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SYMPOSIUM

Glucose Sensor Membranes for Mitigating the Foreign Body Response

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Abstract

Continuous glucose monitoring devices remain limited in their duration of use due to difficulties presented by the foreign body response (FBR), which impairs sensor functionality immediately following implantation via biofouling and leukocyte infiltration. The FBR persists through the life of the implant, culminating with fibrous encapsulation and isolation from normal tissue. These issues have led researchers to develop strategies to mitigate the FBR and improve tissue integration. Studies have often focused on abating the FBR using various outer coatings, thereby changing the chemical or physical characteristics of the sensor surface. While such strategies have led to some success, they have failed to fully integrate the sensor into surrounding tissue. To further address biocompatibility, researchers have designed coatings capable of actively releasing biological agents (e.g., vascular endothelial growth factor, dexamethasone, and nitric oxide) to direct the FBR to induce tissue integration. Active release approaches have proven promising and, when combined with biocompatible coating materials, may ultimately improve the *in vivo* lifetime of subcutaneous glucose biosensors. This article focuses on strategies currently under development for mitigating the FBR.

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Introduction

Development of implantable glucose sensors that operate for extended periods (i.e., several weeks or months) would dramatically improve the quality of life of those afflicted by diabetes and help to reduce morbidity and mortality associated with complications caused by poorly controlled blood glucose levels. While Food and Drug Administration-approved implantable glucose sensors are commercially available, their performance remains plagued by unpredictable accuracy, frequent calibrations, and short implantation lifetime (i.e., ≤1 week), a direct result of the host's foreign body response (FBR) to the implanted device.[1] All implantable medical devices perturb the host medium, damage capillaries, and ultimately lead to an immune response that includes (1) formation of a provisional matrix (minutes–hours), (2) acute inflammation (days), (3) chronic inflammation (weeks), (4) granulation tissue formation (weeks), and (5) fibrous capsule formation (weeks–months).[2,3]

Adsorption of biomolecules (e.g., proteins, mitogens, chemoattractants, cytokines, growth factors, and other bioactive agents that promote or inhibit leukocyte activation and proliferation) to the sensor membrane typically results in a >50% decrease in sensor response to glucose, with

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Abbreviations: (DX) dexamethasone, (FBGC) foreign body giant cell, (FBR) foreign body response, (NO) nitric oxide, (VEGF) vascular endothelial growth factor

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the greatest reduction due to biomolecules <15 kDa.[2,4,5] While this loss of sensitivity is reversible, the extent of signal reduction is unpredictable and requires frequent *in vivo* sensor calibration.[1,4] Following formation of the provisional matrix, acute inflammation occurs through the infiltration of leukocytes, mast cell degranulation with histamine release, and fibrinogen adsorption.[2] The biological role of the acute inflammatory response is to phagocytose foreign material. The attempt by inflammatory cells to engulf and degrade the implant leads to reduced analyte diffusion and often decreases the relative concentration of analyte in the localized tissue. Additionally, consumption of oxygen and glucose by macrophages produces superoxide and peroxide, which, for certain electrochemical sensors, negatively impacts accuracy.[6,7] Moreover, local pH may drop to as low as 3.6 due to this oxidative process, resulting in enzyme degradation.[8] Chronic inflammation, characterized by the presence of macrophages, monocytes, and lymphocytes, as well as the proliferation of blood vessels and connective tissue, ultimately results in frustrated phagocytosis, as the macrophages are unable to individually consume/degrade the implant. Macrophages subsequently fuse to form foreign body giant cells (FBGCs) that further enhance degradation of the underlying implant surface.[9] As a result, sensor lifetime is often further diminished.[10] The extent of the chronic inflammatory response is dependent on not only the physical and chemical properties of the implant, but also on mechanical stresses (i.e., movement) at the implant site.[2] Granulation tissue is formed following resolution of the chronic inflammatory response due to the persistence of macrophages and infiltration of fibroblasts to the wound site.[2] During the final step in the immune sequence, a fibrous capsule is formed with collagen surrounding the implant to completely isolate it from the local tissue environment.[3] The extent of encapsulation is dependent on previous FBR sequences such as protein adsorption and cytokine signaling from macrophages. Ultimately, fibrous encapsulation leads to greatly diminished transport of analytes (i.e., glucose and oxygen) to the surface of the device, significantly increasing sensor lag time.[11,12] Indeed, deleterious effects of the FBR on glucose sensor performance *in vivo* necessitates development of sensor membranes that may enhance tissue integration.

Biocompatibility

When considering *in vivo* biosensors, biocompatibility may be defined as the ability to successfully integrate a device into surrounding tissue, thus facilitating measurement of the target analyte with high accuracy and short lag time over the lifetime of the implant. To successfully develop a biocompatible subcutaneous glucose sensor, the surface of the sensor must mitigate the highly complex FBR. Current strategies for improving glucose sensor biocompatibility may be grouped into two areas: (1) passive coatings and (2) active release. Passive strategies rely on modification of the sensor surface through chemical and physical means. Alternatively, active release relies on the release of molecules that may modify the FBR and direct the wound healing process to favor tissue integration of the sensor. The two strategies are often coupled to further mitigate the host response to foreign material. Herein we review examples of both passive and active approaches with regards to their ability to mitigate FBR and improve glucose sensor performance.

Passive Strategies

Because the surface chemistry at the tissue-sensor interface has a large influence on the activation of the immune response, the outer sensor surface is of great importance.[13,14] Coating a sensor with biomolecules is one passive approach used to circumvent the FBR since certain materials may allow the implant to appear less foreign to the host. A wide range of biomolecules have been used to interact with surrounding tissue and mitigate the FBR, including collagen,[15,16] chitosan,[17] cellulose,[18,19] heparin,[20] and dextran.[21,22] While these may prove beneficial for *in vivo* use, they are capable of eliciting an immunogenic response and are often undesirably biodegradable.[19,23] A similar strategy has utilized phospholipids, a major component of cell membranes, as an outer layer to disguise the implant as more native than foreign.[23] In addition, these phospholipid membranes have a high resistance to biofouling, possibly arising from the high water uptake of the materials.[24] In general, phospholipid membranes have exhibited poor stability when grafted onto a medical device.[25] To improve stability, phospholipids have been incorporated within polymers. Resultant phospholipid-containing polymers also elicit a more favorable inflammatory response. For example, Sawada and colleagues[26] found that macrophage-like HL-60 cells produced less of the proinflammatory cytokine IL-1β when adhered to a polymer consisting of 2-methacryloyloxyethyl phosphorylcholine copolymerized with n-butyl methacrylate. Kim and associates[25] reported surfaces with acrylated phospholipids polymerized onto a methacryloyl-terminated substrate reduced protein adhesion by >50% *in vitro*. When tested with the cage implant system, the materials exhibited decreased FBGC formation *in vivo*.[25] Though *in vivo* macrophage adhesion to phospholipid-containing polymer was reduced at 3 days

relative to controls, it was not significantly affected at 7, 14, and 21 days, indicating only short-term advantages in terms of reducing inflammatory response.[25] The general consensus is that, despite the short-term benefits, phospholipid membranes are not capable of circumventing the FBR that plagues sensors.

Rather than relying on biomolecules to improve biocompatibility, polymers can be designed to reduce biofouling and mitigate the FBR. Synthetic polymers have been used because of their ability to resist biofouling caused by protein adsorption. Nafion, a perfluorosulfonic acid-based polymer, has garnered much attention as a biocompatible sensor membrane.[27] The utility of Nafion is further enhanced by its effective lifetime, particularly for short-term (<1 week) implantations, simple application, and negative charge and hydrophobicity, preventing interfering species from passing through the membrane.[28,29] Despite Nafion's short-term effectiveness, use of hydrogels have been proposed as outer sensor membranes to enhance glucose sensor lifetimes due to mechanical properties that mimic those of surrounding subcutaneous tissue and lead to better tissue integration and reduced biofouling.[30–33] In multiple *in vivo* studies, use of hydrogel coatings of various compositions resulted in less fibrous encapsulation compared with noncoated materials (**Figure 1**).[32–34] When coupled to glucose sensors, the functional lifetime of the sensors was significantly increased and attributed to the improved biocompatibility at the sensor-tissue interface.[32,34] Though many benefits of hydrogels have been reported, their use as a microdialysis probe coating were not shown to improve glucose recovery after 8 days when compared with controls.[35] Due to tunable water uptake, hydrogels are attractive as glucose sensing platforms.[30] As such, diffusion of analyte molecules across the membrane may be adjusted in advance of the FBR to circumvent deterioration of sensor response. Use of hydrogels has improved the linear range and reduced oxygen dependence of glucose sensors due to their ability to store oxygen.[36,37] While hydrogels are a promising strategy to enhance long-term sensor performance, concerns pertaining to their stability (e.g., adherence to underlying substrates, low mechanical strength, and leaching and subsequent cytotoxicity of the polymer precursors) make their use problematic.

In addition to chemical composition, surface characteristics of an implant play an important role in mitigating the FBR. Pore size, even when varied on chemically identical materials, greatly influences the way in which host tissue heals around the implant. Synthesis of porous

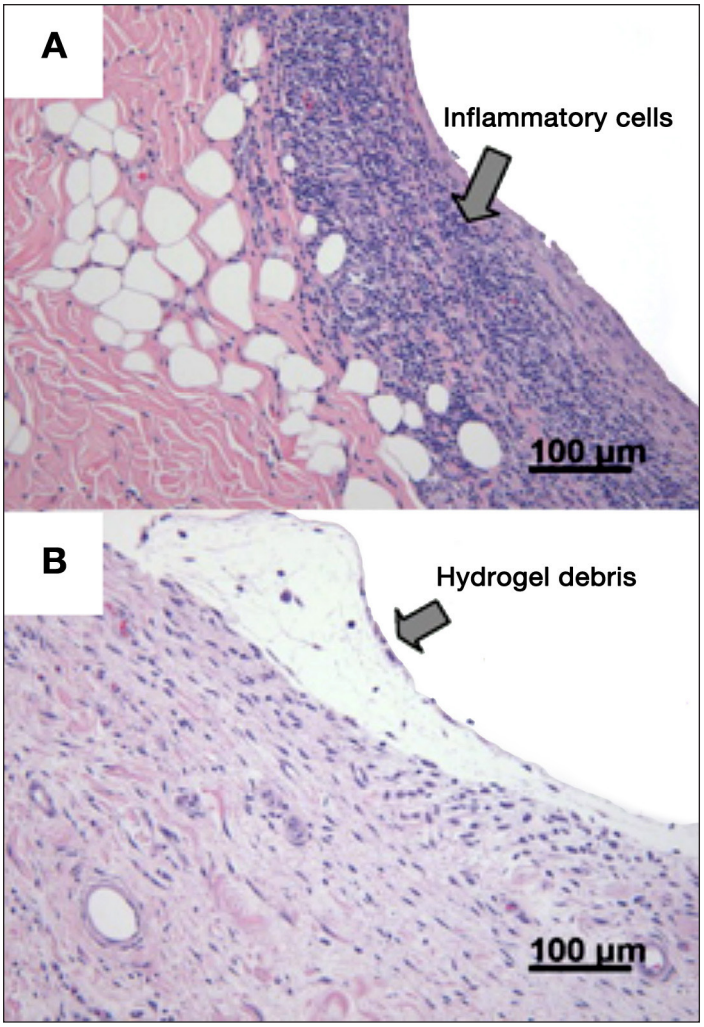

Figure 1. Hematoxylin and eosin-stained tissue surrounding glucose sensors after 28 days for devices coated with either **(A)** epoxy-polyurethane or **(B)** a hydrogel synthesized from hydroxyethyl methacrylate, 2,3-dihydroxypropyl methacrylate, *N*-vinyl-2-pyrrolidinone, and ethylene glycol dimethacrylate. (Reproduced with modifications with the permission of Elsevier Ltd.[32])

materials as biocompatible coatings has been achieved by sphere-templating, gas-foaming, and phase-separation techniques.[38–40] Depending on the desired application, the ideal pore size needed to improve wound healing ranges from 5–500 µm.[41] When implanted *in vivo*, porous materials in this size range have been demonstrated to promote angiogenesis and diminish fibrous encapsulation.[42,43] For example, Marshall and coworkers[43] reported that a hydrogel with 35 µm pore size, synthesized through sphere templating, promoted angiogenesis in murine subcutaneous tissue. The process by which different pore sizes mitigate the FBR has been attributed to disruption of fibrous tissue deposition while fostering vascularized cellular and tissue growth.[44] In contrast, nonoptimal pore sizes promote avascular and fibrotic tissue growth.[45]

In vitro tests have shown that surface roughness also affects protein adhesion[46,47] and leukocyte adhesion and activation.[14,48–51] *In vivo*, roughened surfaces generally lead to a more favorable FBR.[48,49] For example, electrospun fibers of polycaprolactone reduced fibrous encapsulation after 4 weeks of subcutaneous implantation in a rodent model.[48] When fibers were aligned randomly rather than parallel to each other, fibrous encapsulation was further reduced.[48] While potentially beneficial, the influence of surface roughness on biofouling, cell adhesion, and activation remains controversial.[48–52] Although the benefits of utilizing more biocompatible surfaces to mitigate the FBR are clear, development of reliable long-term *in vivo* glucose sensors using passive approaches remains an unattainable goal.

Active Release

In another initiative, implant coatings have been synthesized to release biologically active molecules to improve biocompatibility.[53] Upon release from the coating to the surrounding tissue, active molecules are intended to influence the immune response, reduce encapsulation, and/or increase angiogenesis. Several parameters should be considered in the design of an active-releasing surface, including the desired active molecule, release kinetics and duration, relative amount and delivery with each parameter being dependent on the molecule's properties.

To date, researchers have focused primarily on local delivery of endogenous molecules and anti-inflammatory drugs. Because wound healing response is signaled in part by the generation of cytokines and chemokines from macrophages at the surface of the implant,[3] release of cytokines and chemokines may help direct the FBR at the sensor-tissue interface and ultimately improve tissue integration. While many cytokines exist, vascular endothelial growth factor (VEGF) has appeared in the greatest number of glucose sensor papers.[35,54–59] Increased amounts of localized VEGF has been shown to promote angiogenesis in surrounding tissue.[60] Upregulation of VEGF in a chick chorioallantoic membrane model provided enhanced glucose sensor response compared with controls, exemplifying the usefulness of VEGF for *in vivo* biosensors.[57] Surfaces that release VEGF have been shown to improve vascularity of the surrounding tissue.[35,54–59,61] However, VEGF does not address other problems related to the FBR and may even increase the inflammatory response.[35]

Rather than increasing vascularity, anti-inflammatory drugs may reduce the FBR and represent potential active release agents from glucose sensor coatings. Dexamethasone (DX), an anti-inflammatory glucocorticoid steroid, is widely prescribed because of its ability to inhibit proinflammatory cytokine expression, leukocyte infiltration, and collagen deposition.[62–64] Active release of DX from implants has been demonstrated to reduce inflammation at the implantation site.[35,56,65,66] Patil and colleagues[66] reported that localized zero-order DX release (from an implant surface) significantly diminished the acute and chronic inflammatory response over a 1-month period. To fully circumvent the FBR, hydrogels that release both VEGF and DX from a membrane was shown to reduce inflammatory response to the implant while increasing angiogenesis.[56] Another study examined the effect of concurrent DX and VEGF release from hydrogel-coated microdialysis probes (**Figure 2**).[35] Unfortunately, DX release significantly diminished the angiogenic benefits of VEGF.[35] Other reports have shown that glucocorticoid steroids, in particular DX, inhibit VEGF activity *in vivo*.[67–69] While concurrent release would be a promising approach to address the FBR as a whole, two active release agents that affect the FBR in a synergistic or nonantagonistic manner have yet to be identified.

In lieu of distinct anti-inflammatory and angiogenic agents, it may be possible to achieve more ideal tissue integration with nitric oxide (NO), an endogenously synthesized diatomic free radical involved in a wide range of biological roles, including vasodilation, inhibition of platelet aggregation, angiogenesis, wound healing, and phagocytosis.[70] The short half-life of NO (<1 s in the presence of oxygen and hemoglobin) might also eliminate undesirable cytotoxicity concerns associated with the release of other agents.[71,72] Since NO is a gas, its storage and delivery has been achieved using NO donors.[73,74] A number of macromolecular scaffolds capable of NO storage and delivery have been reported, including xerogels,[75–77] silica nanoparticles,[78–80] dendrimers,[81,82] micelles,[83] NO donor-doped polymer matrices,[84–86] and synthetic polymers.[87–89] The NO release trigger depends on the NO donor employed but may be as simple as water or heat.[70] With respect to mitigating the FBR, Hetrick and associates[75] reported a reduced inflammatory response, thinner capsule formation, and greater blood vessel formation for NO-releasing subcutaneous implants at extended periods (weeks) despite only 72 h of measureable NO release.[75] In subsequent work, Gifford and coworkers[71] also reported mediation of the *in vivo* inflammatory response for needle-type glucose sensors that released NO for 18 h with average fluxes of 7.52 pmol cm^{-2} s^{-1}, with clinically acceptable glucose response up to 3 days. Histological analysis revealed a significantly decreased inflammatory response at 24 h.[71] Additionally, the NO-

releasing glucose sensor was characterized by a reduced run-in time (i.e., time required to stabilize sensor response after implantation).[71] While sensor success with only initial NO release was accomplished, Nichols and colleagues[90] showed that NO-releasing microdialysis probes further enhanced *in vivo* glucose recovery compared with controls over longer periods (up to 14 days).[90] As shown in **Figure 3**, probes with daily NO fluxes of 162 pmol cm^{-2} s^{-1} over an 8 h perfusion period were characterized by constant glucose recovery over 14 days, reduced capsule thickness, and lessened inflammatory cell density at the probe surface.[90] Despite the clear benefit on sensor biocompatibility, future work must elucidate the effects of NO flux and duration on the FBR.

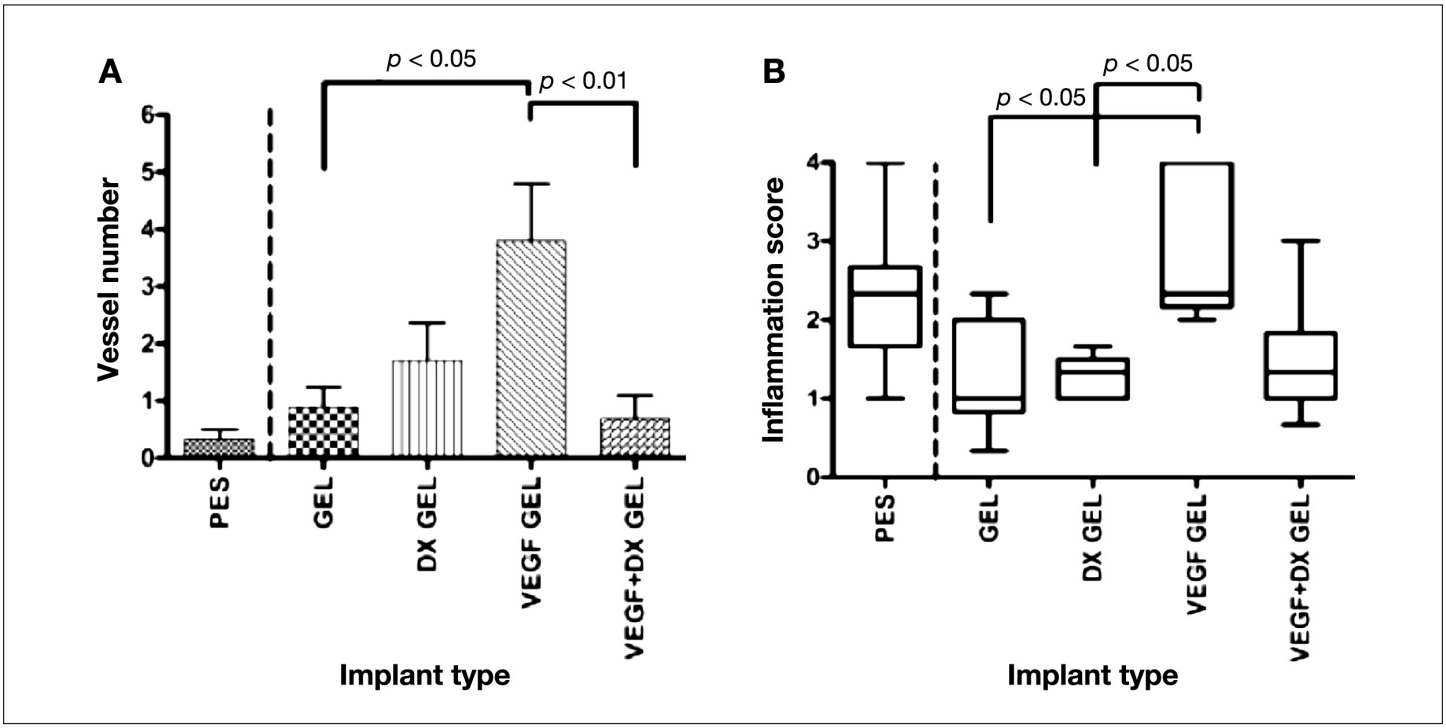

Figure 2. *In vivo* tissue response at two weeks from noncoated polyethersulfone microdialysis probes, probes coated with a hydrogel, or hydrogel-coated probes that released DX, VEGF, or both. The FBR was evaluated via histology for **(A)** angiogenesis and **(B)** inflammation. GEL, hydrogel; PES, polyethersulfone. (Reproduced with modifications with the permission of John Wiley and Sons, Inc.[35])

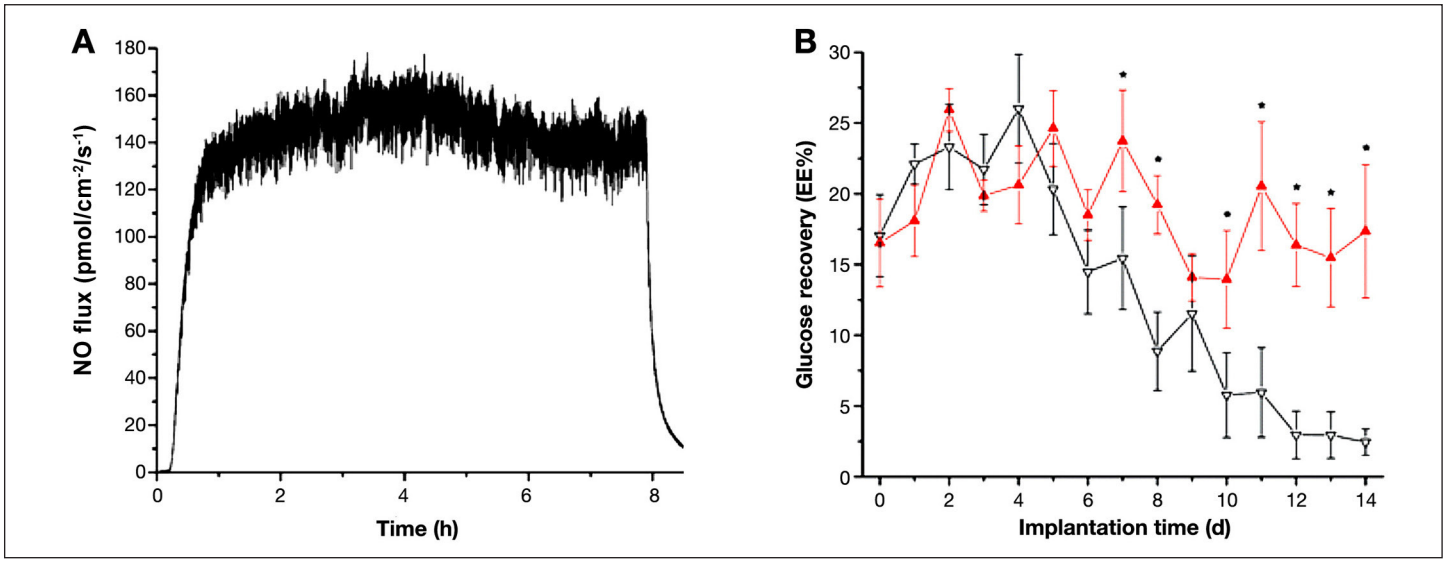

Figure 3. (A) Daily NO release from implanted polyarylethersulfone microdialysis probes. **(B)** Relative glucose recovery from subcutaneously implanted NO-releasing (red) or control (black) polyarylethersulfone probes. (Reproduced with modifications with permission of the American Chemical Society.[90])

Conclusions

The FBR limits the utility of continuous glucose monitoring devices, thus creating a significant need for strategies that mitigate the host response through both passive coatings and active release. Both tissue integration and sensor performance may be improved by changing the physical or chemical properties of glucose sensor coatings. While passive strategies have proven useful for reducing biofouling, active release is necessary to fully integrate sensors into surrounding tissue. Future studies should concentrate on the release kinetics and concentration profiles of VEGF, DX, and NO. *In vivo* studies involving VEGF and DX should determine the ability of the molecules to both decrease the inflammatory response and increase angiogenesis. Studies involving NO must similarly determine the required NO flux to successfully integrate sensors into subcutaneous tissue.

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