Review article

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The therapeutic potential of immunoengineering for systemic autoimmunity

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Abstract

Disease-modifying drugs have transformed the treatment options for many systemic autoimmune diseases. However, an evolving understanding of disease mechanisms, which might vary between individuals, is paving the way for the development of novel agents that operate in a patient-tailored manner through immunophenotypic regulation of disease-relevant cells and the microenvironment of affected tissue domains. Immunoengineering is a field that is focused on the application of engineering principles to the modulation of the immune system, and it could enable future personalized and immunoregulatory therapies for rheumatic diseases. An important aspect of immunoengineering is the harnessing of material chemistries to design technologies that span immunologically relevant length scales, to enhance or suppress immune responses by re-balancing effector and regulatory mechanisms in innate or adaptive immunity and rescue abnormalities underlying pathogenic inflammation. These materials are endowed with physicochemical properties that enable features such as localization in immune cells and organs, sustained delivery of immunoregulatory agents, and mimicry of key functions of lymphoid tissue. Immunoengineering applications already exist for disease management, and there is potential for this new discipline to improve disease modification in rheumatology.

Sections

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Key points

- An unmet need exists for immunoregulatory disease-modifying agents for patients with rheumatological conditions who cannot tolerate immunosuppression and for partial responders and non-responders to current standards of care.

- Immunoengineering is an emerging research area with a major focus on a systems-based approach to rescue disorders of the immune system by leveraging material chemistries to generate immunoregulators.

- Immunoengineering advances now offer the possibility of a new class of therapeutics aimed at immunomodulation rather than at immunosuppression, which could synergize with standard-of-care therapies and personalize treatment in systemic autoimmunity.

- Immunomodulation, tolerization and measurement of disease activity are facilitated by nanoparticles; microparticles enable sustained, localized release of immunomodulatory compounds; and macroscale materials have uses in cell therapy and as immunological niches.

- To improve the safety, efficacy and specificity of T cell-based therapies, immunoengineering can be leveraged to enrich specific cell subsets, generate transient T cells in vivo and improve target identification.

- Immunoengineering could aid in the diagnosis of disease, immunophenotyping for patient-stratification purposes and in developing in vitro models to study autoimmunity.

Introduction

Systemic autoimmune diseases have complex aetiologies resulting from a combination of genetic and environmental factors, and several autoimmunity alleles are each associated with multiple diseases. The cellular and molecular mediators of pathogenesis are incompletely understood, but the importance of innate and adaptive immune responses is known, and powerful immunosuppressive DMARDs are now included in the arsenal of treatment options[1,2]. Although cures are rare, the standard of care for most systemic autoimmune conditions involves immunosuppression using effective and safe medications with the goal of achieving sustained remission. Targeted immunosuppression using biologic DMARDs (bDMARDs) and small-molecule inhibitors of Janus kinases (JAKs) has revolutionized management of rheumatoid arthritis (RA) and spondyloarthritis (SpA)[3], and enhancing expression of checkpoint molecules on T cells is also expected to help with refractory RA[4,5]. Agents targeting B cell activating factor have improved management of systemic lupus erythematosus (SLE). However, a notable fraction of patients with RA, SpA or SLE still struggle to achieve adequate disease control, or they experience adverse events related or unrelated to immunosuppression. Major complications such as interstitial lung disease in RA and severe organ-threatening SLE also remain challenging to manage, even in the context of substantial immunosuppression. For other systemic autoimmune diseases, treatment options are more limited and there is greater room for improvement. For example, there is a need for immune-targeted medication for Sjögren syndrome. In scleroderma and vasculitis,

despite some recent progress, there is a critical need for additional and more effective disease-modifying agents.

The next wave of disease-modifying agents is expected to stem from the large-scale efforts that have attempted to characterize the molecular pathology of rheumatic diseases in affected tissues and via single-cell genomics[6–12]. The results of these investigations are paving the way for interventions designed to target local pathogenic mechanisms in a patient-tailored manner, to improve efficacy and minimize systemic immunosuppression. Here, we would like to suggest that immunoengineering, a discipline at the interface between engineering and immunology, has the potential to help translate the progress in our knowledge of disease mechanisms into precision medicine for rheumatology patients.

In this Review, we highlight examples of immunoengineering applications in immunoregulation, prioritizing reports that included in vivo investigations and/or human trials, as well as mechanistic studies. Because the application of immunoengineering to autoimmunity is nascent, we include examples relating to organ-specific autoimmunity and cancer, which we believe support a similar approach in systemic autoimmunity to resolving the above-mentioned unmet needs. We highlight challenges and include potential new directions to foster interest and further promote the application of the emerging field of immunoengineering to systemic autoimmunity.

General principles of immunoengineering

Immunoengineering applies engineering knowledge gained from nanomedicine, biomaterials and tissue engineering to design targeted methods to activate or suppress an immune response. A major focus of immunoengineering is the development of chemically engineered biomaterials in a range of sizes with a variety of immune cell-instructive capabilities[13–16]. The desired features include localization in immune cells and organs to affect immune function, prolonged therapeutic release to function as in vivo reservoirs for delivering immunotherapy, mimicry of key features of immune organs and functions as diagnostic devices for measuring immune-related parameters[17–19]. A key feature of materials developed through immunoengineering is that they can provide novel avenues for harnessing or repairing pre-existing immune-feedback mechanisms to amplify disease-specific immune modulation and durably restore immunoregulation[20–22].

Nanoparticle-based immunoregulatory agents

Nanoparticles are generally particles with a spherical or well defined morphology in which the largest dimension is up to a few hundred nanometres. The nanoparticle chemical composition, size and geometry can be adjusted to facilitate transport to distinct tissue domains and delivery to cellular subsets. Nanoparticles can also be modified by coating or conjugating with ligands, including peptides, small organic molecules, oligosaccharides and antibodies, to gain new functionality tailored to particular applications (as reviewed elsewhere[23]). The modifications within the nanometre-range scale enables the generation of unique protein corona-based surface profiles in biological fluids that can enable desired pharmacokinetic and biodistribution profiles[24–27]. In addition, nanoparticles can be engineered so that they target specific cells and organs by passive or active targeting mechanisms that each necessitates distinct design criteria[28]. For example, nanoparticles between 5 nm and 200 nm are suitable for passive lymphatic drainage, to be taken up by antigen-presenting cells (APCs) such as dendritic cells and macrophages[29–31]. An emerging strategy to effectively target cells in the lymph nodes relies on active transport using albumin, the most

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abundant protein in the lymph, which recirculates between lymphoid organs and peripheral circulation and enables preferential 'hitchhiking' to lymph nodes proximal to the injection site[32,33]. This general approach has been clinically effective for targeting molecular imaging agents for lymph node mapping procedures and for albumin-based drug delivery for cancer treatment. Inspired by these principles, nanoparticles with albumin-binding functionalities can facilitate in vivo manipulation of immune cell activation, which can be achieved, for example, by synthesizing amphiphiles consisting of an antigen or adjuvant cargo linked to a lipophilic albumin-binding tail by a solubility-promoting polar polymer chain[34]. In preclinical studies, structurally optimized amphiphiles carrying specific antigens accumulated preferentially in the lymph nodes with lower systemic dissemination than their parent compounds. The result was multi-fold increases in T cell priming and enhanced antitumour efficacy with reduced systemic toxicity. The amphiphile technology is now under clinical development for multiple indications in cancer and infectious disease (NCT04853017)[35–37].

Microparticle-based delivery of immunoregulatory factors

Microparticles are geometrically well-defined structures in a range of shapes. The largest dimension is generally between tens and hundreds of microns. A key aim of immunoengineering is to improve drug delivery and reduce adverse events. To this end, microparticles encapsulating immunomodulatory agents have been engineered with precise degradation rates to permit release over a desired time frame. Microparticles are widely employed as biodegradable tissue-resident depots where sustained release of immunomodulatory compounds is desirable. Microparticles with sizes of the order of tens of microns can reside in target tissues for a prolonged period and resist phagocytosis[38,39]. The chemical composition and geometry can be tuned such that microparticles, once administered, remain trapped in local tissue compartments. Moreover, by altering the composition of the particles, the release profile can be altered to meet the therapeutic requirements. Microparticles can even simultaneously deliver more than one agent to the same target or be designed with pulsatile release kinetics that enable drug release over timescales from a few days to a couple of months[40]. For example, in the context of immunization, multiple particle formulations could be co-injected at an initial immunization. These particles would degrade over time, releasing antigen in discrete pulses at time points matching desired vaccination schedules[41]. A widely used microparticle formulation is based on the biodegradable polymer poly-(lactic-co-glycolic) acid (PLGA). The ratio of lactide to glycolide that is used for the polymerization can be adjusted so that various forms of PLGA can be obtained with distinct biodegradation and drug-release profiles. Upon biodegradation, PLGA decomposes into its constituent monomers, which are themselves endogenous products of the metabolic cycle. As of 2019, more than 15 PLGA-based microparticles had been clinically approved[42]. Although there are not yet any clinical PLGA-based therapeutics for systemic autoimmunity, the strong safety profile (demonstrated over decades) has made this material attractive for development in this area.

Macroscale materials-mediated immunoengineering

Macroscale materials span a wide range of sizes and physically interact with cells to promote desired functions. The materials can be broadly classified as biological (those derived from animal tissue or plant material) or synthetic (those that are derived from chemically synthesized polymers). Cell-laden macroscale materials are typically designed to promote a particular cellular phenotype. By contrast, cell-permissive materials can recreate immunological microenvironments and employ common strategies such as cytokine gradients and local cellular signals that attract specific cell populations[43,44]. Macroscale materials might be used for the recreation of 3D microenvironments that better mimic tissue structures: applications range from providing structure to organoids seeded with various cell populations to microfabrication enabling the design of organs-on-a-chip[45]. Macroscale materials can also be generated with tuneable mechanical properties that can be leveraged to test hypotheses about the physiology and microenvironment of immune organs (lymph nodes, thymus and bone marrow) and to elucidate the link between immune cell interactions, migration and activation, and disease mechanisms. The tunability of macroscale materials might also enable the functionalization of cell products to increase safety and efficacy.

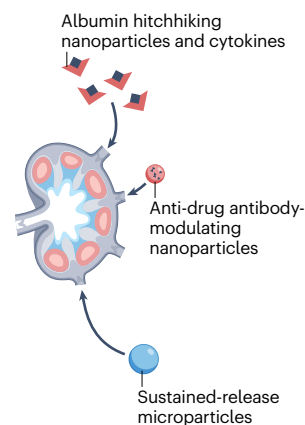## Immunoregulation and tolerization

Although traditional immunosuppression is still the standard of care for some systemic autoimmune diseases, in other common diseases such as RA and SLE, in the past 15 years the success of anti-cytokine bDMARDs and targeted synthetic DMARDs launched the era of immunoregulatory agents and transformed disease management. The advent of the genomics era now holds the promise to set the bar higher and target restoration of local immune homeostasis by patient-tailored immunoregulation. Ultimately, the progress of genomics and molecular phenotyping could enable the long-desired goal of re-establishing tolerance against autoantigens, which has the potential to be both personalized to each patient and curative of disease. As summarized below, immunoengineering approaches are ideally suited to accomplish tissue-targeted immunoregulation or tolerization. In humans, tolerization still has some challenges, a key one being the extensive antigenic drift that can occur in established autoimmunity, and the difficulty of identifying autoantigens and their variations between individuals[46–48]. Here, immunoengineering can complement efforts to improve immunoregulation and tolerization by enabling antigen-agnostic approaches that target local antigen-rich microenvironments (Fig. 1).

Lymph node targeting for immunoregulation

Nanoparticle delivery systems can enable localized delivery of disease-modifying agents to reduce off-target effects and improve safety and efficacy[49,50]. To this end, molecular immunoengineering based on the above-mentioned concept of albumin hitchhiking has been applied to improve the delivery of immunomodulatory cytokines that have demonstrated limited therapeutic potential through systemic administration (Fig. 1a). An example is IL-10, a cytokine with well-documented inflammation-resolving effects mediated through the reduction of antigen presentation and inhibition of T cell activation. IL-10 therapy could be applied to a variety of autoimmune diseases, but the biological form of IL-10 is an unstable homodimer that has a short half-life and is easily degraded in vivo. Seeking to extend the persistence of IL-10 in lymphoid organs, a serum albumin−IL-10 (SA−IL-10) fusion protein had greater persistence within lymph nodes to reduce local autoantigen presentation and immune activation than unmodified IL-10 (ref. 51). In collagen-induced arthritis (CIA) and collagen antibody-induced arthritis mouse models of inflammatory arthritis, SA−IL-10 but not IL-10 suppressed RA progression, supporting the utility of prolonged residence in the lymph node. In these models, the efficacy was comparable with anti-TNF antibody treatment, which is a standard-of-care approach in RA and SpA. SA−IL-10 was effective through multiple routes of delivery, including intravenous and subcutaneous administration, without notable toxicity in preliminary safety
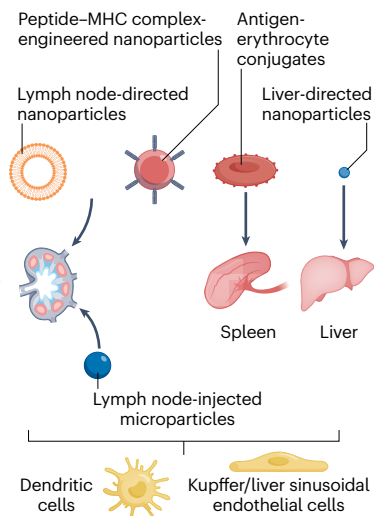
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a | Lymph node-targeted immunoregulation

Local enhancement of immunomodulatory cells (e.g. antigen-presenting and lymphoid cells)

Albumin hitchhiking nanoparticles and cytokines

Anti-drug antibody-modulating nanoparticles

Sustained-release microparticles

Immunomodulatory agents delivered to the lymph node

b | Antigen-specific tolerization

Co-opting tolerogenic pathways for antigen-specific immunoregulation

Peptide–MHC complex-engineered nanoparticles

Lymph node-directed nanoparticles

Antigen-erythrocyte conjugates

Liver-directed nanoparticles

Spleen   Liver

Lymph node-injected microparticles

Dendritic cells

Kupffer/liver sinusoidal endothelial cells

Leveraging immunomodulatory antigen-presenting cells

c | Gut-directed nanomaterials

Immunoregulation through the enhancement of gut microbiota and tissue-resident immune cells

Short-chain fatty acid

Polymeric micelle

Polymer–drug conjugate
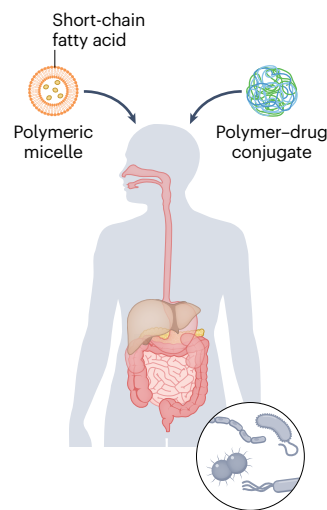
Encapsulated agents: metabolites, gut-derived immunomodulators

d | Leveraging the pro-inflammatory microenvironment for immunoregulation

Immunoregulation through epigenetic modifications of tissue-resident and recirculating cells

Polymeric microparticles

exT_{reg}

Macrophage

T_{reg}

Pro-inflammatory   Immunoregulatory
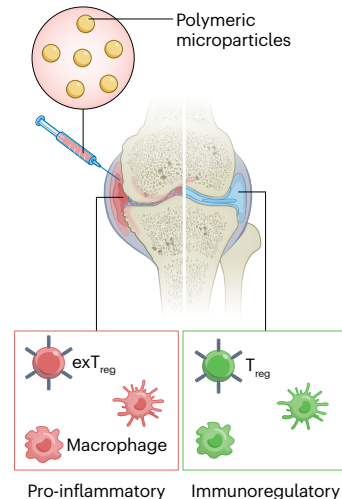
Encapsulated agents: epigenetic modulators

Fig. 1 | Immunoregulation and tolerization. a, Lymph node-directed agents encompass a range of nanoscale mediators that preferentially traffic to the lymph node by virtue of their size or that are chemically functionalized to harness serum albumin-mediated transport to the lymph node in proximity to the site of injection. The nanoparticles contain an immunomodulatory agent or, in the case of cytokines, are inherently immunomodulatory and programme immunoregulatory cell functions. Nanoparticles can also contain a disease-relevant antigen or mRNA coding for a disease-relevant antigen. Microparticles can be used for sustained release of immunoregulatory agents. **b**, Nanoparticles without an immunomodulatory agent that contain only disease-relevant antigens can harness endogenous tolerogenic mechanisms to foster an antigen-specific, protective immunoregulatory programme. **c**, Oral administration of antigen-free nanoparticles that deliver metabolites and/or gut-derived immunomodulatory agents can enhance the gut microbiome and promote a disease-relevant immunoregulatory programme. **d**, Microparticles delivered into the disease microenvironment (such as an arthritis-affected joint via intra-articular injection) can release an epigenetic-modulatory agent that induces and/or reprogrammes regulatory immune cells that, in turn, systemically recirculate and modulate disease. T_{reg}, regulatory T cell; exT_{reg}, T_{reg} cell that has lost regulatory function.

assessments. Importantly, SA–IL-10 treatment was not associated with generalized immunosuppressive effects.

The concept of albumin-mediated lymph node targeting has also been applied to IL-4. As an immunoregulatory cytokine, IL-4 can differentiate naive CD4$^+$ T cells into a T helper type 2 (T_H2) phenotype and reduce differentiation into T_H17 and T_H1 cells. IL-4R signalling is hypothesized to have an important role in SLE[52], and increasing the residence time of IL-4 in the lymph node in a targeted manner is a potential strategy to treat at least a subset of patients with SLE. By fusing IL-4 with serum albumin, the persistence of IL-4 in lymph nodes and the spleen increased through neonatal Fc receptor binding. The fusion protein accumulated and persisted in the lymph nodes and spleen after systemic administration[53]. In an experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis recapitulating neuroinflammation and demyelination, the SA–IL-4 fusion protein persisted in central nervous system-draining lymph nodes. SA–IL-4 prevented disease development with greater potency than wild-type IL-4. The prophylactic effect was comparable with the clinically approved multiple sclerosis drug fingolimod, a sphingosine-1-phosphate receptor modulator. In the same model, SA–IL-4 fusion protein modulated spinal cord immune cell infiltration, reduced the expression of αLβ2 integrin in antigen-specific

CD4$^+$ T cells, increased numbers of granulocyte-like myeloid-derived suppressor cells in spinal cord-draining lymph nodes and decreased numbers of pathogenic T_H17 cells. In mice with chronic EAE, SA–IL-4 abrogated immune responses to myelin antigen in the spleen.

A different but just as relevant immunoregulation approach based on tolerogenic nanoparticles paired with standard-of-care bDMARDs can prevent development of anti-drug antibodies[54–56]. A nanoparticle platform termed ImmTOR has been tested in combination with adalimumab (anti-TNF) and pegadricase (pegylated uricase). The ImmTOR platform leverages sustained release of rapamycin from polylactic acid (PLA) and PLA–PEG polymers combined with an engineered IL-2 agonist delivered in combination with bDMARDs to promote tolerance. When injected subcutaneously, ImmTOR nanoparticles preferentially drain to the proximal lymph nodes, where the PLA-encapsulated rapamycin enhances tolerance towards the co-administered bDMARD. In the transgenic TNF mouse model of RA, free rapamycin was ineffective at sustained inhibition of an anti-drug antibodies response, whereas mice that received ImmTOR remained seronegative even when rechallenged 2 weeks after cessation of treatment[54]. This sustained tolerance might be mediated in part by tolerogenic immune cell subsets, including regulatory T (T_{reg}) cells and dendritic cells.

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Depot-based immunoregulation strategies

PLGA-based microparticles can encapsulate compounds such as autoantigens, to enable 'depot-based' immunomodulation strategies based on controlled release. In autoimmune arthritis, a 'regulatory vaccine' approach has used subcutaneous co-delivery of dual-sized PLGA microparticles for the treatment of CIA[57]. Small microparticles capable of uptake by APCs encapsulated collagen (an autoantigen source) and 1α,25dihydroxycholecalciferol (calcitriol, an immunomodulatory compound). Large particles, more resistant to uptake, released granulocyte–macrophage colony-stimulating factor (GM–CSF; a dendritic cell chemoattractant) and TGFβ1 (a dendritic cell immunomodulator) to create a local immunoregulatory environment. This approach reprogrammed dendritic cells in the joint-draining lymph nodes, effectively reversing arthritis symptoms in mice. Microparticles can also be used as depots to promote a tolerogenic microenvironment to control key immune cell subsets. The TRI microparticle system comprises a mix of PLGA microparticles encapsulating variable combinations of TGFβ1, rapamycin and IL-2 (ref. [58]). Microparticles containing all three agents inhibited the development of arthritis in the CIA model. The amelioration of autoimmune arthritis was linked to an increase in T_{reg} cells in draining lymph nodes, as well as decreased macrophage and neutrophil counts relative to arthritic mice.

Antigen-specific tolerization by lymph node targeting

Conventionally, the components in nanoparticles formulated for immunomodulation include the carrier material, an immune-modulating drug and disease-relevant antigens. An example of such a strategy is a nanoparticle-based liposomal formulation encapsulating calcitriol and antigenic peptide, rather than a full-length protein, to target phagocytic dendritic cells in draining lymph nodes[59–61] (Fig. 1b). Among other functions, calcitriol facilitates regulation of the maturation and activation of APCs[62]. In a proteoglycan-induced inflammatory arthritis model, subcutaneously administered liposomes encapsulating calcitriol and an autoantigenic aggrecan-derived peptide (aggrecan$_{89–103}$) suppressed autoimmune arthritis and reduced the proportion of antigen-specific CD4$^+$ T cells compared with untreated proteoglycan-induced inflammatory arthritis mice[51]. The approach was further validated in a model of Goodpasture syndrome in which HLA–DR15-restricted collagen IV α3$_{135–145}$ is an associated autoantigen[59]. Treatment of mice with liposomes encapsulating calcitriol and α3$_{135–145}$ peptide resulted in antigen-specific reduction of the development of glomerulonephritis and albuminuria. The approach has now been tested for safety in a double-blind, placebo-controlled, exploratory, single-ascending-dose, phase I trial in patients with RA[63]. Here, the formulation used was termed DEN-181, and it comprised liposomes encapsulating self-peptide collagen II$_{259-273}$ and calcitriol. All doses used were well tolerated. Exploratory analysis suggested that improved RA disease activity in DEN-181-treated patients was associated with expansion of collagen II-specific and bystander citrullinated vimentin-specific T cells, reduction of anti-citrullinated protein antibodies, memory B cells and inflammatory myeloid populations, and enrichment of CCR7$^+$ and naive T cells. T cell mRNA transcripts associated with tolerogenic T cell receptor (TCR) signalling and exhaustion were identified by single-cell sequencing.

Antigen-specific tolerization by mRNA-based technology

Regulating immune activation without inducing generalized immune suppression is a major area of focus for nanoparticle-based immunoengineering pl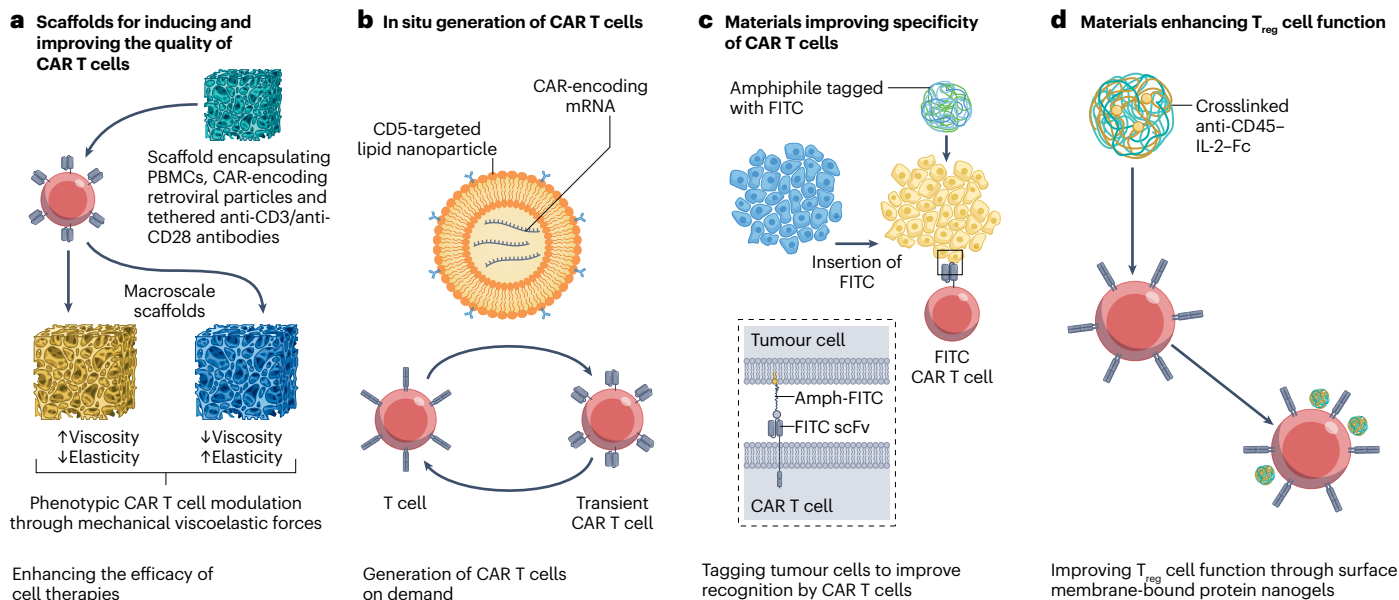atforms. Even though nanoparticles can preferentially target lymph nodes for immunomodulation, immunosuppressant-loaded nanoparticles can still cause dose-dependent systemic immuno-suppression. Experimentation with nanoparticles free of an immunosuppressive agent has shown that they can effectively suppress autoimmune disease in an antigen-specific manner[64]. To this end, lipid nanoparticle-based delivery of mRNA is an area of substantial research and development, spurred by the success in developing vaccines for COVID-19 (ref. [65]). For example, systemic delivery of mRNA-encoded vaccine antigens into lymphoid tissue-resident CD11c$^+$ APCs via a liposomal formulation was highly effective in emulating natural mechanisms of immune tolerance, with delivery of liposome-formulated N1-methylpseudouridine-modified mRNA, resulting in antigen presentation on splenic CD11c$^+$ APCs in the absence of costimulatory signals. In mice with EAE, disease was reversed by treatment with liposome-complexed mRNA. The effect was associated with enhancement of T_{reg} cells over pathogenic effector T cells. Moreover, T_{reg} cells mediated strong bystander immunosuppression, thereby mitigating disease induced by cognate and non-cognate autoantigens. mRNA-based immunomodulation using liposomal nanoparticles might be especially suitable for harnessing endogenous APCs and inducing tolerization against a range of self-antigens (such as citrullinated antigens) in RA and checkpoint inhibitor-induced arthritis.

Antigen-specific tolerization by peptide–MHC complex-engineered nanoparticles

Nanoparticles that are free of an immunomodulatory agent can also effectively interact with T cells to mimic APC-mediated immuno-modulation. For example, dextran-coated or pegylated iron oxide nanoparticles can be conjugated with autoimmune disease-relevant peptide–MHC (pMHC) complexes that directly interact with the TCR[66]. The distance between the pMHC complexes on the nanoparticle is important in inducing the assembly of microclusters with cognate T cells from mice and humans. Nanoparticles coated with autoimmune disease-relevant pMHC class II molecules induce the generation and expansion of antigen-specific type 1 T_{reg} (T_R1)-like cells and the conversion of disease-primed autoreactive T cells into T_R1-like cells in mice[67]. Delivery of nanoparticles displaying mouse collagen II$_{259-273}$ peptide complexed with DR4-IE reduces joint inflammation in *HLA-DR4-IE*-transgenic C57BL/10.M mice subjected to CIA, which correlates with systemic expansion of cognate T_R1-like cells. Given the versatility of the platform, pMHC-engineered nanoparticles might represent another strategy for accomplishing immunomodulation in diseases such as RA, where tolerization against multiple self-antigens is likely to be needed.

Antigen-specific tolerization by leveraging erythrocytes or hepatocytes

One strategy for tolerization is to target autoantigens to pathways that dynamically maintain tolerance in adults. To this end, erythrocytes are rational candidates because they are subject to a high rate of eryptosis, promoting continual uptake by splenic APCs[68]. In preclinical mouse models of EAE and autoimmune type 1 diabetes, the conjugation of disease-relevant antigens with an erythrocyte-specific antibody fragment induced sustained T cell dysfunction with signatures of self-tolerance and exhaustion, including upregulation of expression of PD-1, CTLA4, LAG3 and TOX, and prevented progression of disease[69]. Another strategy is to functionalize antigens with a moiety that targets the asialoglycoprotein receptors that are expressed on hepatocytes and liver sinusoidal endothelial cells, to facilitate antigen-specific immuno-modulation[70–72]. The concept of tolerance mediated by hepatic APCs,

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a | **Scaffolds for inducing and improving the quality of CAR T cells**

Scaffold encapsulating PBMCs, CAR-encoding retroviral particles and tethered anti-CD3/anti-CD28 antibodies

Macroscale scaffolds

↑Viscosity ↓Elasticity

↓Viscosity ↑Elasticity

Phenotypic CAR T cell modulation through mechanical viscoelastic forces

Enhancing the efficacy of cell therapies

b | **In situ generation of CAR T cells**

CD5-targeted lipid nanoparticle

CAR-encoding mRNA

T cell

Transient CAR T cell

Generation of CAR T cells on demand

c | **Materials improving specificity of CAR T cells**

Amphiphile tagged with FITC

Insertion of FITC

FITC CAR T cell

Tumour cell

Amph-FITC

FITC scFv

CAR T cell

Tagging tumour cells to improve recognition by CAR T cells

d | **Materials enhancing T$_{reg}$ cell function**

Crosslinked anti-CD45–IL-2–Fc

Improving T$_{reg}$ cell function through surface membrane-bound protein nanogels

Fig. 2 | Enabling immune cell therapy. a, Macroscale extracellular matrix scaffolds can be used for enrichment of specific chimeric antigen receptor (CAR) T cell subsets that have a desired immunophenotype. Enrichment is achieved by tuning the viscoelastic mechanical properties of the scaffold, which affects T cell activation and fate through the activator-protein-1 signalling pathway. **b**, Lipid nanoparticles have been used to generate transient fibroblast-activated protein (FAP)-targeting CAR T cells in vivo. Such CAR T cells show robust effector function and last about 1 week, thereby reducing the potential for long-term adverse effects. **c**, Difficult-to-target cells can be tagged via nanoscale amphiphiles prior to infusion of CAR T cells that recognize the tag, to improve target-cell killing. **d**, Protein nanogels can be coupled to regulatory T (T$_{reg}$) cells prior to infusion to enhance immunoregulatory function.

including dendritic cells, liver sinusoidal endothelial cells, Kupffer cells and hepatocytes, has inspired multiple nanoparticle-based antigen-specific strategies[32]. Intravenously administered antigens modified with polymeric forms of *N*-acetylgalactosamine or *N*-acetylglucosamine target hepatic APCs, promoting antigen presentation and the induction of antigen-specific tolerance through T cell deletion and anergy. These synthetically glycosylated antigens can also induce expansion of T$_{reg}$ cells. This strategy is under clinical development for the treatment of coeliac disease (NCT05574010) and multiple sclerosis (NCT04602390). Although these strategies have not yet been validated in systemic autoimmunity, in a preclinical adoptive-transfer mouse model of type 1 diabetes, glycosylated autoantigens contributed to the prevention of T cell-mediated diabetes and durably protected against disease through the expansion of antigen-specific T$_{reg}$ cells.

Antigen-specific depot-based tolerization strategies

Polymer-based microparticles have been delivered via lymph nodes to study tolerance induction in a mouse EAE model[73]. A single injection of encapsulated peptide fragments of myelin oligodendrocyte glycoprotein and rapamycin into lymph nodes at the peak of disease activity permanently reversed paralysis. The therapeutic effects were myelin specific, dependent on antigen and enhanced by rapamycin. The effects were accompanied by a reduction in inflammation and immune cell infiltrates in the central nervous system, with systemic expansion of T$_{reg}$ cells.

Leveraging the gut microbiota for immunoregulation

Nanoparticle-based approaches have the potential to accomplish immunoregulation in the gut, which is a physiological site for constant

tolerization and immunoregulation. A dysregulated gut microenvironment (including the gut microbiome, mucosal factors and their complex interactions) is a risk factor for the development and progression of a variety of rheumatic diseases. The gut microbiome is also emerging as a key regulator of DMARD efficacy[74–77]. In a key example of gut-targeted immunoengineering, orally delivered nanoparticles demonstrated immunomodulatory effects in different regions of the intestinal tract[78]. To facilitate this effect, the nanoparticles were designed as polymeric micelles that self-assemble into a bilayer structure with a high core content of butyrate (Fig. 1c). Butyrate is a metabolite of gut microbiota that facilitates immunoregulation through epigenetic modification[79,80]. By engineering the molecular composition of the block copolymers, it is possible to spatially control payload delivery[78]. With a neutral charge the nanoparticles predominantly release butyrate in the ileum. When encapsulated in a nanoparticle with a negative charge, butyrate predominantly releases in the caecum. In this manner, the delivery of butyrate at the target site can be maximized, overcoming existing limitations of oral administration. In addition to the anti-inflammatory effects on gut immunity, there was an increase in the abundance of autoimmunity-protective bacteria such as those in the cluster *Clostridium* XIVα. In another example, nanoparticles contained the abundant extracellular matrix component hyaluronic acid conjugated with bilirubin, a hydrophobic by-product of haemoglobin breakdown with strong reactive oxygen species-scavenging, anti-oxidant and cytoprotective properties[81]. The conjugate, termed HABN, accumulated in inflamed colonic epithelium after oral administration and restored the epithelial barrier in a murine model of acute colitis, suggesting therapeutic efficacy. HABN demonstrated regulation of innate immune cells, including

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modulation of inflammatory macrophages. HABN also modulated gut microbiota, increasing overall richness and diversity and specifically increasing the abundance of *Akkermansia muciniphila* and species from *Clostridium* XIVα, which have important roles in homeostasis of the gut microenvironment. Although these approaches are currently limited to models of inflammatory bowel disease and/or allergy, the concept of gut-targeted antigen-agnostic immunoregulation is attractive for systemic autoimmunity and could be developed into a precision-medicine approach by coupling with non-invasive (for example, microbiomic or metabolomic) assessments of dysbiosis.

## Leveraging the pro-inflammatory microenvironment for immunomodulation

In contrast to subcutaneous injections, which can induce generalized immunosuppression, evidence suggests that inflammatory changes in one RA-affected joint can modify inflammation in other joints through systemic cell recirculation[82]. An example of this approach is immunoregulation by sustained release of all-trans retinoic acid from microparticles in the joint, following intra-articular injection. The all-trans retinoic acid microparticles alter the T cell chromatin landscape, thereby enhancing differentiation to disease-protective T_{reg} cells. These T_{reg} cells migrate from the joint and result in systemic reduction of inflammation and disease control in injected and uninjected joints, reducing proteoglycan loss and bone erosions in SKG and CIA mouse models of autoimmune arthritis (Fig. 1d). Notably, however, this systemic disease modulation is not associated with impairment of response to immunization.

Enabling immune cell therapy

The development of T cells that are engineered to express a chimeric antigen receptor (CAR T cells) specifically for B cell surface antigens has revolutionized the treatment of haematological malignancies. CAR T cells and T cells engineered to express a chimeric autoantibody receptor (CAAR) are now emerging as potential disease-modifying agents for B cell-mediated autoimmunity[83,84]. Anti-CD19 CAR T cell therapy has been used successfully in patients with treatment-refractory SLE[85,86], and anti-B cell maturation antigen CAR T cell therapy has completed a phase Ib/IIa trial in patients with myasthenia gravis[87]. CD19-targeting CAR T cells have also shown promising results for myositis and interstitial lung disease associated with antisynthetase syndrome[88]. Other potential autoimmune-relevant indications of B cell-targeting CAR T cells include idiopathic inflammatory myopathy, dermatomyositis, systemic sclerosis[89] and Sjögren's syndrome (NCT06154252, NCT05085444, NCT05085431, NCT06056921). Additional cell therapy approaches are under development to engineer CAR T_{reg} cells to express T cell receptors against autoantigens of choice and deliver a tissue-specific and antigen-specific anti-inflammatory effect[90]. The development of T cells engineered to express a pMHC–TCR hybrid now paves the way to selectively eliminate autoantigen-specific T cells[91].

A key consideration in manufacturing CAR T cells for the treatment of autoimmunity is the quality of the cell product, to ensure safety and efficacy. To this end, extracellular matrix scaffolds enable the generation of functionally distinct anti-CD19 CAR T cell populations[92]. By adjusting the composition of the scaffold, mechano-signalling
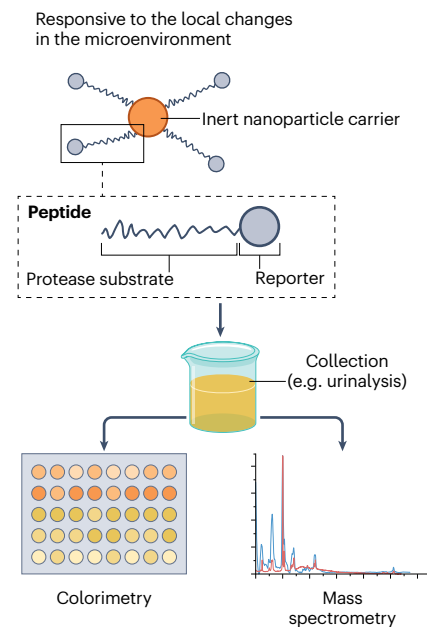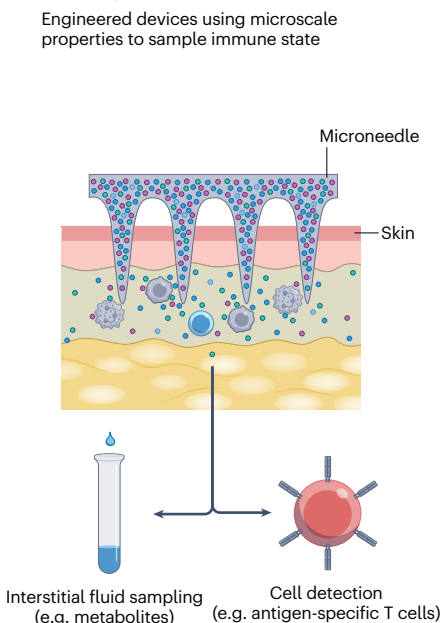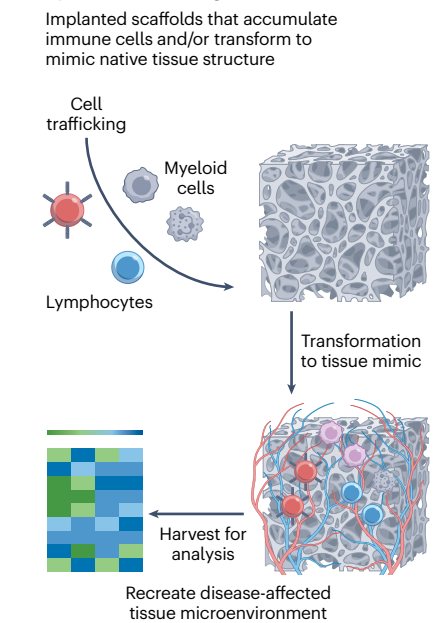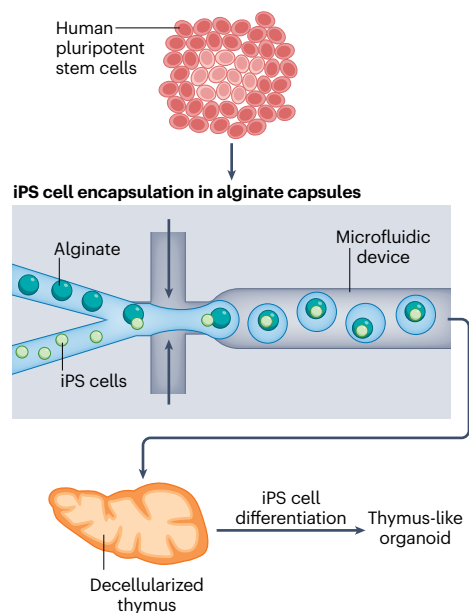

Fig. 3 | Immunodiagnostics. a, Microenvironment-responsive nanoparticles can be engineered with a reporter function that is activated upon encountering disease-relevant signals. For example, reporter molecules can be linked to carriers via peptides that are cleaved in the presence of high protease activity. After cleavage, nanoparticles are collected via a non-invasive method such as urinalysis for further processing and reporter quantification (for example, by fluorescence analysis or mass sp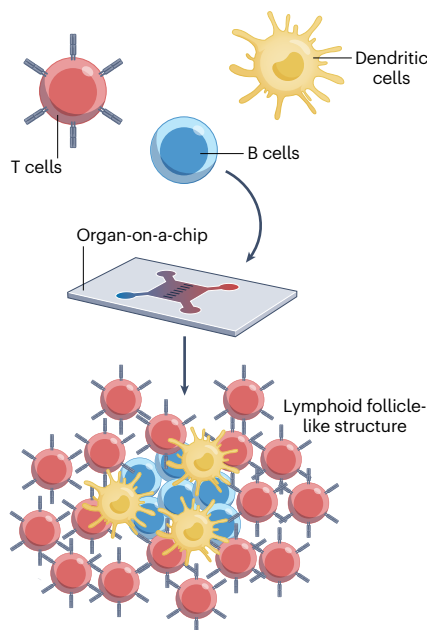ectrometry). **b,** Microscale needles can be designed as minimally invasive devices to sample disease-specific immune cells or to sample interstitial fluid for disease-relevant metabolites. **c,** Scaffolds can be designed as synthetic immunological niches that recreate key aspects of the affected tissue microenvironment and facilitate infiltration of pathogenic cells for disease-relevant diagnosis and potentially for continuous monitoring of disease evolution.

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a Recreating lymphoid structures

Human pluripotent stem cells

iPS cell encapsulation in alginate capsules

Alginate

Microfluidic device

iPS cells

iPS cell differentiation → Thymus-like organoid

Decellularized thymus

Develop and test immunoregulatory strategies

b

T cells

Dendritic cells

B cells

Organ-on-a-chip

Lymphoid follicle-like structure

Fig. 4 | In vitro models of lymphoid organs. In vitro models of primary and secondary lymphoid organs can be created by leveraging microfluidic devices that recapitulate key tissue and organ features. **a**, Human induced pluripotent stem (iPS) cells can be encapsulated in alginate and incorporated into a decellularized murine thymus, enabling the production of haematopoietic humanized mice. **b**, Ectopic lymphoid follicles can be generated by the co-culturing of human immune cells in a 3D extracellular matrix gel in an organ-on-a-chip microfluidic device. These lymphoid follicles demonstrate antibody and cytokine responses to vaccination.

stimuli can be tuned to regulate CAR T cells via the activator-protein-1 signalling pathway, resulting in T cells with distinct effector phenotypes (Fig. 2a). Even though ex vivo-generated CAR T cells are clinically effective, the complexity of manufacturing can limit their use. To potentially simplify the generation of CAR T cells, other immunoengineering-based technologies have been leveraged to generate CAR T cells in vivo. In particular, chemically modified macroscale biological scaffolds, termed Multifunctional Alginate Scaffold for T Cell Engineering and Release (MASTER), have been used to co-encapsulate human peripheral blood mononuclear cells, CD19-encoding retroviral particles and tethered anti-CD3/anti-CD28 antibodies[93]. Following subcutaneous implantation, MASTER released functional CAR T cells in mice.

Although CAR T cells are effective at targeting B cells, a potential limitation is that persistent targeting of other autoantigens, which might also be expressed in normal cells and tissue, could pose a long-term risk. To address potential safety issues, nanoparticles have been leveraged to transiently induce CAR T cells in vivo. In particular, lipid nanoparticles targeting CD5, a marker expressed by T cells, and encapsulating fibroblast-activated protein (FAP) CAR mRNA, induce FAP-targeting antifibrotic CAR T cells[94] (Fig. 2b). In a mouse model of myocardial injury, FAP CAR T cells reduced fibrosis and restored cardiac function. Because mRNA is intrinsically transient, the CAR T cells were also transient, lasting for about 1 week. FAP is a pleiotropic marker with relevance to multiple systemic autoimmune disorders and is also involved in normal physiological processes[95], and a transient CAR T cell therapy might maximize therapeutic efficacy and minimize adverse effects.

The clinical success of CAR T cells against autoimmune disease is so far limited to targeting B cells, and effectiveness beyond this target has been hindered by difficulties in the selection of effective target antigens. In the context of cancer, an immunoengineering strategy to help CAR T cells to find their targets is the intra-tumoural administration of a fluorescein isothiocyanate (FITC)-conjugated amphiphile that inserts itself into the cell membranes of cancer cells[96] (Fig. 2c). In preclinical studies, such 'amphiphile tagging' of tumour cells was demonstrated to promote durable tumour regression by enabling the proliferation and accumulation of FITC-specific CAR T cells in the tumours. Amphiphile tagging also induced infiltration by host T cells, elicited endogenous tumour-specific T cell priming and led to activity against distal untreated tumours. This strategy might be relevant to autoimmunity as it could facilitate the development of adoptive cell therapies that work independently of antigen expression and of tissue of origin.

Immunoengineering has also enabled improvement of adoptive T_{reg} cell transfer therapies[97]. In one approach, protein nanogels with cleavable cross-linkers and IL-2–Fc fusion proteins were used for the formation of particles that released IL-2 under reducing conditions, such as those that occur on T cell activation (Fig. 2d). T_{reg} cells that were surface-conjugated with IL-2 nanogels resulted in greater protection of allografts than unmodified T_{reg} cells or T_{reg} cells stimulated with systemic IL-2. Moreover, adoptively transferred nanogel-modified T_{reg} cells outperformed conventional T_{reg} cells in the suppression of alloreactivity in murine and in humanized mouse allotransplantation models.

Immunodiagnostics

The increasing availability and variety of disease-modifying agents (at least for the most common forms of systemic autoimmunity) has created a need for novel diagnostic assays in rheumatology. Patients with SLE or RA whose disease is relatively well controlled nonetheless experience flares that necessitate therapeutic escalation and that can progress to organ or structural damage. Patients vary in their responses

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to DMARDs, and early identification of the best treatment option can save precious time and help to spare patients from unnecessary immunosuppression and decline in quality of life. Thus, areas of unmet need include dynamic and in situ assays for early detection of disease flare, and microenvironment-based immunophenotyping for patient stratification.

Disease-responsive nanodiagnostics

In addition to therapeutic applications, nanoparticles have the potential to yield a novel class of diagnostics that can be deployed in vivo to query specific microenvironments, amplify disease signals and serve as biomarkers for early detection of disease or flares[98]. These strategies can involve design principles and advances from chemistry, synthetic biology and cell engineering to produce a readout of the disease state for easy assessment (for example, by a urinalysis-based colorimetric assay or mass spectrometry)[99,100]. A common method of functionalization involves the use of protease-sensitive linkers that upon cleavage generate a fluorescent signal (Fig. 3a). The initial applications of this approach have been in early cancer detection[101,102]. However, the results from preclinical models support the idea that the approach could guide treatment decisions for systemic autoimmune diseases in which proteases are involved, such as RA and SpA[103,104].

Sampling tissue-resident immune cells

Immunoengineering can be leveraged to assess immune responses that are associated with tissue-resident immune cells. An example is a PLGA-based microneedle array that can be applied to the skin[43] (Fig. 3b). The microneedles are coated with an alginate hydrogel layer in which adjuvants and antigens of interest can be embedded to attract responding immune-cell subsets, which can subsequently be assessed by ex vivo phenotypic and functional analysis. Proof-of-concept for this approach was demonstrated in mice immunized with antigen or infected with vaccinia virus. Subsequent sampling by microneedles enabled detection of tissue-resident memory T cells in the skin for many months, even after antigen-specific T cells in the systemic circulation were reduced to low or undetectable counts. Microneedles also enable sampling of dermal tissue interstitial fluid as a potential source of biomarkers[105]. In diabetes, glucose levels might be continuously monitored in interstitial fluid, avoiding the requirement for an implanted sensor. Similarly, microneedles might enable non-invasive spatiotemporal monitoring of interstitial fluid for a more accurate understanding of immune responses in cutaneous systemic manifestations of autoimmune conditions.

Synthetic immunological niches for disease diagnostics

Through the use of biodegradable polymers functionalized with immunomodulating cytokines, macroscale scaffolds can serve as artificial synthetic immunological niches that enable monitoring of immune functions or that provide signals to inform disease treatment. In a model of EAE, subcutaneous implantation of porous materials led to cell ingrowth and vascularization, which was accompanied by extravasation of immune cells into the newly forming tissue[106] (Fig. 3c), thereby serving as an easily accessible tissue mimic suitable for a biopsy procedure to monitor the disease state. An analysis of the inflammatory signature of immune cells infiltrating the new tissue revealed differences between EAE and control mice. Several genes were predictive of the disease state and were upregulated in biopsy samples of implanted immunological niches from diseased mice prior to detection of the disease via clinical scoring. These genes normalized to levels comparable with those in healthy controls following treatment, indicating that the immunological niche biopsy samples were responsive to disease state and treatment. This strategy might be leveraged for personalized monitoring of autoimmune disease activity in patients in remission, to detect disease flares before onset.

In vitro models to study autoimmunity

Macroscale materials can enable the recreation of key lymphoid structures, including the thymus and secondary lymphoid organs, to enable studies relating to the development and differentiation of immune cells involved in autoimmunity and for initial testing of drug safety and efficacy. Immunoengineering has produced scalable stem cell-derived thymic organoid models based on human pluripotent stem cell-derived thymic stromal cells. In one example, using an alginate cell-encapsulation approach and incorporation into a decellularized murine thymus, differentiation of human pluripotent stem cell-derived thymic stromal cells into subset lineages recapitulated transcriptional features of cells from the human thymus[107] (Fig. 4). Transplantation of these thymic organoids into humanized mice resulted in the generation of cells of myeloid and lymphoid lineages, with TCR variable-segment usage resembling that of peripheral blood mononuclear cells from healthy individuals. Besides primary lymphoid organs, secondary lymphoid organs have been generated using human PBMCs in an

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Box 1

Potential applications of immunoengineering in future precision and/or patient-tailored rheumatology

Nanoscale and microscale agents

- Antigen-specific tolerization and/or local conversion of pathogenic immune cells into protective cells
- Modulation of the gut–joint axis in rheumatoid arthritis or spondyloarthropathies through the targeting of selected gut locations
- Improvement of the efficacy of disease-modifying agents through a reduction of anti-drug antibody formation and a reduction of systemic immunosuppression via lymph node or other tissue targeting of DMARDs
- Development of devices for secondary prevention in pre-rheumatoid arthritis and undifferentiated autoimmunity, and for early detection of disease flares
- Antigen-agnostic tolerization via single or repeated injections
- Improvement of the efficacy and durability of cell-based immunosuppressive therapies

Macroscale agents

- Immunoengineering to enable cell therapy
- Establishment of immunological niches as proxies for lymphoid organs

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organ-on-a-chip model[108]. Self-assembly of B cells, T cells and dendritic cells into lymphoid follicles was characterized by the expression of human lymphoid follicle-associated immunophenotypic markers, plasma cell survival and differentiation.

Outlook for translation of immunoengineering-based strategies in systemic autoimmunity

The current progress of immunoengineering has the potential for deeply impacting the practice of rheumatology in the future. Box 1 summarizes envisioned applications of immunoengineering in precision and personalized rheumatology. However, some challenges are expected, stemming from the interfacial and early-stage nature of the discipline, the intrinsic complexity of disease mechanisms and the variable maturity stage of therapeutic interventions in rheumatology.

One challenge is that most immunoengineering studies focus on in vivo applications of materials in disease models (Table 1), which in rheumatology rarely recapitulate the complex pathogenesis and variability of human disease. We advocate instead for more translational studies utilizing human disease specimens and the expanding repertoire of humanized models to improve the translational aspect of autoimmunity-applied immunoengineering. Leveraging materials and human specimens to generate sophisticated organoid and organ-on-a-chip models of autoimmunity could provide a translational platform complementary to genomics and proteomics approaches to investigate disease mechanisms and develop new disease-modifying agents.

The choice of materials for developing immunoengineering-based technologies (such as PLGA and PEG) is often based on prior history of

use in humans, to avoid safety concerns and thereby facilitate translation to clinical use. However, there remains an opportunity for testing novel materials and chemistries that might be designed from the bottom up. To this end, early and close interactions between engineers and rheumatologists can ensure that technological development is geared towards meeting unmet medical needs, with appropriately selected materials and experiments in preclinical models designed to enable selection of the best candidates.

Drug discovery and development programmes focused on generalized immunosuppression of inflammatory pathways are well established, and these therapies will likely remain the mainstay of disease management for some time. Cell-based therapies are also rapidly emerging as attractive options for the treatment of refractory disease. Thus, it is important to clearly define the positioning of immunoengineering-based therapies that avoid generalized immunosuppression in relation to current agents in terms of scalability, cost of goods manufactured, safety and acceptance for clinical use. To this end, more effort should be focused on the identification of potential biomarkers for predicting successful outcomes, as well as stratification markers to identify those individuals who might benefit from a personalized approach. Furthermore, the evaluation of immunoengineering-based technologies in preclinical studies would benefit from more frequent benchmarking with standard-of-care agents in relevant disease models. The outcomes of such comparisons would help to refine clinical trial design to maximize benefit and potential synergies with the standard-of-care therapies (Table 2). Chemically modified materials have intrinsic design flexibility that positions them well as potential adjuvants to current disease-modifying drugs. Thus, there is a need for broader and earlier screens of materials to

Table 1 | Commonly used preclinical models of autoimmune disease

Disease model	Advantages	Limitations
Proteoglycan-induced arthritis	Knowledge of initiating antigen enables testing of antigen-specific tolerization methods; well-defined disease progression; chronic model of disease	Initiating antigens in human disease are not known and might vary from patient to patient; limited commercial availability of necessary reagents
Collagen-induced arthritis	Knowledge of initiating antigen enables testing of antigen-specific tolerization methods; well-defined disease progression; chronic model of disease	Initiating antigens in human disease are not known and might vary from patient to patient; inconsistent, non-symmetrical presentation
Collagen antibody-induced arthritis	Enables investigation of non-T cell-mediated aspects of rheumatoid arthritis; rapid development; commercially available	Transient disease model; non-symmetrical presentation
Anti-drug antibody formation in murine transgenic TNF model	Captures anti-drug antibody formation against humanized anti-TNF treatment; susceptible to disease protection from humanized anti-TNF treatment	Primarily cytokine-mediated and does not fully capture key immunological drivers of human disease
SKG arthritis model	Mimics key factors of human disease including development of rheumatoid factor and anti-cyclic citrullinated peptide antibodies; chronic model of disease; well-defined, symmetrical disease progression; mimics sex-differences associated with human disease	Limited B cell involvement in disease induction; limited model availability
Experimental autoimmune encephalomyelitis	Knowledge of inducing antigens enables testing of antigen-specific tolerization methods; well-defined disease progression that can mirror relapsing and remitting or continuous progressive disease	Does not fully capture gut microbiome contributions to disease progression; initiating antigens in human disease are not known and might vary from patient to patient
BDC2.5 T cell transfer-induced diabetes	Antigen-specific T cell-mediated model of disease enables in-depth evaluation of T cell contribution to disease progression	Disease-participating T cells in human disease might recognize multiple epitopes; requires adoptive cell transfer of a sufficient number of antigen-specific T cells from non-obese diabetogenic mice
Non-obese diabetogenic mice	Spontaneous development of disease in a manner consistent with human pathology	Disease onset can be unpredictable and inconsistent; disease onset can be limited by microbial exposure, requiring specific-pathogen-free conditions for high disease incidence

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Table 2 | Immunoengineering technologies in clinical development

Approach	Indication(s)	Phase	Trial ID
Peptide–calcitriol liposomes to promote antigen-specific tolerance	Rheumatoid arthritis	I	ACTRN12618001482358
Amphiphile-conjugated antigens for lymph node targeting to generate immune response	*KRAS*-mutated pancreatic ductal adenocarcinoma	I	NCT04853017
Uricase in combination with tolerizing nanoparticles to prevent anti-uricase antibody formation	Refractory gout	III	NCT04513366
Liver-targeted glycosylated antigen to promote antigen-specific tolerance	Coeliac disease	I/II	NCT05574010
Liver-targeted glycosylated antigen to promote antigen-specific tolerance	Relapsing/remitting multiple sclerosis	I	NCT04602390
Scaffold-based vaccine to generate an immune response	Melanoma	I	NCT01753089

identify potential combinations with current medications, as well as refinements of material design, synthesis and characterization strategies to bring early focus on aspects of adjuvant rather than monotherapy efficacy.

Sex bias is a key feature of the immune response and autoimmunity, and it should be considered when developing or applying immunoengineering approaches. Around 80% of autoimmune disorders occur in females, who often experience more severe disease and bear a disproportionate burden of the high morbidity associated with these chronic conditions, compared with males[109]. Sex can affect how an agent is metabolized and how well a patient responds to a drug. Design of experiments needs to be carefully assessed for sex bias when considering the application of immunoengineering approaches to rheumatic diseases. Furthermore, preclinical studies to evaluate immunoengineering-based approaches to rheumatology should be designed to evaluate sex-related differences in efficacy and safety.

Despite successes in preclinical studies, a greater focus on regulatory strategy and the design of clinical trials is needed to ensure the usefulness and acceptance of immunoengineering-based interventions for diagnosis or disease modification in systemic autoimmunity. For example, several of the immunoengineering strategies that are effective preclinically include multiple components within a formulation, whereas a simplified formulation could find wider acceptance by patients and providers participating in trials. Because of the complexity and variability of autoimmune diseases, developing immunoengineering-based precision medicines for this family of diseases will likely demand many distinct and complex formulations. However, developing a regulatory strategy as early as possible — even

at the discovery stage — is probably an even more critical risk-reducing strategy for immunoengineering-based approaches than for conventional ones.

Conclusions

The widespread application of modern genomic approaches to systemic autoimmune diseases holds promise in identifying patient-specific disease mechanisms and enable the development of new safe, effective and personalized immune-targeted medications. The ultimate goal of restoring immune homeostasis in a patient-tailored fashion and potentially accomplishing cure of disease seems increasingly within reach. However, curative immunomodulation will likely require a degree of spatiotemporal control over immune functions superior to what traditional pharmacological interventions can provide. The new discipline of immunoengineering offers the opportunity to apply key engineering concepts, such as regulated operation of complex systems, to immunomodulation, thereby enabling development of transformative therapies for autoimmunity. In the short term, immunoengineering is poised to enable complementary approaches to existing disease-modifying therapies in rheumatology. However, immunoengineering is also a natural fit for the tailoring of interventions to mechanism of disease and other patient-specific variables and to the dynamic delivery of therapeutic agents. Thus, it is easy to predict in the future the rise of personalized immunoengineering from the integration of patient-based genomic diagnostics and the systematic selection of material composition to distinctly target specific tissues, cell subsets and biochemical mechanisms.

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