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Advances in polymeric islet cell encapsulation technologies to limit the foreign body response and provide immunoisolation

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Islet transplantation for the treatment of type 1 diabetes (T1D) is hampered by the shortage of donor tissue and the need for life-long immunosuppression. The engineering of materials to limit host immune rejection opens the possibilities of utilising allogeneic and even xenogeneic cells without the need for systemic immunosuppression. Here we discuss the most recent developments in immunoisolation of transplanted cells using advanced polymeric biomaterials, utilising macroscale to nanoscale approaches, to limit aberrant immune responses.

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Diabetes mellitus is a chronic disease characterised by high blood glucose due to inadequate insulin production and/or insulin resistance which affects 415 million people worldwide (It is estimated to increase to 642 million by 2040) [1]. Of these patients, 5% have Type 1 diabetes (T1D) which is characterised by autoimmune destruction of β-cells within the pancreatic islets, resulting in lifelong inadequate insulin secretion and an inability to regulate plasma glucose levels. The global cost of diabetes is now $825 billion per year and the economic burden per case of diabetes is greater for T1D than for type 2 diabetes (T2D) [2]. Pancreatic islet transplantation has gained considerable attention as an advanced therapeutic treatment option, with the potential of re-establishing naturally regulated insulin production, greatly reducing the risk of hypoglycemic unawareness, and reducing the risk of mortality from severe hypoglycemic events. However, there are significant technical and scientific hurdles to overcome before islet replacement can become a translational reality, with advances in materials science offering the potential to ameliorate the immune responses and provide controlled immunoisolation at a local level (Figure 1).

Immunosuppression

In subclinical T1D there exists opportunities to try to arrest the disease before the complete destruction of pancreatic function [3]. One of the more promising strategies involves antigen-specific targeting to inhibit the aberrant immune response via the induction of regulatory T cells, which play a key role in preventing the progression of autoimmune disorders such as T1D [4]. The administration of exogenous GAD-65 (glutamic acid decarboxylase) has been the subject of a number of phases II/III trials as an autoantigen treatment to preserve residual β-cell function (6 trials currently ongoing through Diamyd Medical). GAD-65 has been shown to increase serum C-peptide levels, indicative of endogenous insulin production levels, in phase II trials at 24 weeks versus placebo controls in latent autoimmune diabetes in adults [5]. While early Phase III evidence suggests that GAD-65 can arrest the progression of subclinical T1D [6], it has been shown to be ineffective in patients who already display clinical T1D symptoms [7]. Therefore, strategies are needed to augment/replace remaining pancreatic function such as the delivery of allogenic islets.

Despite its great promise, success of cadaveric islet transplantations, via perfusion into the portal vein using the Edmonton protocol has been limited by the availability of functional pancreata of acceptable quality, 2–3 of which are usually needed for sufficient cells to achieve insulin independence [8]. Additionally, trials involving the use of allogeneic cells require systemic immunosuppression (e.g. tacrolimus, cyclosporine) to prevent rejection which poses additional risks to the patient (e.g. increased infection risk, organ damage and cancer). With this in mind, local or short-term immunomodulation and

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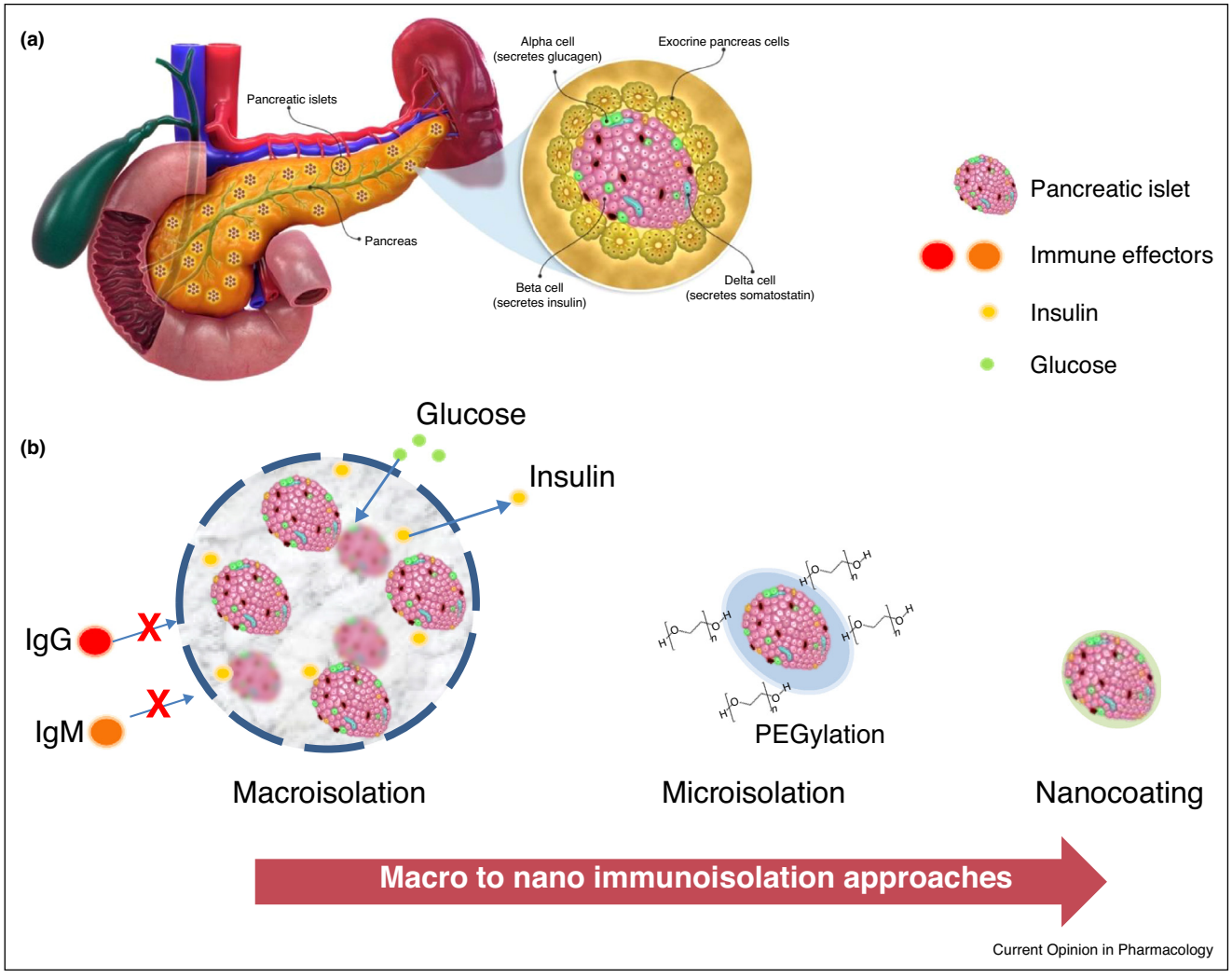
Figure 1



Strategies for encapsulation and surface engineering of pancreatic islets. **(a)** Isolated pancreatic islets can be encapsulated via a number of different methods. **(b)** Encapsulation methods range from the macroscale utilising porous devices, microisolation via hydrogel encapsulation (which may have surface modification such as PEGylation), through to nanocoatings utilising a thin polymer coat.

non-systematic immunosuppressive treatment have been investigated to improve survival and overall efficacy of encapsulated islet transplants [9,10]. One approach is to engineer materials to release factors for dampening local inflammation and creating immune-privileged sites. Cytokines (such as transforming growth factor-β (TGFβ) and IL-10, chemokines (MCP1 and SDF), cellular enzymes (IDO1) and prostaglandins (PGE2) are some of the factors that have been locally delivered to attenuate the local inflammatory response [11]. However this immunomodulation is limited by the effects being observable for as long as the therapeutics are being administered. Balancing the threats of chronic diabetes mellitus against the risks of chronic immunosuppression requires careful consideration. As immunosuppression becomes safer and means to induce stable immunological tolerance to autoantigens and alloantigens are developed, the demand for islet transplantation will expand exponentially. The opportunity to remove the need for immunosuppression by physical or chemical methods demonstrates great promise for opening the patient cohort to include young patients (<18 years old) and those with more stable insulin-requiring T1D (Figure 1).

Macroscopic encapsulation

Whole pancreas and islet allotransplantation can be effective treatments for T1D; however, they are limited by donor scarcity and the risks of life-long immunosuppression. Therefore, development of novel therapies that can tackle these issues is highly desirable. Adopting an immunoisolation approach that is, hiding the islet grafts from the recipients immune system, fundamentally differs