IMMUNO-ISOLATION MEMBRANE FOR A HYBRID ARTIFICIAL PANCREAS


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According to recent estimates, 400,000 Americans have insulin-dependent (Type I) diabetes, characterized by deficient insulin production and/or release. A hybrid artificial pancreas, defined as a device consisting of artificial materials and living islet cells, could provide approximate normoglycemia through insulin release in response to changing glucose concentrations in the area of the device. For these patients, this could reduce the incidence and severity of microvascular complications of Type I diabetes.

A commercially-successful and clinically-safe and effective hybrid artificial organ must:
1. Protect cultured cells from macrophages and the immune system
2. Maintain cell viability for extended periods
3. Permit free passage of nutrients, secretagogues, and cell products
4. Present the blood and tissue with a biocompatible surface
5. Be constructed of biodegradation-resistant materials
6. Facilitate surgical implantation and cell reseeding
7. Be easily fixed in place and easily removed if needed.

Device designs have been proposed which address points 6 and 7, but, to date, no biomaterial exists which completely satisfies points 1 to 5. These requirements are of particular importance as they relate to so-called barrier membranes which may provide immuno-isolation through selective permeability of solutes while preventing attack of islets by cellular perperants.

The feasibility of direct islet transplantation has been demonstrated in animal models, according to Scharp, et. al. (1). A major obstacle to long-term survival of the islet graft is immunologic rejection of the allografted or xenografted tissue. Standard immunosuppression poses acute risks for a diabetic patient, such as nephrotoxicity in the use of cyclosporin, (2) and is difficult to justify in young diabetic patients. The concept of immuno-isolating live tissue from the host immune response has been studied by many investigators, who have reported some early successes, yet no long-term success has been achieved (2-6). Four methods of immuno-isolation used to date include: extravascular diffusion chambers, intravascular diffusion chambers, intravascular ultrafiltration chambers and microencapsulation. Problems with these approaches are discussed in a review by Scharp, et. al. (1) and are:
1. Host fibrotic response to the implant and material's instability, e.g., in alginate microencapsulation
2. Nutrient diffusion limitations across semi-permeable membranes with decreasing permeability as protein deposition, blood clotting or fibrous ingrowth blocks passage of nutrients through the pores
3. Glucose and insulin permeability and diffusion lag time across semi-permeable membrane barriers, i.e., transportation lag in the control of host glucose levels

Membranes used in the previously-mentioned implants (with the possible exception of microencapsulation) have employed microporous semi-permeable membranes fabricated from impermeable materials with pores introduced through processing method/conditions and/or leachable additives. Millipore® and Nucleopore® (polycarbonate) microporous membranes, made from inherently impermeable polymers, do not support long-term islet viability (1, 2). Other semi-permeable membranes demonstrate poor blood compatibility, as well as low permeability coefficients for glucose and insulin transport (3). In direct blood contact the microporous membranes often accumulate a fibrin layer which becomes a major barrier to mass transport.

We have developed a self-supporting membrane which is inherently permeable to concentration-driven transport of nutrients, secretagogues and cell products, yet maintains an environment of immuno-isolation. This smooth membrane is highly permeable to glucose and insulin and is totally impermeable to IgG and macrophages.

- Glucose: 9620 ± 1065 μg/cm²·day·g/cm²
- Insulin: 4903 ± 2148 μg/cm²·day·g/cm²
- IgG: 0 ± 0 μg/cm²·day·g/cm²

Good physical-mechanical properties and thermoplastic properties permit easy construction of implantable devices using heat sealing and adhesive bonding of sheet or hollow-fiber membrane geometries:

- Tensile Strength: 20.7 ± 1.21 MPa
- Initial Modulus: 12.3 ± 1.94 MPa
- Ultimate Elongation: 1060 ± 29 %

We have used an unsteady-state diffusion experiment for rapid permeability measurements of candidate membrane in sheet and hollow-fiber form.

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c_{10} = \text{initial permeant concentration in chamber 1 (g/cc)} \\
v_1 = \text{volume of chamber 1 (cc)} \\
c_{20} = \text{initial permeant concentration in chamber 2 (g/cc)} \\
v_2 = \text{volume of chamber 2 (cc)} \\
a = \text{membrane area (sqcm)} \\
l = \text{membrane thickness (cm)} \\
t = \text{time (days)}
\]

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p = \text{permeability coefficient [μg·cm/day·sqcm·g/cc]} = -((v_1 \cdot v_2 \cdot \log((c_{20} - (c_{10} \cdot v_1 - c_2 \cdot v_2))/(c_{10} - c_{20}))/a \cdot t/(v_1 + v_2))
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Permeability measurements of hollow fiber geometries have used radiolabeled permeants both in static and flow experiments with good agreement to the unsteady-state diffusion cell experiment.

%Equilibrium Glucose

Initial in vivo studies of membrane biostability and cell function and viability indicate that the membrane material has sufficient permeability/barrier properties and biodegradation resistance to function for extended periods in a hybrid artificial pancreas. Results of long-term material and device implants will be presented.

References

*Somatix Therapy Corporation, Alameda, CA 94501