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Engineering immunomodulatory biomaterials for type 1 diabetes

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Abstract

A cure for type 1 diabetes (T1D) would help millions of people worldwide, but remains elusive thus far. Tolerogenic vaccines and beta cell replacement therapy are complementary therapies that seek to address aberrant T1D autoimmune attack and subsequent beta cell loss. However, both approaches require some form of systematic immunosuppression, imparting risks to the patient. Biomaterials-based tools enable localized and targeted immunomodulation, and biomaterial properties can be designed and combined with immunomodulatory agents to locally instruct specific immune responses. In this Review, we discuss immunomodulatory biomaterial platforms for the development of T1D tolerogenic vaccines and beta cell replacement devices. We investigate nano- and microparticles for the delivery of tolerogenic agents and autoantigens, and as artificial antigen presenting cells, and highlight how bulk biomaterials can be used to provide immune tolerance. We examine biomaterials for drug delivery and as immunoisolation devices for cell therapy and islet transplantation, and explore synergies with other fields for the development of new T1D treatment strategies.

Introduction

Autoimmunity is an abnormal immune response, wherein the immune system selectively targets and destroys healthy cells. The worldwide incidence of autoimmune conditions is increasing, with current estimates suggesting that nearly 10% of the population suffer from at least one form of autoimmune disease¹. One of the most pernicious autoimmune diseases is type 1 diabetes (T1D), which is diagnosed in more than 542,000 children worldwide². Incidence in adults (> 30 years) is also increasing, with estimates that more than 40% of all new T1D cases occur in adults³. Aggregating medical costs and income lost, T1D annually costs the U.S. over \$14.4 billion⁴.

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Contributions

CLS and BGK conceived of the manuscript; CLS designed the figures; and all authors made substantial contributions to the content, writing, and editing of the manuscript.

Competing interest

Stockholder (BGK) of OneVax, LLC (Gainesville, FL), a company focused on particle based immunotherapies.

While the pathogenesis of T1D is heterogeneous, it results in the immune-mediated destruction of insulin-producing pancreatic beta cells within the islet of Langerhans, which eventually results in an insulin deficiency. Clinical indicators of T1D are fasting and/or post-prandial hyperglycemia with concomitant detection of islet-associated autoantibodies^{5,6}. Lifelong exogenous insulin supplementation is required to treat this life-threatening disease,⁴. Despite aggressive glycemic management, people with T1D have a 10-fold higher risk for cardiovascular disease than healthy individuals and up to 30% of patients suffer from life-threatening chronic kidney disease, among other comorbid complications⁷. As most T1D complications are attributed to the nonphysiological glycemic levels imparted by long-term subcutaneous insulin delivery, approaches that halt the progression of this disease and/or replace the destroyed beta cells would provide substantial benefits.

T1D is a complex immunological disease (BOX 1). The intricate interplay between innate and adaptive immunity and the role of non-traditional immune players in T1D pathogenesis are still being investigated. The continuous and systemic administration of broad spectrum immunosuppressive agents can dampen beta cell destruction, as demonstrated in beta cell replacement therapy⁸. However, resurgence or even elevation of autoimmune responses occurs once the suppressive therapy is terminated. Importantly, the long-term delivery of immunosuppressive agents causes broad and adverse side effects, such as increased opportunistic infections and cancer⁸. Thus, clinical trials seeking to delay or prevent T1D progression in children typically test only transient, single agent immunotherapy⁹. These modest interventions have largely failed to preserve or restore beta cell function in a significant cohort of T1D subjects, likely owing to low drug potency, poor targeting, and insufficient treatment duration⁹.

An alternative approach to generalized immune suppression is the use of tolerogenic strategies. Immunological tolerance is defined as the lack of a destructive immune response against specific antigen(s) while retaining the full capacity of the immune system to react to other foreign antigens or insults¹⁰. To halt T1D progression, tolerogenic approaches aim to reinstruct autoreactive immune cells to accept beta cells. For advanced T1D disease with extensive beta cell damage, cellular replacement therapy can be employed in conjunction with tolerogenic approaches to allow immunological acceptance of the cellular graft.

The most clinically effective tolerance induction regimen to date is bone marrow transplant-mediated chimerism, in which immune tolerance to a disparate human leukocyte antigen (HLA) donor cell is achieved by the hematopoietic engraftment of host and donor cells and the central thymic deletion of donor- and host-reactive T-cells¹⁰. However, substantial health risks and inconsistent stability of allograft tolerance associated with this approach currently limit its translation to T1D¹¹. Less risky strategies for the induction of tolerance include antigen-specific deletion or anergy of autoreactive lymphocytes and the boosting of regulatory immune cells. Regulatory immune cells, such as CD4⁺ T regulatory (Treg) cells¹², suppressive and tolerogenic dendritic cells¹³ and alternatively-activated or M2 macrophages¹⁴ provide a balance to aggressive immunological responses by deactivating effector immune cells following the resolution of an antigen challenge or by removing aberrant self-reacting clones. However, in patients with T1D, regulatory immune cells, in particular Tregs, have less suppressive capacity when compared to healthy individuals^{15,16}.

Multiple clinical trials have been conducted with the aim to restore Treg function through infusion of exogenously-expanded CD4⁺ Tregs or tolerogenic dendritic cells (BOX 1), but with variable and limited efficacy¹⁷⁻¹⁹. Improving cellular engraftment and trafficking would increase the durability and consistency of these cellular transplants; however, the cost, complexity, and personalization requirements for harvesting, expanding and validating autologous immune cells will likely impair widespread clinical translation. An alternative to cell infusions is the delivery of agents and/or cytokines that promote the recruitment to and/or the proliferation and expansion of regulatory immune cells at the site of antigen reactivity. For example, systemic delivery of mycophenolate mofetil – an immunosuppressant drug used to prevent organ transplant rejection – together with vitamin D₃ or interleukin (IL)-10 leads to an increase in the number of circulating Tregs compared to naïve mice²⁰. However, the most potent inducers of regulatory cell phenotypes are typically not amenable to systemic delivery. For example, transforming growth factor (TGF)-β1, a powerful inducer of CD4⁺ Foxp3⁺ Tregs through soluble and cell surface interactions²¹, cannot be systemically delivered owing to broad off-target effects, such as fibrosis²². Thus, improvements in the retention, stability, potency and localization of tolerogenic treatment strategies are needed to improve their safety and efficacy.

Biomaterials have long played a role in treatment for T1D, from insulin delivery platforms to cell replacement devices, and they offer a powerful tool for the induction of tolerogenic immune responses to provide long term and specific immunomodulation. In this Review, we discuss approaches for the engineering of immunomodulatory biomaterial platforms for T1D therapies, including vaccines that prevent, delay or reverse the disease, and strategies for beta cell replacement. We investigate biomaterial features that are key for the induction of desired immune responses and highlight applications of immunomodulatory biomaterials for other autoimmune diseases, such as multiple sclerosis.

Immunomodulatory biomaterials

Biomaterials are commonly used for controlled drug delivery for the modulation of T1D-related immune responses and for immunoisolation of cellular transplants. An extensive array of materials has been investigated for these applications, including natural polymers such as alginate, chitosan, extracellular matrix (ECM), hyaluronic acid and silk, and synthetic polymers, such as polyethylene glycol (PEG), polydimethylsiloxane (PDMS), poly lactic-co-glycolic acid (PLGA), and self-assembling peptides²³⁻²⁶. Biomaterial-based drug delivery platforms enable localized and targeted drug delivery and thus, compared to systemic infusion of immunosuppressive agents, can decrease the total drug burden, reduce distal impacts, and minimize side effects. Moreover, biomaterials can be designed for controlled drug release, carrying multiple agents and providing localized and prescribed release kinetics to extend the window of immunosuppression. Biomaterials can further be applied to encapsulate foreign cell transplants to block direct immune cell interactions with the implant. However, these approaches have struggled in clinical translation, because the drug within these delivery platforms eventually runs out and encapsulating biomaterials typically induce a foreign body response²⁷.

To address these limitations, biomaterial design strategies are shifting towards the induction of tolerogenic, in lieu of immunosuppressive, responses, which should result in durable and specific immunomodulation. Biomaterial design parameters can be customized and combined to generate a more nuanced immune response. Material surface properties (for example, topography, charge, and adhesive ligands) can be manipulated to induce a desired immune cell phenotype. Immunomodulatory motifs and/or targets can be tethered to the material surface to engage specific immune cell subsets and direct apoptosis or conversion to a regulatory phenotype. Furthermore, material formulations and geometry (for example, particles, fibres, films, or sponges) and scale (macro-, micro-, or nanoscale) can be tailored to improve the localization of the material within specific organs and tissues. Importantly, biomaterials offer the possibility to trigger temporal recruitment of specific cells and immune suppression during instigating events.

Engineering vaccines for T1D

The prevention and reversal of T1D through the induction of immune tolerance has been a long-standing goal. Conventional prophylactic and therapeutic immune-stimulatory vaccines generate robust adaptive immune responses and understanding their features can inform the fabrication of T1D tolerogenic vaccines. Conventional vaccines generally contain antigen(s) (for example, live or attenuated whole pathogens or an antigenic subunit thereof) and an adjuvant (an agent that serves to augment the immune response²⁸). The response to vaccines involves several key immune populations. First, the delivered antigen(s) is endocytosed and processed by antigen presenting cells (APCs), which degrade the antigen into peptides of suitable length to present it in high amounts via surface major histocompatibility complexes (MHCs). T-cells recognize antigenic peptide-MHC via antigen-specific T-cell receptors (TCR). The MHC-TCR interaction is referred to as signal 1 of T-cell activation²⁹. In the absence of further APC co-stimulation (known as signal 2), T-cells do not become fully activated and instead undergo clonal deletion or anergy²⁹. Therefore, a conventional vaccine must also promote robust APC activation through upregulation of co-stimulatory molecules (for example, cluster of differentiation (CD)80, CD86, and CD40). These signal 2 co-stimulatory molecules on APCs are recognized by complementary T-cell receptors (for example, CD28, cytotoxic T-lymphocyte-associated protein (CTLA)4, and CD40L). Effective vaccines further provide soluble cues (collectively known as signal 3), which is typically achieved by promoting endogenous immune cell secretion of inflammatory cytokines (for example, interleukin (IL)-12, IL-6, and IL-4). Altogether, these three signals activate and shape a highly aggressive, but specific, adaptive immune response to the delivered antigen³⁰.

In contrast to conventional vaccines, negative or tolerogenic vaccines seek to instigate alternative forms of signals 1, 2 and 3 that result in the suppression or non-activation of immune cells. Such negative vaccines are used in allergy immunotherapy³¹ and are typically comprised of only antigen, delivered in the absence of stimulatory signals or adjuvant. To reduce adverse events associated with antigen delivery (for example, IgE-mediated hypersensitivity) and to improve efficacy, customized peptides are typically used³². For example, it has been shown in pre-clinical and clinical trials for multiple sclerosis that a custom designed soluble peptide mimicking naturally-processed disease-relevant

autoantigen epitopes can directly bind to MHC molecules on immature dendritic cells and effectively dampen Th1 and Th2 immune responses without inducing autoimmune complications^{33,34}. Several clinical trials have also explored this approach for T1D by administering T1D-specific autoantigens, such as insulin and glutamic acid decarboxylase (GAD). Unfortunately, despite trying multiple autoantigen candidates and routes of administration (for example, oral, intranasal, subcutaneous, and intravenous), minimal impact has been reported³⁵⁻³⁸. The potential efficacy of a synthetic immunodominant proinsulin peptide, which binds the T1D HLA risk allele DR4(*DRB1*0401*), has renewed optimism for this approach³⁹. Similarly, reports suggesting that autoreactive T-cells recognize epitopes of neo-autoantigens, such as hybrid insulin peptides and post-translationally modified peptides, have revitalized interest for antigen immunotherapy⁴⁰⁻⁴³.

The efficacy of negative vaccines can be further improved using biomaterial platforms. Biomaterials can serve as antigen-delivery depots and/or adjuvants and provide elements of controlled release and particulate delivery to recruit and program APCs, which subsequently migrate to local draining lymph nodes and stimulate T-cell responses. The physical form of biomaterials plays a role in inflammatory responses and antigen delivery, indicating that geometry and length scale can direct immune responses³⁰. Commonly employed material configurations include nanoparticles, microparticles, and bulk biomaterials (for example, hydrogels and scaffolds), which can directly deliver antigen and impact the nature of the immune response (FIG. 1). Depending on the cellular targets and site of administration, polymers, ceramics, emulsions, and lipid-based materials and interfaces can be used for delivery of antigen to APCs, controlled release, and incorporation of immunomodulatory agents.

To induce tolerance in T1D, biomaterials can deliver tolerogenic agents and/or antigen and serve as artificial antigen-presenting cells. They can further be designed to target specific cells and tissues (TABLE 1).

Nano- and microparticles for tolerogenic T1D vaccines

Nano- and microparticles are commonly used as mobile targeting agents owing to their capacity to directly deliver agents to distinct locations within tissues and/or cells⁴⁵. The route of administration and size of the particles play an important role in the localization and kinetics of particle trafficking⁴⁶. For example, ultra-small nanoparticles (diameter ~25 nm) drain directly into the lymphatics through interstitial flow following intradermal administration^{47, 48}. Conversely, larger nanoparticles (diameter ~100 nm) are less efficient at entering the lymphatics from the subcutaneous space and typically require APC phagocytosis and trafficking for migration to the lymph nodes; however, rapid drainage of larger particles (diameter of 1 µm) has been reported⁴⁹. Intravenous administration of nanoparticles is an efficient way to target circulating leukocytes or to facilitate localization within specific organs. Size can further enhance this effect; 50–100 nm nanoparticles localize more in the spleen and liver than smaller (that is, 15 nm) nanoparticles, which are mainly retained in the kidneys and lungs⁴⁶.

Nano- and microparticles can also target specific immune cell populations. Professional APCs with phagocytic capability (that is, macrophages and dendritic cells) are primary

targets for particle-based vaccines owing to their pivotal roles in modulating adaptive immune responses⁵⁰. Immunomodulatory factors or antigen can be intracellularly delivered to APCs by tailoring the particle size. Particles $\sim 5 \mu\text{m}$ in diameter are efficiently taken up by phagocytic APCs without the need for receptor-mediated endocytosis (that is, without surface modifications with targeting ligands)⁵¹. Alternatively, ligands can be conjugated to the particle surface, such as α -CD11c, α -CD205 and α -CD40^{52,53}, to enhance uptake by dendritic cells. Functionalization with ligands for receptor targeting has been reported to be more impactful for nano- than microparticles phagocytosis⁵⁴. This phenomenon may be due to the difference in cellular endocytosis of nanoparticles, with ligand binding shifting it from slow macropinocytosis to a more efficient uptake mechanism. Alternatively, particles can be functionalized to target non-phagocytic immune cells, for example, the conjugation of α -CD4 or α -CD8 to target T-cells⁵⁵. When targeting non-phagocytes, off-target phagocytic or endocytic uptake of nano- and microparticles works against the intended delivery, particle functionalization with inhibitory molecules, such as CD47 ('don't eat me' signal) and/or CD200, can be added^{56,57}.

In addition to size and surface features, degradation and encapsulation properties of the particle material can be tailored for specific applications. Biostable and solid nano- and microparticles, such as gold or iron oxide particles, enable stable surface presentation and targeting. Alternatively, alginate, PEG or PLGA can be leveraged for soluble drug delivery (TABLE 1); PLGA further provides degradability. Of note, specific combinations of biomaterial design parameters trigger distinct effects.

Delivery of particles—⁵⁸Nano- and microparticles delivering general immunosuppression to targeted locations can provide a viable treatment strategy, as endogenous self-antigen presentation may synergize with targeted suppression. Delivery of only nano- or microparticles can influence leukocyte phenotype (FIG. 1a). For example, negatively charged, unloaded polymeric nanoparticles, administered intravenously, provide immunosuppressive effects, resulting in the amelioration of inflammatory diseases, for example, in autoimmune mouse models of multiple sclerosis and colitis⁵⁹. Uptake of these inert nanoparticles by inflammatory monocytes via the scavenger receptor macrophage receptor with collagenous structure (MARCO) triggers migration of monocytes to the spleen, where they undergo apoptosis⁵⁹. Material properties of nano- and microparticles can also modulate immune cells. For example, degradation byproducts of PLGA can induce a suppressive phenotype in dendritic cells, with downregulation of the stimulatory molecules MHC-II, CD80 and CD86⁶⁰. If administration of a simple, material-only formulation can be proven effective, this strategy is expected to have a high safety profile.

Delivery of tolerogenic agents—Nano- and microparticles can also directly diminish aberrant inflammation by delivering immunomodulatory genetic material to targeted inflammatory leukocytes (FIG. 1a). For example, the delivery of anti-sense oligonucleotides targeting the primary transcripts of APC co-factors CD40, CD80 and CD86 can be used to suppress dendritic cell activation⁶¹⁻⁶⁴. While the infusion of autologous dendritic cells treated with these anti-sense nucleotides ex vivo can significantly delay T1D incidence in non-obese diabetic (NOD) mice (BOX 2)⁶², phase I clinical trials using these treated

dendritic cell infusions did not detect changes in the immunological profile of T1D patients or impact circulating c-peptide (the connecting polypeptide cleaved from proinsulin upon enzymatic conversion to insulin in beta cells)^{61,65}. Encapsulating these same anti-sense oligonucleotides in microparticles and injected them subcutaneously is an alternative approach^{61,63,64}. Dendritic cells that phagocytose these subcutaneously delivered particles adopt a suppressive phenotype and downregulate the expression of T-cell activating molecules, which leads to reversion of hyperglycemia in a subset of NOD mice^{63,64}. Therefore, the incorporation of genetic material in nano- and microparticles can avoid the need for ex vivo cell manipulation, decrease drug dosage, and address safety concerns typically associated with engineered viral vectors and cell culture⁶⁶.

Although not yet applied for T1D, polymeric nano- and microparticle approaches can be designed to generally augment Treg induction and/or survival. For example, PLGA nanoparticles can be functionalized with α -CD4 for T-cell targeting and loaded with soluble IL-2, a T-cell supporting cytokine, and TGF- β 1, a Treg promoting agent⁵⁵. In vitro, interactions between the nanoparticles and T-cells are substantially improved by the addition of α -CD4, and intraperitoneal injection leads to doubling of the number of splenic Tregs, compared to untreated naïve mice. Similarly, PLGA microparticles can be applied for local immunomodulation, for example, by delivering a cocktail of rapamycin, TGF- β 1 and IL-2, to modulate the activation and regulatory function of T-cells⁶⁷. In vitro, this combination of agents leads to an increase in the expansion of human and murine Tregs, compared to single agent treatments. In a mouse model of allergic contact dermatitis, the multi-factor tolerogenic PLGA microparticles promote antigen-specific Treg expansion and prevent an allergic response following allergen challenge, if administered adjacent to the site of cutaneous sensitization⁶⁸. As systemic administration of TGF- β 1 is generally not pursued in the clinic owing to its significant fibrosis-inducing effects²², targeted and/or local delivery of TGF- β 1 is preferred for Treg induction.

Alternative to inducing Treg differentiation, pre-existing natural T regulatory cells (nTregs) can be recruited through controlled drug release from biomaterials. For example, sustained release of the chemokine CCL22 from PLGA microparticles leads to recruitment of nTregs to the administration site⁶⁹. In murine models of immune inflammation in periodontal⁷⁰⁻⁷² and dry eye disease⁷³, administration of CCL22 microparticles causes an increase in Tregs recruitment and a decrease in the number of effector T-cells in the diseased tissues. However, a potential drawback of this system is the lack of specificity of CCL22. Its corresponding receptor CCR4 is an important chemotactic receptor on Tregs, but is also expressed on effector T-cells. Thus, concerns remain whether pleiotropic effects of administered factors may negatively influence systemic immunity.

Delivery of autoantigen—Antigen-specific tolerogenic T1D vaccines differ from general immunosuppression approaches in that they seek acceptance of autoantigens by deletion and/or conversion of antigen-reactive immune cell subsets. Clinical trials testing the delivery of T1D-specific autoantigen(s) have often resulted in disappointing outcomes⁹. However, prolonged antigen persistence may be associated not only with expansion of memory CD8⁺ T-cells, but also with the induction of immune tolerance through T-cell anergy, effector T-cell exhaustion, and Treg conversion^{74,75}. Therefore, a biomaterial providing controlled

autoantigen release could be used to modulate the duration, magnitude and localization of autoantigen delivery and thus, to induce immune tolerance (FIG. 1c).

Applying the wealth of knowledge gained from the combination of biomaterial systems with metabolically active insulin for improved glucose control⁷⁶, particle platforms could be designed for the sustained release of T1D autoantigens to generate long-lasting antigen-specific tolerance. Moreover, nano- or microparticle delivery can modulate antigen processing and presentation by APCs⁷⁷. According to traditional immunological paradigms, antigen taken up by endocytosis is processed and presented on MHC-II molecules to CD4⁺ T-cells. By contrast, antigen within endocytosed particles can transfer to the cytosome for cross-presentation⁷⁸ on MHC-I molecules and present to CD8⁺ T-cells^{78,79}. As T1D is mediated by CD8⁺ T-cell pathology (BOX 1), autoantigen delivery and release by nano- or microparticles may increase treatment efficacy by promoting CD8⁺ T-cell specific immunomodulation. For example, the intravenous delivery of peptide antigen-coupled or antigen-encapsulating PLGA nanoparticles can re-educate immunity towards a tolerant state, in an antigen-specific manner, and prevent diabetes in multiple defined antigen transgenic T1D mouse models (BOX 2)⁸⁰. In this study, NOD SCID mice first received the adoptive transfer of CD4⁺ BDC2.5 (chromogranin A (ChgA)-specific) or CD8⁺ NY8.3 (islet-specific glucose-6-phosphatase catalytic subunit-related protein; islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP)-specific) diabetogenic T-cells, followed by systemic administration of PLGA nanoparticles carrying the cognate peptide. In the CD4⁺T-cell T1D model, administration of the nanoparticles leads to an increase in the number of intra-islet Tregs compared to mice treated with PLGA nanoparticles carrying an irrelevant antigen, while studies using the CD8⁺ T-cell T1D model found these particles to inhibit CD8⁺ NY8.3 T cell-mediated beta-cell destruction. Mechanistic studies attributed impacts to the immunosuppressive T-cell surface markers programmed cell death protein (PD)-1 and CTLA-4^{80,81}. Delivering antigen with PLGA nanoparticles is an attractive strategy from a safety standpoint, because traditional immunomodulatory agents are not needed. However, systemic administration is a concern and it remains to be seen if this approach is also effective in the poly-antigenic NOD mouse model (BOX 2).

To generate a more comprehensive coverage against autoantigens, multiple autoantigens can be delivered. Although not yet explored for T1D, antigen-specific tolerance in a murine model of multiple sclerosis can be generated by delivering antigen cross-linked to apoptotic leukocytes using ethylene carbodiimide, which leverages apoptotic self-tolerance promoting clearance pathways⁸². Following extensive pre-clinical efforts⁸³, seven myelin peptides coupled to isolated autologous human PBMCs intravenously reinfused in a dose-escalation⁸⁴ clinical trial found the expanded antigen repertoire protects against epitope spreading with a favorable safety profile⁸⁴. Furthermore, patients who received a high-dose treatment (>1 x 10⁹ cells) show a decrease in antigen-specific T-cell proliferation upon ex vivo re-stimulation compared their pre-treatment levels. The engineered autologous leukocytes can be replaced by polystyrene or PLGA nanoparticles, and in a mouse model of multiple sclerosis, delivery of nanoparticles crosslinked with myelin peptides resulted in significant mitigation of disease-induced physical impairment, compared to the placebo control group⁸⁵. This therapeutic effect is partly achieved through nanoparticle uptake by marginal zone macrophages that express the scavenger receptor MARCO. This approach, in which

apoptotic debris clearance is upregulated, is similar to particle-based strategies that promote tolerance which also engaged the MARCO scavenger receptor.

Similarly, biomimetic erythrocyte-mediated apoptotic cell clearance can be applied in a murine T1D model⁸⁶ by linking antigenic peptides to the erythrocyte-binding antibody fragment TER119, which promotes antigen processing by apoptotic clearance mechanisms. In contrast to free peptide antigen, erythrocyte-bound antigenic peptide is taken up by dendritic cell subsets in the spleen and hepatic stellate cells in the liver, leading to deletion of antigen-defined T-cells. In an accelerated autoimmune diabetes mouse model, which is established by the adoptive transfer of diabetogenic transgenic BDC2.5 CD4⁺ T-cells into NOD mice (BOX 2), prophylactic administration of the p31 peptide (a chromogranin A (ChgA) mimotope specific for the BDC2.5 T-cell receptor) fused to TER119 completely prevented onset of diabetes⁸⁶ (TABLE 1). Interestingly, mechanistic studies using single antigen model murine systems indicates that the checkpoint markers PD-1/PD-L1, but not CTLA-4/CD28, are crucial for antigen-specific T-cell deletion and/or anergy⁸⁷. Additionally, antigen-specific Treg expansion increases in response to administration of the erythrocyte-antigen complex, but not in response to soluble antigen. A potential regulatory advantage of this approach is the simplicity of formulation, and efficacy in the NOD mouse model would further support the case for translation to T1D treatment.

Targeted antigen delivery can induce immune tolerance and biomaterials can be used to improve efficacy of antigens. However, antigen delivery alone is likely insufficient to overcome the robust autoimmunity and chronic inflammation associated with T1D.

Co-delivery of tolerogenic agents and autoantigen—Administration of tolerogenic agents without the context of antigen may lead to non-specific immunosuppression, and delivery of only antigen may be ineffective in managing a poly-antigen heterogeneous disease such as T1D. Therefore, tolerogenic agents and autoantigen can be co-delivered to re-establish immune tolerance in T1D (FIG 1b). For example, the ligand 2-(1'-H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE), which⁸⁸⁻⁹⁰ induces a tolerogenic phenotype in dendritic cells via activation of its aryl hydrocarbon receptor⁸⁹, and the beta cell antigen proinsulin were absorbed to the surface of gold nanoparticles⁹⁰. In a prophylactic study, weekly intraperitoneal injections these ITE and proinsulin functionalized gold nanoparticles prevented T1D onset in more than 70% of treated pre-diabetic NOD mice⁹⁰, attributed to an increase in Foxp3 gene expression and suppression of Th1 and Th17 gene signatures in the pancreatic lymph nodes. Administration of nanoparticles also causes the generation of anti-inflammatory dendritic cells, characterized by reduced expression of the co-stimulatory molecules CD40, CD80 and MHC-II, and the inflammatory cytokines IL-12 and IL-6⁹⁰, compared to pro-inflammatory dendritic cells⁹⁰. The fact that T-cells and dendritic cells become tolerant can be expected, given the reciprocity between innate and adaptive immunity. As various immune culprits are involved in T1D pathogenesis, leveraging materials to modulate multiple arms of immunity towards a tolerogenic state would be advantageous for the prevention of T1D. However, clinical translation of gold nanoparticles requires careful consideration owing to safety concerns and liver toxicity⁹¹.

Antigen targeting can be combined with localized immunosuppression for the modulation of specific immune responses. For example, a PEGylated PLGA nanoparticle delivering the potent immunosuppressive agent rapamycin and myelin-sheath antigen ameliorated hind-limb paralysis in a murine model of multiple sclerosis, when compared to nanoparticle only or rapamycin-only controls⁹². Interestingly, nanoparticle-mediated delivery mitigates disease when administered intravenously or subcutaneously, highlighting the lymphatic localization of administered nanoparticles⁹². This combinatorial nanoparticle platform can also be applied to modulate humoral immunity. In a model of allergic hypersensitivity, wherein mice receive repeated immunization with ovalbumin peptide, a single prophylactic injection of nanoparticles delivering rapamycin and ovalbumin peptide protects mice from anaphylaxis upon antigen challenge⁹². Similarly, mice with hemophilia A, which lack the crucial blood-clotting protein Factor VIII (FVIII) owing to autoantibody destruction, show a significant reduction in anti-FVIII antibody levels if intravenously treated with nanoparticles before or after FVIII sensitization⁹², compared to mice receiving anti-FVIII antibody and empty nanoparticles⁹². Co-administration of free antigen and rapamycin-nanoparticles further prevents the production of anti-drug antibodies in a murine model.⁹³ Translating to non-human primate models, the monkey that received an intravenous injection of rapamycin-nanoparticles and pegsiticase – a PEGylated uricase enzyme used to remove deposits of uric acid in gout – exhibited a decrease in the anti-drug antibody response compared to a pegsiticase-only control animal⁹³. The capacity of this nanoparticle system to induce suppression in models of both humoral and cellular immunity suggests a potent and versatile tolerogenic vaccine and thus, translation to T1D would be of interest. Importantly, modification of the nanoparticle vaccine (that is, substitution of tolerogenic drug, change of nanoparticle size, or conjugation with targeting ligands to target specific immune cells) was not required to demonstrate efficacy in humoral and cellular tolerance, simplifying clinical translatability. Moreover, the co-delivery of soluble antigen, rather than via nanoparticle-bound antigen, eliminates the need for disease-targeted nanoparticle fabrication protocols.

Microparticles containing rapamycin and an antigen capable of preventing disease in an experimental autoimmune encephalomyelitis (EAE) mouse model of multiple sclerosis⁹⁴, can also be applied to T1D⁹⁵. Rapamycin and peptide P31 are encapsulated within microparticles (diameter of ~0.7 μ m) fabricated from acetalated dextran, an acid-sensitive polymer with pH-neutral degradation products of dextran, acetone, and ethanol. The subcutaneous administration of these immunomodulatory particles into a single antigen T1D model (adoptive transfer of BDC2.5 CD4⁺ T-cells into NOD SCID mice, BOX 2) prevents diabetes onset⁹⁵. Ex vivo analysis of the adoptively transferred CD4⁺ T-cells treated with rapamycin and P31 particles shows a decrease in their proliferative capacity and an increase in their ratio of FoxP3⁺ to interferon (IFN) γ ⁺ cells, compared to rapamycin-only or rapamycin with irrelevant antigen controls. In vitro analysis of dendritic cells cultured with the microparticles reveals that dendritic cells adopt an immature phenotype, resulting in reduced CD4⁺ T-cell proliferation and increased expression of inflammatory cytokines and inhibitory PD-1 expression, compared to cells cultured with particle-only controls. Therefore, polymeric biomaterials can be used for the targeted co-delivery of antigen and a powerful immunosuppressant for autoimmune disease treatment. Co-encapsulation of

factors into a single particle formulation potentially presents regulatory and quality control advantages, but efficacy in the NOD mouse model needs to be shown.

Microparticles of different size encapsulating distinct factors can serve as a multipronged platform to target and modulate specific immune cell subsets (Fig 1b)⁷⁷. For example, encapsulation of a dendritic cell chemokine, multiple pro-tolerogenic factors, and a T1D-antigen into distinct microparticles and subsequent administration in NOD mice⁹⁶ prevents diabetes onset⁹⁶. To enable cellular targeting and partitioning, two differently sized PLGA microparticles can be used. Large, non-phagocytosable microparticles (~30 µm in diameter) can deliver granulocyte-macrophage colony-stimulating factor (GM-CSF, a DC chemokine and supporting factor) and TGF-β1 to the subcutaneous injection site. The generation of this local tolerogenic microenvironment results in dendritic cell recruitment and the induction of immunosuppressive phenotypes. Simultaneously delivered small microparticles (~1 µm in diameter) containing the T1D-specific autoantigen insulin B₉₋₂₃ and vitamin D₃, a pro-tolerogenic agent, are phagocytosed by the recruited dendritic cells. Two subcutaneous injections of the combinatorial microparticle system could prevent T1D onset in 40% of treated pre-diabetic NOD mice⁹⁶, whereas subcutaneous administration of individual microparticle formulations did not prevent diabetes onset as effectively; highlighting the requirement for antigens and multiple factors to achieve full therapeutic efficacy. Importantly, tailoring the size of microparticles allows targeting of specific cellular sites; for example, loading vitamin D₃, a membrane-permeable molecule, into small, phagocytosable microparticles enables delivery to its cognate receptor, which is located in the cytoplasm⁹⁷. Conversely, release of GM-CSF and TGF-β1 into the extracellular space promotes their ligation to surface receptors on dendritic cells. This approach can also be applied to other autoimmune diseases, for example by substituting insulin B₉₋₂₃ with the myelin peptide to mitigate autoimmune responses in a mouse model of multiple sclerosis⁹⁸.

The use of multiple tolerogenic drugs is also an attractive idea for T1D immunotherapy⁹⁹, because multiple drugs modulating different arms of the immune system can act synergistically and thus, more robustly mitigate disease than single agent treatments. However, multi-component approaches will require more complex regulatory, manufacturing, quality control, and assurance procedures than single-component drugs.

Tolerogenic artificial antigen presenting cells—Nano- and microparticles can be designed to deliver antigen presented on MHC molecules to promote efficient antigen presentation, improve specificity, and induce a suppressive T-cell phenotype (FIG. 1d). Such tolerogenic artificial APCs can be used to target antigen-specific effector T-cells to ensure that systemic immune activity is kept intact. For example, iron oxide nanoparticles can be decorated with a T1D-specific peptide bound to MHC molecules to engage cognate T-cell receptors (TABLE 1). Treatment of NOD mice with these nanoparticles, without any supporting co-stimulatory ligands, can inhibit the onset of diabetic symptoms through interaction of the particles with autoreactive T-cells^{100,101}. In one iteration of this approach, the administration of nanoparticles functionalized with MHC class I molecules bound to the IGRP₂₀₆₋₂₁₄ mimotope NRP-V7 can prevent and reverse T1D in NOD mice¹⁰⁰. Interestingly, nanoparticle administration leads to an expansion in the number of circulating and intra-islet low-avidity cognate CD8⁺ T-cells (BOX 1), rather than their deletion.

However, the total number of non-cognate CD8⁺ clones within the pancreatic islets is reduced compared to mice that did not receive the MHC-peptide nanoparticles. It has further been suggested that the expanded CD8⁺ T-cells have immunoregulatory properties and are capable of suppressing proliferation of other CD8⁺ T-cells in response to peptide-pulsed dendritic cells through IFN- γ and indoleamine 2,3-dioxygenase (IDO) signaling. CD8⁺ T-cells directly block antigen presentation by killing APCs through perforin release. Iron oxide nanoparticles coated with MHC class II molecules and the islet-specific peptide IGRP (IGRP_{4–22} or IGRP_{128–145}) can be administered to generate regulatory CD4⁺ T-cells¹⁰¹ (BOX 1). Over 90% of NOD mice treated two times weekly with an intravenous infusion of these nanoparticles show euglycemia restoration owing to the expansion of immunosuppressive type 1 regulatory cells (T_R1) cells, classified by CD49b, lymphocyte-activation gene -3, CD278, and TGF- β expression¹⁰². Importantly, no immunosuppressive effects were observed in mice treated with soluble T1D-specific peptide or with nanoparticles functionalized with peptide not bound to MHC class II or nanoparticles conjugated with an irrelevant peptide bound to MHC-II, indicating design specificity. This nanoparticle platform also shows robust therapeutic efficacy in various other autoimmune models¹⁰¹. However, clinical application of MHC-bound autoantigen(s) requires HLA matching and needs further validation owing to the potential risk of exacerbating autoimmunity.

More complex artificial APCs can be designed by conjugating additional ligands to the surface of nano- or microparticles. For example, artificial APCs composed of latex beads coated with peptide-loaded HLA molecules and apoptosis-inducing alpha-first apoptosis signal (Fas) monoclonal antibodies can cause the depletion of autoreactive T-cells in vitro^{103, 104}. This approach has not yet been explored for T1D, but has the potential to be applied to kill multiple types of antigen-specific human T-cells in vitro¹⁰⁴. Similarly, direct conjugation of cytotoxic agents can be used to specifically delete autoreactive T-cells in T1D. For example, toxin-coupled tetrameric peptide-MHC complexes can be administered to target cognate T-cell receptors and eliminate autoreactive T-cells in NOD mice¹⁰⁵. These MHC class I tetramers were loaded with the NRP-V7, which is recognized by a high percentage of islet-reactive CD8⁺ T-cells, and coupled by the ribosomal toxin saporin. Administration of the complexes into 8-week old NOD mice leads to antigen-specific ablation of NRP-V7-reactive CD8⁺ T-cells and mitigation of diabetes incidence after 50 weeks¹⁰⁵. Translation of this approach to a nano-or microparticle platforms to enable ligand multimerization has the potential to substantially improve treatment.

Alternative targeting strategies—Tailoring the injection site and particle size of the particle can further fine-tune biomaterial-mediated drug delivery to maximize co-localization of immunomodulatory drugs and immune cells. Comparing intranodal (into the lymph node) and intramuscular injection of an antigen-specific PLGA-based vaccine¹⁰⁶ finds increased particle retention in lymph nodes after intranodal injection than after intramuscular injection¹⁰⁶. Furthermore, uptake of intranodally injected nanoparticles (diameter = 300 nm, but not microparticles (diameter = 5 μ m), is 8-, 10-, and 13-fold higher in dendritic cells, macrophages and B cells, respectively, compared to intramuscular injection. Interestingly, a single intranodal injection of adjuvant poly(I:C) microparticles and

soluble ovalbumin antigen increases the number of antigen-specific CD8⁺ T-cells by over 8-fold compared to intramuscular administration. This phenomenon can be attributed to the sustained release of activating poly(I:C) in the local lymph node. Applied to a disease model, the intranodal injection of a PLGA-based vaccine comprised of the immunosuppressive drug rapamycin and a myelin sheath antigen¹⁰⁷ prevents and reverses disease in a mouse model of multiple sclerosis at higher efficacy than an intramuscular injection¹⁰⁷. While this targeted injection site may elevate efficacy, concerns remain that the physical disruption of the lymph node could induce the release of damage associated molecular pattern molecules (DAMPs), which can interfere with tolerance induction.

A different noteworthy targeting strategy exploits natural lymphatic drainage patterns by designing an 'albumin-hitchhiking' vaccine composed of antigen or adjuvant cargo linked to an albumin-binding lipophilic tail¹⁰⁸. Subcutaneous administration of this vaccine results in an 8-fold increase in lymph node accumulation of the adjuvant construct, compared to free adjuvant. This approach was used to deliver a TLR9 adjuvant to induce anti-tumour immunity; however, a similar strategy could also be employed for T1D using pro-tolerogenic adjuvants and/or T1D-specific autoantigen. Similarly, biomaterial-based strategies could be combined with immunomodulatory approaches that have demonstrated promise in immunotherapy; for example, lentiviral-mediated gene transfer of islet-specific T-cell receptors into human polyclonal Tregs¹⁰⁹, or chimeric antigen receptor (CAR) Treg cell therapy¹¹⁰. However, the complexity of CAR-T cell generation and isolation, large-scale manufacturing limitations, and exorbitant costs limits the translation of CAR T-cell therapy for autoimmune diseases thus far. Biomaterials may be used to overcome these challenges, enabling biomaterial-based delivery of CAR genes in vivo. For example, polymeric DNA-carrying nanoparticles can be intravenously injected to transfect T-cell nuclei with leukemia-targeting CAR genes in situ, eliminating the need for leukapheresis and ex vivo cell handling¹¹¹. This approach could also be applied to generate and expand antigen-specific Tregs for the treatment of T1D.

Finally, immunomodulatory monoclonal antibody approaches can be used to modulate and/or delete specific immune populations, an approach examined in multiple clinical trials for T1D, for example, anti-CD20 (B-cell depletion) and anti-CD3 (T-cell depletion)^{112,113}. Similarly, clinical administration of an Fc receptor protein fused to CTLA-4 (which inhibits the interaction of APCs with T-cells) decreases disease progression, resulting in greater preservation of insulin production in treated patients, compared to a placebo control group, in the course of two years¹¹⁴. However, in these monoclonal antibody immunotherapy trials, metabolic benefit, such as insulin independence, is not maintained¹¹⁵. Additionally, systemic immunosuppression leaves patients at risk for opportunistic infections, cancer, and adverse reactions. Alternatively, controlled-release of suppressive antibodies or surface presentation of suppressive molecules (for example, PD-L1 or immunoglobulin-like transcript 3 (ILT3)) within local tissues may localize inhibitory effects and target autoreactive effector cells.

Bulk material approaches

Bulk biomaterials, typically in the form of scaffolds and gels, can be loaded with antigen and/or tolerogenic agents. Compared to particle-mediated delivery, bulk materials are

retained at the injection site, providing a higher and more localized concentration of immunomodulatory agents and a higher drug loading capability. Moreover, most nano- and microparticles fabrication protocols require organic solvent and intense agitation for the generation of discrete particles, potentially inhibiting the incorporation of fragile biomolecules, such as DNA or enzymes. By contrast, hydrogels can be crosslinked at gentle conditions, for example, using Michael addition, copper-free click reaction, or Staudinger reactions, which preserves agent bioactivity¹¹⁶. Porous scaffolds can be tailored to allow leukocyte infiltration, while the local delivery of immunomodulatory agents can induce suppressive phenotypes of recruited cells for in situ programming. Polarized cells can then traffic to treatment sites or proximal lymph nodes to exert their function (FIG. 1e). In situ immunomodulation by biomaterial implants is desirable if the aim is to generate a clearly-defined area of immunomodulation in peripheral tissue. Additionally, the implantation site can be chosen to be upstream of disease-specific draining lymph nodes, which is an area rich in autoantigen, to augment immunomodulation.

Biomaterial implants as vaccine strategies have mainly been applied for cancer immunomodulation. For example, a macroporous PLGA scaffold can be loaded with the dendritic cell-recruiting chemokine GM-CSF, the TLR9-activating signal CpG (oligodeoxynucleotides) and a tumour-specific antigen to program recruited immune cells in situ, resulting in a robust cytotoxic T-cell response in an established melanoma mouse model¹¹⁷; a modified version is currently in a phase I clinical trial for stage IV melanoma¹¹⁸. Similarly, an implantable alginate scaffold can serve as a multi-functional construct for the delivery and modulation of engrafted tumour-specific T-cells¹¹⁹. The scaffold contains silica microparticles for the sustained release of an IL-15 superagonist, which provides a survival signal to improve adoptive cellular transfer, and surface-bound stimulatory ligands to stimulate in situ T-cell proliferation. Moreover, alginate can be functionalized with adhesive ligands to promote T-cell migration out of the implant¹¹⁹.

Immune tolerance

Bulk materials can be employed to induce immune tolerance. For example, GM-CSF-coated gold nanoparticles and PLGA microparticles containing a peptide mimotope of chromogranin A (ChgA) can be entrapped within an alginate microgel¹²⁰. Following subcutaneous injection in NOD mice (BOX 2), antigen-specific T-cells migrate into the porous hydrogel and then to draining lymph nodes, in comparison to non-antigen loaded hydrogels. Although this hydrogel platform did not significantly prevent T1D onset in NOD mice, it caused an increase in antigen-specific Treg conversion, with 60% of ChgA-specific T-cells isolated from the hydrogel co-expressing hallmarks of Tregs. Of note, the identification and/or isolation of antigen-specific autoreactive cells in NOD mice is exceptionally challenging owing to very low cell numbers; for example, only ~1,000 autoreactive T cells could be quantified in all secondary lymphoid organs using tetramers against insulin B₁₀₋₂₃¹²¹. Thus, this hydrogel platform may also be beneficial for enriching antigen-specific T-cells for subsequent ex vivo analysis of biomarkers for T1D or for the expansion of antigen-specific Tregs.

Macroscopic peptide hydrogels can be implanted to recruit and modulate dendritic cells. For example, a RADA peptide (RADARADARADA-NH₂) hydrogel, GM-CSF, CpG, and denatured, non-metabolically active insulin (serving as the T1D autoantigen) can be co-delivered to promote antigen-specific tolerance of dendritic cells in situ for the treatment of T1D^{122, 123}. Three subcutaneous injections of the dendritic cell-targeting hydrogel in 8-week-old pre-diabetic NOD mice prevented diabetes incidence in 40% of treated mice. Notably, microparticle controls lacking insulin antigen did not exhibit similar therapeutic efficacy,, suggesting that antigen is required to mediate diabetes prevention.

Therapeutic administration of ex vivo expanded Tregs is clinically explored for the treatment of T1D^{17,18}. The purification steps to isolate human circulating Tregs can be adapted to enrich specific subsets, such as CD25⁺ and CD127^{low/-} cells; however, in most clinical trials, non-antigen specific, polyclonal Tregs have been used for adoptive cellular therapy^{17,18,124}. Antigen-specific Tregs are likely to achieve more robust, T1D-specific immune tolerance¹²⁵, but the isolation and expansion of a sufficient number of antigen-specific Tregs remains challenging. Biomaterials can be used to support the expansion of antigen-specific Tregs¹²⁶, although this approach has yet to be applied for T1D. For example, mesoporous silica micro-rods agglomerate into a scaffold upon subcutaneous injection. A liposome-coating on the micro-rods enables membrane-bound T-cell activation, can provides proliferation signals, such as anti-CD3 and anti-CD28, and sustained release of soluble factors, such as IL-2. Additionally, biotin molecules distributed throughout the liposome coating allow the addition of streptavidin-conjugated molecules, for example, to incorporate peptide-functionalized HLA molecules to augment antigen-specific primary T-cell expansion. Similar to particle-based artificial APC platforms¹²⁷, this membrane-based antigen-specific T-cell activation and expansion system is capable of delivering APC-directed signals (stimulation, co-stimulation, and cytokine support) for T-cell activation, resulting in 2- to 10-fold more activated T-cells than can be achieved with commercially available polyclonal anti-CD3/28 Dynabeads®¹²⁶. Moreover, this in vitro platform can be applied to expand mouse and human antigen-specific T-cells, and thus, can be potentially used for the expansion of Tregs.

Cell therapy and islet transplantation

Progress has been made in modulating autoimmune responses to halt beta cell destruction; however, it is unclear if such interventions can be initiated and/or clinically effective in time to preserve adequate beta cell mass to sustain normal glycemic control. Therefore, treatment of autoimmune T1D will likely have to be paired with beta cell replacement and/or restoration (BOX 3; FIG. 2). The efficacy of intrahepatic pancreatic islet transplantation in conjunction with systemic immune suppression was first described in 2000¹²⁸. Since this initial clinical islet transplantation trial, patients have been treated worldwide, with recipients exhibiting improved glycemic control, elimination of severe hypoglycemia, decreased progression of diabetic complications and transient insulin independence⁸, and thus, multiple countries have classified clinical islet transplantation as an approved and reimbursable procedure for T1D patients that meet selection criteria⁸. While the restricted availability of cadaveric islets limits this approach, stem-cell derived beta cells with glucose-responsive insulin secretion and islets from other species (for example, porcine islets)

provide alternative sources^{129,130}. . Regardless of the cell source, beta cell transplantation induces unique and potent host immune responses that eventually lead to graft failure despite the use of systemic immunosuppression (BOX 3; FIG. 2)⁸. Therefore, limiting early post-transplant inflammation and fibrotic reactions, minimizing off-target effects, and increasing the specificity of immunosuppression are key to improving clinical islet transplantation.

Local immunomodulation of islet transplants by drug delivery

Immunomodulatory drugs can be locally delivered to the transplant site to avoid side effects associated with systemic regimens and to precisely modulate host responses within the implant microenvironment. Achieving local modulation at the intrahepatic islet transplantation site is challenging, because islets infused into the hepatic vein randomly engraft into various parts of the liver. Thus, alternative extrahepatic implant sites that meet the vascular needs of the transplant with minimal surgical risk (for example, intraperitoneal, intramuscular, subcutaneous, omentum and venous sac)¹³¹ are being explored. It is feasible to infuse cells into these sites, but to control islet distribution and transplant mass, permit retrieval, support implant engraftment, and deliver immunomodulatory agents, a defined 3D islet microenvironment is needed.

Biomaterials play a pivotal role in the design of the 3D islet niche¹³². Biomaterial platforms can be designed in a way to permit host cell migration into the implant or as immunoisolation barriers (FIG. 3). Macroporous scaffolds that enable cell infiltration can be fabricated from synthetic and natural materials, such as PDMS, PLG, silk, and PEG^{26,133,134}. Immunomodulation can be provided through specific material properties, for example, by using naturally anti-inflammatory materials such as chitosan and hyaluronic acid, or by using materials that allow controlled drug delivery, such as PDMS and PLG.

Modulation of inflammatory response—Inflammation activates innate and adaptive pathways and therefore, inhibition of early inflammatory events is expected to have a substantial and positive impact on long-term islet function. Steroids, particularly glucocorticoids, are anti-inflammatory drugs, which can polarize human blood-derived monocytes towards the anti-inflammatory (M2) phenotype while retaining their migratory function (FIG 3a-d)¹³⁵. However, the dosage and duration of local steroid release must be carefully tailored to prevent overloading at the implant site. For example, local delivery of dexamethasone (Dex) within a PDMS macroporous scaffold promotes M2 macrophage polarization; however, at high Dex loadings (> 0.5% w/v), host cell infiltration is suppressed, resulting in poor implant efficacy owing to failure of graft vascularization¹³⁶. Alternatively, a modular peptide amphiphile nanofibre gel can be used to control Dex delivery through labile hydrazone linkage, resulting in potent anti-inflammatory activity¹³⁷.

Curcumin is a free radical scavenger, which can also be applied to protect islets from inflammatory responses¹³⁸. In one example, PLGA microparticles can release curcumin within re-aggregated islet spheroids¹³⁹, leading to a decrease in islet apoptosis in vitro and local curcumin delivery in vivo. Similarly, other biomaterial platforms, for example peptide hydrogels¹⁴⁰, cellulose nanofibers¹⁴¹, hyaluronate¹⁴², and mesoporous composite scaffolds¹⁴³, could be used.

Anti-inflammatory agents currently used in clinical islet transplantation regimens provide additional candidates for biomaterial-based release. Although not yet applied for islet transplantation, examples of controlled release platforms incorporating these agents include anti-TNF α released from chitosan, hyaluronic acid or PEG–PCL composites^{144–146}, and IL-1Ra released from pluronic-based gels, elastin-like polypeptides or co-polymer particles^{147,148}. Other candidates that have exhibited anti-coagulation effects on islet in vitro include and thus could be explored for biomaterial-based delivery in vivo include , the thrombin inhibitor Melagatran¹⁴⁹, anti-coagulant enzyme activated protein C¹⁵⁰, low molecular weight dextran sulfate¹⁵¹, C5a-inhibitory peptide¹⁵², Withaferin A and other nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) inhibitors^{153,154}, as well as reparixin (an CXCL1/2 inhibitor)¹⁵⁵.an,. Finally, anticoagulant materials, such as heparin-conjugated silk fibroin¹⁵⁶, and anti-complement surfaces, such as factor H, a serum protein, modified surfaces¹⁵⁷, can provide anti-inflammatory materials within the islet microenvironment. While impactful, anti-inflammatory approaches will need to be paired with more potent immunomodulatory approaches to permit long-term beta cell Survival. 144–146147,148

Suppression of allo- and autograft rejection—Direct antigen recognition is a powerful and efficient way to clear foreign cells, but requires direct cell–cell contact at the transplant site to impart its effect (BOX 3). Contrarily, indirect allograft rejection is mediated by interactions of the alloprimed host APCs with host T- and B-cells in the draining lymph nodes, resulting in the migration of activated T-cells to the graft site. Multiple pathways and cells are involved in graft rejection and therefore, material-based approaches to prevent rejection need to be multifaceted. Key targets include inhibition of host APC activation, alloreactive T-cell migration, and alloreactive T-cell activation, as well as the induction of graft tolerance (FIG. 3).

Host APCs initiate indirect allograft rejection and thus, suppression of APC maturation is a promising approach for effective immunomodulation (FIG 3e). In islet transplantation, antigen specificity can be imparted by the foreign islets. Once the antigen(s) are processed by dendritic cells, dendritic cell-tolerizing microparticles or scaffolds can be applied to promote regulatory dendritic cell responses. For example, the immunomodulatory properties of PLGA can be used to deliver cell lysate from BALB/c mice into C57BL/6J mice as a means to generate tolerance toward this allogeneic strain prior to the transplantation of BALB/c islets¹⁵⁸. In this approach, long-term transplant survival of the BALB/c islets was modest, with 80% graft rejection in treated animals; however, the addition of a three-day regimen of systemic rapamycin treatment improved graft survival to 60%.

Following T-cell activation in the lymph node, effector T-cells migrate to the antigen-bearing graft through chemotaxis. To inhibit T-cell migration, immunomodulatory reagents can be designed to sequester T-cells in lymph nodes (FIG 3f). For example, fingolimod (FTY-720) is a sphingosine-1-phosphate analogue that suppresses T-cell egression by binding to sphingosine-1-phosphate receptors on effector T-cells. Systemic delivery of FTY-720 inhibits autoimmune diabetes development and allograft rejection in rodent models¹⁵⁹. FTY-720 can also be locally delivered via biomaterials. For example, the implantation of islets within macroporous PDMS scaffolds loaded with FTY-720 shows a dose dependent

effect: high doses (1-5% w/v) impair implant engraftment, whereas lower dosages (0.1-0.5% w/v) increase T-cell infiltration¹⁶⁰. FTY-720 delivery using poly(3-hydroxybutyrate-co-3-hydroxyvalerate (PHBV)/PCL nanofibers also show negative impacts of local FTY-720 delivery on islet viability and function¹⁶¹, which can be addressed by delaying islet implantation until local drug release rates are minimized¹⁶¹. Of note, this problem was not observed for systemic FTY-720 delivery^{160,162}, indicating that the route of delivery impacts its islet toxicity. Coupling FTY-720 with chemotactic stromal derived ¹⁶²factor-1 α (SDF-1 α /CXCL12) can mitigate these negative impacts by the recruitment of wound-resolving macrophages¹⁶³, but this has not yet been tested in islet transplants.
^{160,161}Material-based intranodal drug delivery or sphingosine-1-phosphate analogues with better receptor selectivity, such as KRP203¹⁶⁴, could be investigated to overcome this challenge.

To selectively interrupt effector functions, co-stimulatory signals can be blocked or inherent inhibitory pathways can be leveraged (FIG 3g). The most important co-stimulatory signal for T-cells is full complexation of their CD28 receptor with CD80/CD86, which leads to robust T-cell activation and expansion¹⁶⁵. CTLA4-Ig can block this activation pathway¹⁶⁶; however, systemic delivery of this agent may impart broad T-cell suppression and disrupt regulatory T-cell function¹⁶⁷. To avoid this effect, the receptor Fc fusion protein CTLA-4-Ig can be bioprinted on acellular dermal scaffolds¹⁶⁸. Local CTLA-4-Ig delivery demonstrated substantial, albeit incomplete, protection in a chemically-induced diabetes murine allogeneic transplant model, showing an increase in the concentration of local tolerogenic cytokines and Treg numbers in the draining lymph nodes. Alternatively, FK506 (tacrolimus), a potent immunosuppressive agent already used in systemic immunosuppressive regimens for islet transplantation¹⁶⁹, can be incorporated into PLGA microparticles and co-delivered with islets in a Matrigel matrix to suppress T-cell activation¹⁷⁰.

The induction of alloantigen-specific immune tolerance prior to or during transplantation is the holy grail of allograft transplantation (FIG 3h). This requires the selection of a tolerance-promoting agent that can be locally released, because standard immunosuppressive protocols are typically not supportive of tolerance induction; for example, calcineurin inhibitors, such as cyclosporine and tacrolimus, block a IL-2 gene transcription, a key signal required for sustaining Treg function¹⁷¹. Tolerance-promoting agents are also being investigated for diabetes vaccines, which have the goal of Treg generation. For example, TGF- β 1-releasing PLGA scaffolds improve allogeneic islet engraftment in a chemically-induced diabetic mouse model (BOX 2), owing to delayed allogeneic rejection and local suppression of pro-inflammatory cytokines (TNF- α , IL-12, and monocyte chemoattractant protein-1 (MCP-1))¹⁷². TGF- β 1 can also be conjugated to an alginate scaffold through affinity binding, resulting in a durable immunoregulatory microenvironment that recruits immature dendritic cells and Tregs¹⁷³. Similarly and complementary, IL-33, which is a broadly acting cytokine that promotes T_H2 responses (BOX 1), recruitment of Tregs and M2 macrophage polarization¹⁷⁴, can be incorporated into PLGA scaffolds for local release¹⁷⁵. Following implantation of this scaffold in a chemically-induced diabetic mouse model (BOX 2), the transplant microenvironment is substantially altered exhibiting less T_H1 responses and leukocyte infiltration compared to BSA-releasing PLGA control scaffolds; however, local IL-33 release delays islet function and murine allograft rejection within a chemically-

induced diabetic model was only modestly delayed (19 days)¹⁷⁵. In summary, immunoregulatory biomaterial approaches have advanced the field of tolerogenic therapies by promoting the acceptance of clinical islet transplants.

Immunoisolation devices

Stable permselective biomaterial barriers can provide 3D support to the transplanted cells and prevent allograft rejection by abrogating direct host–donor cell contact. Protecting the islet graft through biomaterial encapsulation has been an active area of research for the past 30 years^{23–25} and multiple clinical trials using immunoisolated cells have been conducted.

Immune responses to encapsulated islets—Microcapsules and macroencapsulating sheets have been validated in rodent models, larger animal studies and/or clinical trials. Microcapsules have a surface-to-volume ratio favourable to efficient mass transport (compared to other geometries) and can be easily implanted at various injection sites. Macroencapsulation devices, typically formulated as flat cylinders coated with immunoisolation membranes, are easier to retrieve than microcapsules and are typically placed at accessible sites, such as the subcutaneous or intraperitoneal space.

Alginate is most commonly used for microcapsules, exploiting its different material properties such as molecular weight, ratio of D-mannuronic acid and L-guluronic acid residues, and gelation agents^{176,177}. Numerous studies have demonstrated allograft protection by alginate microcapsules in rodent T1D models for up to approximately 3 months (one study examined the material for up to 350 days in NOD mice, BOX 2)^{178,179}. Alginate microcapsules used for the protection of xenograft transplants show less consistent prevention of rejection, but can still provide enhanced protection of transplants compared to unencapsulated control transplants, in both chemically-induced and NOD diabetic murine recipients (BOX 2)^{180,181}, albeit with shorter therapeutic windows than equivalent allograft transplants (for example, porcine islets transplantation in NOD mice exhibit efficacy only for up to 50 days)¹⁸². Evidence for protection from autoimmune rejection in rodent models has also been demonstrated¹⁷⁹, illustrating the capacity of biomaterial encapsulation to dampen immunological responses. However, efficacy of microcapsules in larger pre-clinical (for example, non-human primates or pigs) and clinical models, has been limited. The implantation of microencapsulated xenogeneic islets into chemically-induced diabetic non-human primates has resulted limited therapeutic efficacy thus far, with most studies report only a transient detection of c-peptide^{183–185}. Many studies do not report a direct comparison with unencapsulated control islets, restricting interpretations on the benefit of capsules or their reason for failure. Clinical trials have also suffered from weakly powered studies (that is, small patient numbers and no controls), as well as variability in islet source (xeno- or allografts), dosage (8,000 – 25,000 islet equivalents (IEQ) per kg body weight) and capsule formulation (for example, alginate/polyaminoacidic and alginate/poly-L-ornithine/alginate)^{186–188}. In general, recipients of encapsulated islets have exhibited modest and transient declines in exogenous insulin requirements, with most patients returning to their pre-transplant exogenous insulin level requirements after a couple of years^{186–188}. Upon retrieval, most clinical studies report the presence of aggregated capsule clumps that adhere to tissues and contain fragmented and poorly insulin-expressing islets^{187,188}. Delineating the

factors that contributed to these poor clinical outcomes is challenging, because capsules were typically assessed only after functional decline.

Insufficient efficacy of encapsulated islets in large animals and humans has been primarily attributed to the foreign body response, poor islet function and islet necrosis post-transplantation. The foreign body response is driven by macrophages and activated fibroblasts and causes fibrotic graft encapsulation²⁷. Islets within this fibrotic capsule are hypoxic, surrounded by cytokines and ROS, and cut-off from nutrient supply. To reduce or eliminate the foreign body response, alginate can be purified to remove pathogen-associated molecular patterns (PAMPs)¹⁸⁹ or covalently modified¹⁹⁰. Moreover, the capsule scale can be modulated¹⁹¹ and macrophage inhibitors can be systemically added¹⁹². However, host foreign body responses are instigated by both the material and the encapsulated cells¹⁸¹. For example, implantation of islets into nutrient-poor sites, such as the peritoneum or subcutaneous, causes the upregulation and release of stress factors from these cells, such as damage associated molecular pattern molecules (DAMPs) and inflammatory cytokines (for example, IL-8 and TNF- α)¹⁹³, which can diffuse out of the capsule and accelerate immune reactivity¹⁹⁴. Thus, dampening islet stress and hypoxia should also reduce negative host immune responses. To mitigate hypoxia, encapsulated islets can be implanted within more nutritionally favourable sites, such areas rich in native^{195,196} or engineered^{131,197,198} vasculature, or they can be co-delivered with agents that provide supplemental oxygenation^{199,200}. Reducing capsule scale may also decrease islet stress by decreasing the distance between the metabolically active islet and its nutritional supply²⁰¹⁻²⁰³; however, closer contact between the host and the implant may also increase the exchange of detrimental agents, such as DAMPs from the islets and ROS from the host cells¹⁹⁴.

Modulation of the foreign body response and islet stress may decrease the activation of innate host cells; however, adaptive immune responses are still engaged by antigens released from the capsule, which causes indirect and antigen-specific immune cell activation in response to encapsulated transplants (FIG 3i&j)^{24,204}, with the intensity of the host response correlating with the degree of antigen diversity (that is, auto < allo < xeno). The presence of the biomaterial barrier cannot prevent the indirect activation of host innate and adaptive cells, which are clonally specific to the foreign (or auto-) antigens and thus, might play a role in decreasing the long-term function of grafts by generating a toxic local environment and driving the foreign body^{205,206} response²⁰⁶ (FIG. 3j). For example, the foreign body response to encapsulated porcine islets in non-human primates can be decreased by systemic treatment with T-cell co-stimulation inhibitors (CTLA4-Ig and anti-CD154 monoclonal antibody)¹⁸⁴. In NOD mice, the addition of the same T-cell co-stimulatory blockade extended the function of encapsulated porcine islets from 35 to > 450 days^{182,207}. Alternatively, encapsulation strategies can be combined with systemic immunosuppression, for example, using cyclosporin A (CsA)²⁰⁸, anti-LFA1²⁰⁹ and FK-506²¹⁰. These observations support the hypothesis that the foreign body response around transplants is not exclusively driven by non-specific biomaterial-initiated inflammatory responses. Thus, biomaterials designed to provide both immunoisolation and local, active modulation of immune cells can address this limitation.

Anti-inflammatory encapsulation approaches—Islet encapsulation combined with biomaterial coating with anti-inflammatory agents can provide complementary effects (FIG 3k-m). The encapsulating material protects the host environment from potent inflammatory agents expressed on the islet surface (for example, thrombin or tissue factor) and many coating strategies are amendable to intrahepatic infusion, for example, ultrathin coatings or islet surface engineering. Anti-inflammatory agents linked to these coatings include heparin²¹¹, alpha1-antitrypsin²¹², urokinase²¹³, thrombomodulin²¹⁴, human soluble complement receptor 1 (sCR1)²¹⁵, and IL-1 receptor antagonist²¹⁶. Nano- or microparticles can be linked to the coating for local delivery of anti-inflammatory agents, such as ketoprofen²¹⁷, curcumin²¹⁸, dexamethasone²¹⁹ and others²²⁰. Bioactive material coatings can also be used as sinks to deactivate detrimental inflammatory by-products and impede inflammatory-mediated activation of adaptive immune pathways, for example through scavenging ROS^{221,222} or sequestering TNF- α ²²³. Overall, the implantation of islets in such functionalized biomaterials enables potent suppression of coagulation and/or complement pathways in vitro, and can improve graft durability.^{211,215,220}

Immunosuppressive and tolerogenic encapsulation approaches—To provide further protection for encapsulated islet allografts, combinatorial material approaches can be applied to destroy immune effectors and/or promote graft tolerance (FIG 3n&o). For example, alginate can be used to generate immunomodulatory capsules through incorporation of the chemokine CXCL12, which repels effector T-cells and recruits Tregs, among other effects²²⁴. Implantation of these capsules leads to an improvement in the protection of autograft (NOD mice) and xenograft (porcine islets into murine recipients) transplants, correlated with a high number of local Treg cells^{224,225}. Alginate capsules can also serve as antibody depots for local delivery, for example, for the local release of anti-CD3 to provide islet protection against rejection in a single-antigen model system (BOX 2)²²⁶.

Drug delivering nano- and microparticles can also be combined with encapsulation. For example, PLGA nanoparticles containing FK506 and coated with dopamine to promote matrix adhesion can be assembled on the islet surface²²⁷. The particle-coated islets are viable and functional; however, the potency of immunomodulation in a concordant (rat to mouse) xenograft model was modest (~10 day delayed rejection)²²⁷. Similarly, leukemia inhibitory factor (LIF) can be loaded into PLGA nanoparticles, which can be tethered onto PEGylated islets²²⁸. Transplanted LIF-coated islets significantly improved allograft protection in a murine model²²⁸. Similarly, a thin rapamycin-eluting PEG coating can be applied to an alginate porcine islet capsule, which, upon implantation, leads to a decrease in foreign body response compared to uncoated alginate bead controls²²⁹; however, no difference in therapeutic efficacy was observed between the two groups. Further investigation in larger animal models is warranted to validate the translational nature of these approaches.

As an alternative to soluble drug release, immunomodulatory agents can be bound to the encapsulating biomaterial to provide local and targeted immunomodulation without inducing detrimental effects on the entrapped cells or diffusing away from the implant site (FIG 3p-s). For example, the Fas–Fas ligand (FasL) dependent apoptosis mechanism can be leveraged

by linking streptavidin-FasL to short PEG groups grafted onto the pancreatic islet²³⁰. FasL coating of islets, when combined with 2 weeks of systemic rapamycin delivery, prevents allograft rejection and triggers an increase in Treg migration into the graft, compared to unmodified islet controls²³⁰. Similarly, cell-free FasL-coated PEG microbeads can be co-transplanted with uncoated islets. This approach leads to an improvement in allograft protection, when combined with 2 weeks of systemic rapamycin delivery^{231,232}. TGF- β 1 or jagged1 (JAG-1), a Notch ligand implicated in the generation of Tregs, can also be grafted to the islet surface through PEG linkers^{233,234}. TGF- β 1 can be conjugated to cell surfaces through biorthogonal Staudinger ligation, triggering the generation of polyclonal (general stimuli) or monoclonal (to model ovalbumin antigen) Tregs from activated CD4⁺ T-cells²³³. JAG-1-coating also modulates immunogenicity in vitro, with an increase in the conversion of activated CD4⁺ T-cells to Tregs compared to uncoated islets²³⁴. Transplantation of xenogeneic JAG-1-coated islets into diabetic mice leads to reduced blood glucose levels, although the testing window was only 6 days²³⁴. Such surface engineered islets could be intrahepatically transplanted owing to the lack of a microscale encapsulation barrier; however, additional transplant studies are needed to validate Treg conversion and immunosuppressive function in vivo.

Other promising immunomodulatory agents, such as CD200, which is a regulatory molecule that targets myeloid lineage immune cells expressing CD200R, such as neutrophils, macrophages, and dendritic cells²³⁵, are also promising candidates for islet coating to suppress inflammatory and indirect allograft rejection. Recombinant CD200 bound to a material surface has already been shown to modulate macrophage activation^{235,236}.

The identification of signals and pathways that promote regulatory phenotypes will enable the development of biomaterials capable of specific and localized immunomodulation. Using materials to integrate immunoisolation with immune instruction could result in a clinically-relevant implant, reduce the need for systemic immunosuppression, and improve safety and retrievability.

Future directions and challenges

Various materials and material compositions are being explored to target and modulate specific immune cell populations for the treatment of T1D; however, preclinical outcomes in animal models are varied thus far. We posit that the ideal vaccine for T1D should induce long-term, antigen-specific tolerance, integrate personalized or broad antigen-specificity, and be compatible with clinical islet transplantation. Antigen-specific targeted tolerance is preferable to broad immunosuppression, owing to safety concerns of systemic immunosuppression, which requires continuous administration for therapeutic efficacy and thus, places a compliance burden on the patient. Antigen-specific tolerance and the generation of memory Treg cells should provide durable suppression without unremitting manipulation of immune functions. The network for pancreatic organ donors with diabetes (nPOD) has highlighted that there exists disease heterogeneity within the T1D population²³⁷, and therefore, an ideal vaccine must either be customized to the individual patient, tailored to a cohort expressing a similar disease phenotype or exhibit broad but T1D-specific antigen-specificity to treat all patients. A bank of T1D vaccines tailored to several

T1D cohorts on T1 autoreactivity classification²³⁸ will likely be the most cost effective option for T1D patients²³⁸. Prophylactic negative vaccines might also become clinically feasible owing to the improvement in the prediction of T1D high risk populations²³⁹. However, the vast majority of T1D patients have minimal predictable genetic risk and are unaware of the disease until it becomes symptomatic; at that stage, a critical beta cell mass has already been lost. Therefore, a vaccine for patients with compromised pancreatic function, should work concomitantly, or even synergistically, with islet transplantation.

The global acceptance of clinical islet transplantation as a therapeutic option for selected T1D patients, despite the requirement for systemic immunosuppression, demonstrates the potential of cellular therapy to provide unparalleled physiological glucose control^{8,240}. With advancements in the procurement of stem cell-derived beta cells, the research community must now push to mitigate the need for systemic immunosuppression. Biomaterials coupled with immunomodulation can provide multifaceted tools to locally modulate immune responses. Scaffold and particle platforms can suppress fibrosis and inflammation by local drug delivery and hydrogel encapsulation can block direct immune cell interactions with the transplant. Biomaterials can also mimic regulatory host cell cues through the delivery of tolerogenic agents or through the surface presentation of tolerogenic signals. Immunomodulatory biomaterial-based islet transplantation platforms show great promise in extending the durability of cellular therapies, with minimal dependency on systemic immunosuppression. To provide longterm durability of a cellular implant, modulation of immune cells beyond the transplant niche will likely be necessary. Therefore, tolerogenic protocols are required that do not only act within the local implant, but also trigger broad immune acceptance of the foreign graft, either by targeting the local draining lymph node or by providing peripheral tolerance.

Next-generation biomaterials for T1D treatment should be informed by transdisciplinary approaches. For example, 3D printed cell-laden hydrogel scaffolds could not only provide precise spatial distribution of the transplanted cells²⁴¹, but also allow co-printing with immune regulatory cells or agents²⁴², enabling highly localized immunoregulation. Biomaterials and microprinting technologies can further assist in improving stem cell-derived beta cell differentiation and pseudo islet formation^{243,244}. The transition from cadaveric islet sources, with unpredictable HLA profiles, to a defined stem cell-derived beta cell source, with the capacity to generate HLA-typed cell banks, provides the opportunity to decrease allogeneic beta cell rejection by tailoring the donor MHC to the patient. Knowledge of the beta cell MHC profile would also facilitate the development of tolerogenic vaccination prior to transplantation. The convergence of cellular therapies and vaccination strategies is feasible for T1D treatment, owing to the non-urgent nature of islet transplants compared to other organs.

Uncovering the immunological mechanisms that lead to T1D will advance the design of immunomodulatory biomaterials. Therapeutic success using α -CD20 to deplete B cells in patients with multiple sclerosis supports the theory that autoimmune diseases are not only mediated by Th1 and Th17 cells²⁴⁵. Learning from fundamental mechanisms of other autoimmune diseases will help to address the problem of the ‘streetlight effect’ in T1D research²⁴⁶. Diabetes researchers frequently investigate ‘safe’ areas, which perpetuates and

affirms existing dogmas of T1D pathophysiology. However, the initial events causing T1D are still unknown and research is currently limited to human samples to study pre-disease progression. Thus, tools to elucidate islet-immune system interactions ex vivo using disease-on-a-chip platforms could be highly informative. The investigation of non-traditional cellular targets for T1D modulation (for example, B-cells or plasmacytoid dendritic cells) should also be promoted. Moreover, the connection between the gut microbiota and transplantation outcomes can be explored. Thus far, such studies are limited and not yet applied to clinical islet transplantation, but pilot experiments suggest that the composition and diversity of the microbiota could alter immune interactions between the host, the transplant, and the commensal community, impacting transplantation outcomes²⁴⁷⁻²⁴⁹. Therefore, biomaterial approaches could be used for probiotics administration and/or to modify the intestinal immune environment to inhibit native beta cell attack and improve acceptance of foreign cell therapies. Transdisciplinary approaches that merge tools and knowledge from multiple fields are needed to appropriately treat this multifaceted disease.

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BOX 1.**Immunological players in type 1 diabetes**

The genetic and acquired factors that lead to targeted beta cell destruction in type 1 diabetes (T1D) have not yet been clearly identified. Hallmarks of the disease are CD8⁺ T-cell infiltration, chronic inflammation, and the increased presence of CD4⁺ T-cells and CD11c⁺ dendritic cells^{250,251}. Autoreactive CD8⁺ cytotoxic T-cells are the primary killers of beta cells. Their activation and clonal expansion are assumed to be initiated in the lymph node, from where they home to the pancreas to initiate insulinitis. CD4⁺ helper T-cells play a key supportive role, evidenced by the detection of autoreactive T_H1 biased CD4⁺ T-cells in T1D patients^{252,253}. B-cells further contribute to T1D pathogenesis through the production of autoantibodies and inflammatory cytokines and by initiating the clonal expansion of autoreactive T-cells^{40,254-256}. Innate immune cells are also involved in T1D^{257,258}.

At the stage of diagnosis, beta cell mass is depleted to a level at which glycemic dysregulation is evident; however, autoimmune responses continue to progress. Over the course of disease, a broad autoreactive T-cell response with epitope spreading is observed^{259,260}, which can elevate T-cell reactivity and pose problems for targeted immunosuppression. The detection of multiple circulating autoantibodies further indicates the presence of polyclonal effector B-cells²⁶¹. Furthermore, the presence of local effector T-cells and resident beta-antigen-specific memory T-cells in the pancreas of patients with established T1D²⁵⁹ provides evidence of a potent and lifelong autoimmune response to beta cells.

BOX 2.**Mouse models for type 1 diabetes**

Various T1D mouse models are available for the screening of type 1 diabetes (T1D)-relevant therapies^{262,263}. The choice of model is often dictated by the research questions. However, each model has limitations that need to be considered in the interpretation of results. Chemical induction methods (for example, streptozotocin) are used for the generation of the diabetic condition in the absence of autoimmunity. Such models are typically used for the screening of allogenic-based immune rejection to beta cell transplants in the absence of complex autoimmune responses. To mimic autoimmunity, single beta-cell autoantigen transgenic mouse models (for example the BDC2.5 strain that carries the a beta-specific CD4⁺ T cell clone or the NOD8.3 strain that carries the beta-specific CD8⁺ T-cell clone) can be used to initiate and perpetuate T1D-relevant autoimmune responses, typically through adoptive transfer of diabetogenic cells into immunodeficient hosts (for example, the nonobese diabetic-severe combined immunodeficiency (NOD-SCID) strain)²⁶². These T1D single-antigen models can provide control over disease initiation, single antigen simplicity, and ²⁶², by using a single diabetogenic cell population such as CD4⁺ or CD8⁺ T-cells from BDC2.5 or NOD8.3 mice, respectively, permits clear identification of immune pathways involved in diabetes onset or immune tolerance²⁶². For virally- or genetically-inducible models (for example, viral induction in NOD.RIP-GpLCMV mice), induction of beta cell destruction can be expedited and/or precisely timed, with overt hyperglycemia occurring within 1-2 weeks of infection²⁶². These models are highly useful, but do not reflect the complexity of human spontaneously-occurring, poly-autoantigen-driven T1D, nor do they address epitope spreading caused by neoantigens released during autoreactive lymphocyte-driven tissue damage, which expands the autoantigen repertoire⁸¹.

To date, the best mimic of human T1D is the NOD mouse model^{263-264,265}. NOD mice exhibit spontaneous autoimmune-mediated diabetes, insulinitis, islet-reactive T-cell clones, and islet autoantibodies²⁶³. Coupled with genetic manipulation, NOD mice can provide insight into the impact of therapeutic approaches on specific T1D-relevant pathways. However, the model shows sex bias in the manifestation of T1D symptoms (> 85% of females develop overt hyperglycemia while only ~50% of males exhibit the same symptoms) and environmental-induced variability (for example, changes in disease presentation due to diet, viral exposure, and housing conditions^{263,266}). Humanized mouse models could provide a powerful tool to study T1D; however, they are currently limited by graft versus host disease and lack essential homology requirements for full effector function.²⁶⁷

BOX 3.**Immune responses to transplanted allogeneic islets****Inflammation and instant blood-mediated inflammatory responses (IBMIR):**

Direct contact of islets with blood during intrahepatic infusion results in the prompt activation of coagulation and complement systems, which can account for ~60% loss of the islet mass within the first few days post-transplantation²⁶⁸⁻²⁷⁰. Syngeneic and clinical islet autographs experience similar losses²⁷¹, indicating that these responses are not primarily antigen-driven.

Allogeneic host responses:

In contrast to other organ transplants, human leukocyte antigen (HLA) matching of the islet donor and recipient is minimal and multiple disparate donor islet sources can be used to treat one T1D patient²⁷². This leads to a broad HLA profile for immune recognition through direct and indirect pathways. Direct antigen presentation is the major allo-recognition pathway in naïve recipients. Islet resident non-endocrine antigen presenting cells (APCs) (for example, macrophages, dendritic and endothelial cells) are the dominant antigen presentors^{273,274}. Expansion and graft-site migration of indirectly activated CD4⁺ T-cell effectors has also been observed in islet allograft rejection, indicating that antigens shed from the islet transplant also stimulate immune responses²⁷⁵. Once recognized, the graft is efficiently destroyed by infiltrating alloreactive CD8⁺ cytotoxic T-cells. Host CD4⁺ T helper cells also assist in multiple immune cell responses, for example, by supporting B-cell alloantibody generation. Furthermore, host innate immune cells (for example, natural killer cells and macrophages) contribute to the clearing of foreign cells through recognition of non-host major histocompatibility complex (MHC) class I or alloantibody tags²⁷⁶.

Autoimmune host responses:

Islet antigen(s)-specific T and B memory cells can cause beta cell graft rejection, regardless of the beta cell source, owing to their autoimmune memory. Specific autoimmune attack of beta cells has been detected in clinical islet transplantation patients, despite maintenance of systemic immunosuppression and retention of other allogeneic cells^{277,278}. Autoreactive CD4⁺ T-cells have been implicated as the key instigator in this response^{279,280}.

Systemic immunosuppression:

Various immune populations are stimulated at different time points pre- and post-transplantation. Selecting systemic agents to suppress immune responses to clinical islet transplants is complicated, because many common agents also impair beta cell function⁸. Current regimens include an induction phase (that is an elevated immunosuppressive drug dosage that typically induces lymphocyte depletion) and a maintenance phase (that seeks to maintain trough levels that prevent acute rejection of the graft)⁸, with newer regimens moving from broad pharmaceutical inhibitors to targeted biological blockers and integrating concurrent use of systemic anti-inflammatory agents^{8,281}. Despite optimized protocols, the clinical potency of suppression is unpredictable, due to variations in islet

quality, dosage and the immune profile of the patient^{282,283}. Furthermore, current regimens do not effectively suppress indirect activation pathways, evidenced by de novo emergence of auto- and allospecific antibodies post-transplantation^{284,285}.

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Figure 1. Immunomodulation biomaterial vaccines.

a) Nano- and microparticles can be used to target phagocytic cells, such as dendritic cells, and they can incorporate immunosuppressive agents or genetic material. Alternatively, non-phagocytic cells can be targeted, for example T-cells, by exploring ligand-T-cell receptor interactions. b) Nano- and microparticles can deliver antigens and immunomodulatory agents through surface presentation and/or soluble delivery to generate antigen-specific immunomodulation. Nanoparticles are phagocytosed and release their payload intracellularly. Microparticles can be used in combination with nanoparticles to release immunomodulatory agents to the extracellular space. c) Nano- and microparticles can be used for the sustained release of antigens or for antigen presenting cell (APC) targeting through surface conjugation of ligands. These platforms are designed to induce antigen-presentation on APCs in the absence of inflammatory cues, resulting in T-cell anergy, exhaustion or tolerance. d) Artificial APCs present antigen on major histocompatibility complex (MHC) I or MHC II in the absence of co-stimulation to target CD8+ or CD4+ T-cells, respectively, and can be additionally functionalized with immunomodulatory ligands. Artificial APCs can target antigen-specific T-cells and generate Tregs or induce cell death. e) Bulk materials can serve as local depots for in situ immune instruction, containing chemokines for cell recruitment to the scaffold, local immunomodulatory agents for inducing a tolerogenic phenotype and antigen to trigger a specific response.

Figure 2. Temporal sequence of host immune response to islet transplants.
T1D, type I diabetes; IBMIR, inflammation and instant blood-mediated inflammatory responses.

Figure 3. Immunomodulatory biomaterial approaches for islet and beta cell transplantation. Scaffolds housing the foreign islet transplant can serve as a drug delivery depot. To modulate inflammation, scaffolds can release agents that inhibit monocyte migration and/or macrophage maturation (a), inhibit macrophage infiltration (b), scavenge detrimental products from activated macrophages, such as reactive oxygen species (ROS) (c) and/or promote an M2-like macrophage phenotype (d). To modulate adaptive immunity, drugs can be released or presented to inhibit antigen uptake or promote a tolerogenic dendritic cell phenotype (e), to inhibit migration of activated T-cells from lymph nodes (f), to induce immune cell apoptosis (g) and/or to promote a tolerogenic phenotype (h). Encapsulation of the foreign transplant blocks direct antigen presentation pathways (i), but can activate indirect pathways (j). Drugs incorporated within the biomaterial (k) or tethered to the material surface (l) can dampen inflammatory responses to the material and encapsulated cells by inhibiting macrophage activation, scavenging detrimental agents and/or by

promoting an M2-like phenotype (m). To dampen adaptive immune responses, immunomodulatory agents can be incorporated into the encapsulating material and released for local modulation of antigen presenting cells (APCs) (n) and/or T-cell activation(o). Immunomodulatory agents conjugated to the surface of the biomaterial can instruct immune cells towards apoptotic (p and q) and/or tolerogenic (r and s) phenotypes. Local antigen delivery by the transplanted cells provides antigen-specificity.

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TABLE 1.

Biomaterial vaccines for type I diabetes

Approach	Target	Biomaterial	Biomaterial features	Drugs	Antigens	Model	Immunomodulatory effects	Effect on disease model	Refs
Peptide-coupled NPs ⁸⁰	APCs	PLGA	Controlled release of encapsulated factors; NP size facilitates phagocytosis	N.A.	ChgA minitope (p31) and/or IGRP minitope (NRP-A7)	Adoptive transfer of CD4 ⁺ BDC2.5 or CD8 ⁺ NY8.3 T cells in NOD SCID mice	Induction of Ag-specific Tregs; tolerance dependent on PD-1 and CTLA-4 expression	Prevention	80
Peptide- and tolerogenic agent-coupled NPs ⁹⁰	APCs	Gold	Surface bound immunosuppressive ligand and antigen; NP size facilitates phagocytosis	AhR ligand (ITE)	Proinsulin	NOD	Generation of tolerogenic DCs; increase in Treg differentiation; decrease of Th1 and Th17 gene signatures	Prevention	90
Dual-sized MPs for DC recruitment and conditioning ⁹⁶	APCs	PLGA	Controlled release; two MP sizes for facilitating or inhibiting APC-mediated phagocytosis	GM-CSF, TGF- β 1, vitamin D ₃	Insulin B(9-23)	NOD	Generation of tolerogenic DCs capable of inhibiting allogeneic T cell proliferation in vitro	Prevention	96
NPs decorated with MHC-bound autoantigen without supporting stimulatory ligands ^{100,101}	T cells	Iron oxide	Surface conjugation of MHC-I/II-bound peptide; acts as an artificial APC	N.A.	IGRP minitope (NRP-V7) or various IGRP peptides	NOD	Expansion of CD8 ⁺ T cells with immunoregulatory properties (according to MHC-II/I decoration on NPs)	Prevention; Reversal	100,101
NPs and MPs encapsulating anti-sense oligonucleotides ^{63,64}	APCs	PROMAXX [®] MPs or PLGA NPs	Controlled release of encapsulated factors; NP size facilitates phagocytosis	Anti-sense oligonucleotides against CD40, CD80 and CD86	N.A.	NOD	Downregulation of expression of CD40, CD80 and CD86 in DCs and increase in Treg numbers	Prevention; Reversal	63,64
NPs and MPs co-encapsulating immune-suppressive drug and peptide antigen ⁹⁵	APCs	Acetalated dextran	Controlled release of encapsulated factors; NP size facilitates phagocytosis	Rapamycin	ChgA minitope (p31)	Adoptive transfer of CD4 ⁺ BDC2.5	Decrease in proliferation of adoptively transferred CD4 ⁺ T cells and increase in the ratio of FoxP3 ⁺ to IFN γ + T cells; in vitro, DCs have less mature phenotype	Prevention	95
Hydrogel loaded with DC chemokine, adjuvant and MPs containing antigen ¹²²	APCs	Peptide hydrogel and PLGA MPs	Controlled release of encapsulated chemokine from hydrogel; MP size facilitates phagocytosis	GM-CSF and CpG	Denatured insulin	NOD	Increased IL-10 production in vitro	Prevention	122
Hydrogel with embedded NPs functionalized with DC chemokine and autoantigen ¹²⁰	APCs	Alginate hydrogel, gold NPs and PLGA NPs	Controlled release of chemokine and antigen from hydrogel	GM-CSF	ChgA minitope	NOD	Increase in the number of antigen-specific Tregs in pancreatic islets	Not Effective	120

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AHR, aryl hydrocarbon receptor; APC, antigen-presenting cell; CHGA, chromogranin A; DC, dendritic cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; IGRP, islet-specific glucose-6-phosphatase catalytic subunit-related protein; IL-10, interleukin-10; INF- γ , interferon- γ ; ITE, 2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester; MHC, major histocompatibility complex; MP, microparticle; NA, not applicable; NOD, nonobese diabetic mice; NP, nanoparticle; PD-1, programmed cell death protein 1; PLGA, poly(lactic-co-glycolic acid); TGF β 1, transforming growth factor- β 1; TH1 cell, T helper 1 cell; Treg cells, regulatory T cells.