatory drugs; additionally, it may be possible to functionalize these agents onto implant surfaces to enhance delivery specificity over traditional systemic drug administration.[138]

Using small polymeric carriers complexed with oligonucleotides, including small interfering ribonucleic acid to silence harmful genes, cellular uptake of anti-inflammatory agents can be optimized.[139,140] Delivery of nucleic acid structures has proven to be an effective strategy to downregulate specific endogenous inflammatory factors.[141–145] These approaches may create less inflammatory macrophages and attract wound-healing cells. In one particular case, multilayered polyelectrolyte assemblies complexed with deoxyribonucleic acid (DNA) were coated onto intravascular stents;[146] this process could be extended to incorporate DNA encoding a variety of anti-inflammatory mediators. Although many of these techniques utilize micro- and nanoscale polymeric systems to deliver biomolecules, similar strategies could be implemented to develop anti-inflammatory coatings for biomaterials and implants as a general platform to release nucleic acid-based therapeutics at sites of inflammation.

Existing Considerations and Future Prospects

Biomaterial-mediated inflammation poses a complex problem, limiting the function of implanted devices and influencing overall patient health. Significant efforts have focused on developing passive nonfouling surface treatments to prevent protein adsorption and leukocyte adhesion, as well as active mechanistic approaches for the delivery of anti-inflammatory agents. While these coating technologies have reduced protein adsorption and cell adhesion *in vitro*, considerable fibrous encapsulation and adverse inflammatory responses are still evident following implantation.[107,115,147] These marginal reductions in adverse inflammation can be attributed to persistent leukocyte adhesion and activation *in vivo* and suboptimal pharmacodelivery.[74,107]

Although current polymeric coatings successfully modulate acute inflammatory events, new strategies will be critical to extend the *in vivo* lifetime and performance of implanted devices. Coating designs will probably need to be material and application-specific in order to achieve the desired *in vivo* response. Biologically interactive implants are gaining considerable interest. Tunable, stimuli-responsive materials and biomimetic molecules may be able to actively direct cell behavior and activity surrounding the implant, encouraging more desirable interactions.[68,69] In addition, these "smart" materials will lend a higher degree of sensitivity and specificity to polymeric coatings, enabling tighter control over pharmacokinetics and complex dosing schemes using multiple biomolecules or drugs. For example, the use of anti-inflammatory polymeric carrier systems enables modifications, including biomolecule conjugation, which may promote targeted delivery of therapeutics to specific cells or tissues.[139] In addition, these systems may be engineered for controlled release of anti-inflammatory cargo molecules based on external stimuli.[148]

It will also be important to focus on successfully integrating implanted devices with surrounding tissue and regenerating damaged microvasculature. Tissue integration is particularly important in neural and orthopedic applications.[9,13] In addition, the delivery of angiogenic factors may help facilitate *in vivo* performance of implanted biosensors by offsetting tissue fibrosis.[107,110,149] Clearly, progress in the development of effective and long-term implantable materials, including biosensors, will require the integration of multiple strategies and disciplines, as well as rigorous testing in relevant *in vivo* models.

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