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Microfabricated microporous membranes reduce the host immune response and prolong the functional lifetime of a closed-loop insulin delivery implant in a type 1 diabetic rat model

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ABSTRACT

Implantation of a medical implant within the body inevitably triggers a host inflammatory response that negatively impacts its function and longevity. Nevertheless, the degree and severity of this response may be reduced by selecting appropriate materials, implant geometry, surface topography and surface treatment. Here we demonstrate a strategy to improve the biocompatibility of a chemically-driven closed-loop insulin delivery implant. A microfabricated microporous, poly(ethylene glycol)-grafted polydimethylsiloxane membrane was placed on top of the glucose-responsive insulin release plug of the implant. Implant biocompatibility was assessed in healthy rats while implant function was evaluated in a type 1 diabetic rat model. The microporous membrane with a small distance to the plug provided a geometric barrier to inflammatory cell migration and prevented leukocyte-mediated degradation of the plug for at least 30 days. Membrane-protected devices elicited a significantly milder inflammatory response and formation of a well-defined fibrous capsule at the device opening compared to unprotected devices. The device's glucose-responsiveness was nearly unchanged, although the insulin release rate decreased with decreasing pore size. The microporous membrane improved biocompatibility and prolonged *in vivo* efficacy of the implant by ~3-fold. This work suggests the importance of implant design in modulating inflammatory response and thereby extending the functional duration of the implant.

1. Introduction

Implantable medical devices improve patient care and quality of life in many aspects of medicine including cardiology, orthopedics, neurology and ophthalmology. Proper implant function is strongly dependent on the interaction between the body and the implanted material that contacts the host tissue [1–6]. As such, the use of biologically inert materials in pacemakers, cardiovascular stents, and catheters has resulted in prolonged device lifetimes and reduced incidence of complications [7].

In spite of these achievements, long-term implantable sensors, macromolecular drug-delivery systems, and combination closed-loop drug-delivery systems remain elusive as these systems often feature active components made from non-biocompatible materials that must contact and interact unimpeded with the host tissue [8]. Examples of such materials include metallic/semiconducting sensing electrodes [9–13], stimuli-responsive polymers [14–18], enzymes [16,18,19], and allogenic or transgenic cells or tissues [20]. As these components cannot simply be masked using biologically inert materials, these devices often fail shortly following implantation due to biocompatibility issues, namely fibrous encapsulation and cell-mediated degradation [21]. Innovative strategies have thus been extensively explored to overcome the foreign body response (FBR) whilst simultaneously enabling efficient mass transport to and from these devices; both of which are vital to prolonging implant lifetime and viability in the clinic, and technologically challenging to achieve [22].

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Active strategies to mitigate the FBR rely on the sustained local release of anti-inflammatory agents (e.g., dexamethasone [23–25] or nitric oxide (NO) [26]) or pro-angiogenic mediators (e.g., vascular endothelial growth factor (VEGF) [27]) from the implant surface. The continuous release of dexamethasone or NO has been shown to reduce inflammatory cell recruitment and minimize fibrous capsule formation around implants; however it is difficult to provide a steady supply of these agents throughout a device's lifetime [26]. Other coatings such as sirolimus or paclitaxel coatings are also conceivable, and are already used in interventional cardiology as so called drug eluting stents. Nevertheless, contraindications with the patients' medical condition must also be carefully considered with the use of bioactive compounds, as is the case for dexamethasone and type 1 diabetes mellitus in which dexamethasone may exacerbate the underlying condition and increase the risk of both diabetes-related complications and the onset of type 2 diabetes [28]. Similarly, sirolimus has been associated with insulin resistance and the onset of type 2 diabetes in kidney transplant recipients [29,30].

Passive strategies for limiting the FBR involve alteration of the implant surface topography [6,31,32] and chemistry [33,34] to minimize serum protein adsorption, subsequent leukocyte adhesion, and downstream inflammatory responses. These strategies make use of non-fouling self-assembled monolayers, polymer brushes, or hydrogel coatings made from hydrophilic polymers such as poly(ethylene glycol) (PEG), alginates, poly(2-hydroxyethyl methacrylate), poly(N-isopropyl acrylamide), poly(acrylamide), and phosphoryl choline-based polymers [8]. Hydrogels are of particular interest to sensory and drug-delivery applications as they may be optimized to permit selective diffusion of biomolecules, drugs, and analytes. Despite these advances, surface coatings that completely eliminate protein adsorption over the lifetime of a device have yet to be attained [8,35]. These coatings are also prone to cellular overgrowth, infiltration and degradation, and may reduce molecular transport to and from the implant surface.

As both fibrous encapsulation and cellular degradation of implanted materials proceed *via* recruitment of immune cells to an active implant surface, we hypothesize that the biocompatibility of an implant can be improved by limiting cell migration to the implant surface using a microporous membrane placed between the active implant surface and the host tissue. Incorporation of the microporous membrane serves as a barrier to surface-bound cell migration by altering the implant geometry without significantly impeding the diffusion of analytes and drugs from the device.

We demonstrate this approach on a chemically-driven closed-loop insulin delivery system that features a glucose-responsive hydrogel plug that is responsible for the self-regulated release of insulin from the implant reservoir in the presence of glucose [16,17,36]. Closed-loop insulin delivery systems offer diabetic patients improved glycemic control, compliance and quality of life over conventional insulin therapy [12,37,38]. To date a number of such systems have demonstrated short-term success (~1 week) in maintaining normal blood-glucose levels in diabetic rats [17,18],

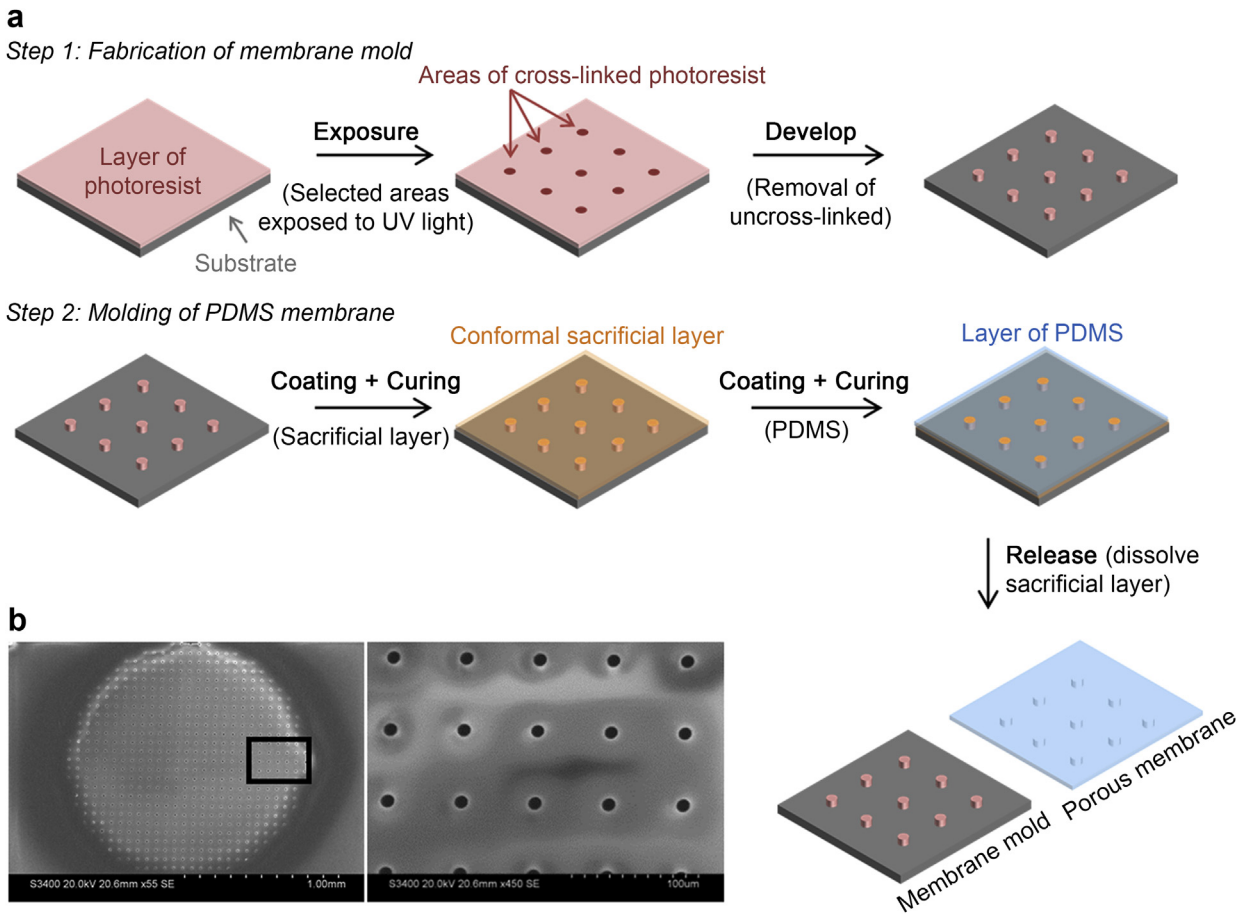

Fig. 1. a) Schematic illustrating the process for fabricating microporous PDMS membranes. b) Scanning electron microscope images of micro-fabricated microporous membranes (10 μm pore diameter membrane shown). Pores traverse the width of the membrane as evidenced by the absence of charging.