Emerging strategies for nanomedicine in autoimmunity

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GRAPHICAL ABSTRACT
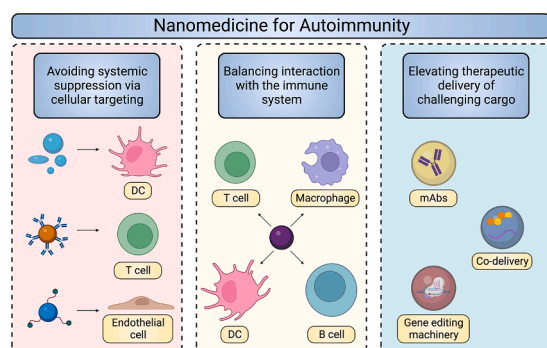
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ABSTRACT

Autoimmune disorders have risen to be among the most prevalent chronic diseases across the globe, affecting approximately 5–7% of the population. As autoimmune diseases steadily rise in prevalence, so do the number of potential therapeutic strategies to combat them. In recent years, fundamental research investigating autoimmune pathologies has led to the emergence of several cellular targets that provide new therapeutic opportunities. However, key challenges persist in terms of accessing and specifically combating the dysregulated, self-reactive cells while avoiding systemic immune suppression and other off-target effects. Fortunately, the continued advancement of nanomedicines may provide strategies to address these challenges and bring innovative auto-immunity therapies to the clinic. Through precise engineering and rational design, nanomedicines can possess a variety of physicochemical properties, surface modifications, and cargoes, allowing for specific targeting of therapeutics to pathological cell and organ types. These advances in nanomedicine have been demonstrated in cancer therapies and have the broad potential to advance applications in autoimmunity therapies as well. In this review, we focus on leveraging the power of nanomedicine for prevalent autoimmune disorders throughout the body. We expand on three key areas for the development of autoimmunity therapies – avoiding systemic

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immunosuppression, balancing interactions with the immune system, and elevating current platforms for delivering complex cargoes – and emphasize how nanomedicine-based strategies can overcome these barriers and enable the development of next-generation, clinically relevant autoimmunity therapies.

1. Autoimmune diseases: current therapies and limitations

Autoimmune disorders have risen to be among the most prevalent chronic diseases across the globe, affecting approximately 5–7 % of the world's population [1]. These disorders, which include over 80 different diseases, have been thought to be a product of the synergy between genetic predisposition and environmental factors [2,3]. In autoimmune disease, the immune system aberrantly attacks the body's own tissues as though they are foreign pathogens. The resulting irreversible tissue damage leads to chronic, debilitating, and potentially lethal disease. While there are no cures for autoimmune diseases, treatments generally aim to suppress the immune system and compensate for the function of damaged tissues [4,5]. These therapies are insufficient, requiring life-long compliance and often imposing unmanageable healthcare costs on patients. Further, systemic immunosuppression leaves patients vulnerable to infectious diseases and cancer, compounding the complications associated with autoimmune disease [6–8]. Nanomedicine has the potential to offer paradigm-shifting solutions for autoimmune disease through the design of multimodal therapeutics and capacity to selectively target relevant tissues.

While all individuals exhibit immune self-recognition, autoimmune diseases are generally characterized by an abundance of self-reactive lymphocytes, or T and B cells [9–11]. Normally, self-reactive lymphocytes are deleted through a process of positive and negative selection in the thymus and bone marrow known as central tolerance [12]. Any self-reactive lymphocytes that do escape central tolerance become anergic when exposed to autoantigen without inflammatory cues – a process known as peripheral tolerance [13]. As a result, during normal immune homeostasis, lymphocytes that recognize self-antigens are primarily tolerogenic and prevent immune responses against healthy tissues [12]. However, self-reactive lymphocytes in autoimmune disorders evade anergy, proliferate beyond control and propagate pro-inflammatory and cytotoxic pathways [14]. Their self-reactivity often leads to the destruction of healthy tissues and release of self-antigens, leading to reactivity to self-neoantigens and causing pathogenic epitope spreading [15].

Immune homeostasis is also maintained by regulatory T (T_{reg}) cells, which suppress immune responses to self-antigens [16,17]. T_{reg} cells can develop in the thymus or in peripheral tissues and exert their effects by producing immunosuppressive cytokines (IL-10, TGF-β, IL-35) to suppress effector T cell functions, inducing apoptosis in self-reactive antigen-presenting cells (APCs) or T cells, or by upregulating the surface receptor CTLA-4, which inhibits inflammatory signaling between APCs and T cells [17]. A key goal for nanomedicine in autoimmune disease is to restore immune homeostasis by boosting internal tolerogenic pathways and inducing self-tolerance.

Current FDA-approved therapies for autoimmune disorders cannot restore immune homeostasis, but instead aim to reduce the resultant inflammation (Fig. 1) [4]. One large classification of therapies includes small molecule drugs as well as corticosteroids (Table 1). Through both intracellular and extracellular mechanisms, these therapies suppress various components of the inflammatory cascade found in most autoimmune diseases. Small molecules such as methotrexate—commonly prescribed for RA—are within a large class of disease-modifying anti-rheumatic drugs (DMARDs) that act by inhibiting nucleotide synthesis and parts of the NF-κB and JAK-STAT pathways [6,18]. Similarly, corticosteroids like prednisolone, hydrocortisone, triamcinolone and dexamethasone are drugs that block inflammation by inducing transient lymphocytopenia and modulating T cell activity by blocking molecular interactions of cells and cytokines [19,7,8].

More recently, the FDA has approved several monoclonal antibodies (mAbs) as biological therapeutics, or 'biologics', for autoimmune disease (Table 1) [20–22]. mAbs have antigen-specific binding sites, making them a therapeutic strategy for achieving more targeted therapy. mAbs targeting inflammatory soluble factors and cell surface receptors are used clinically to suppress autoimmune inflammation. For
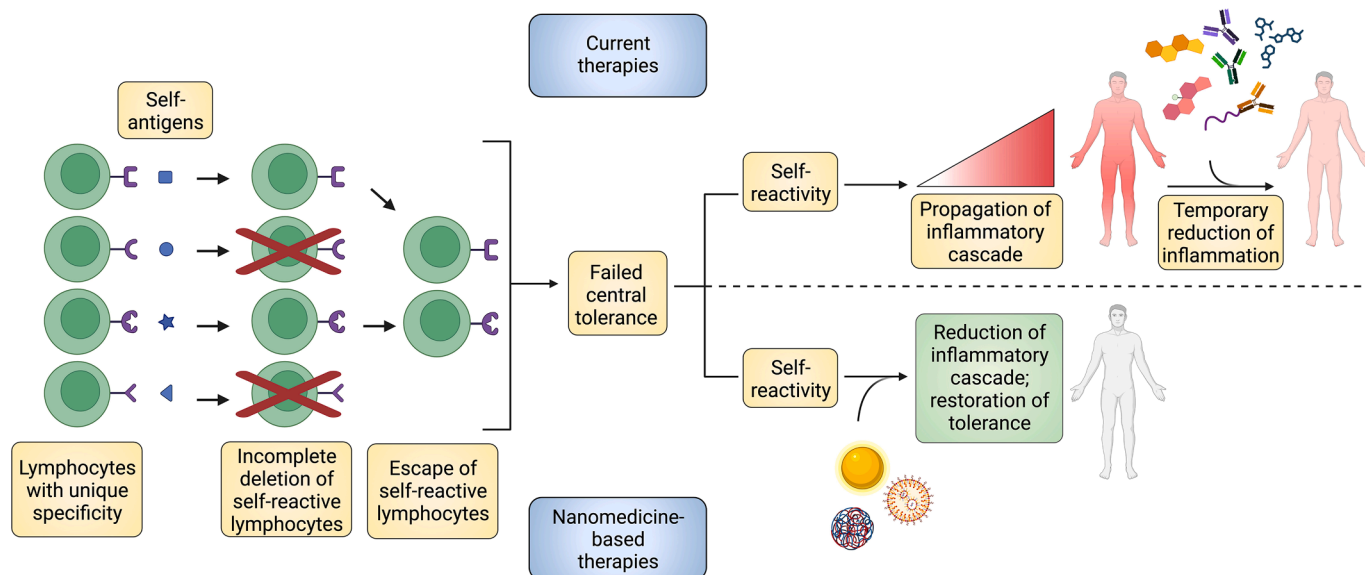

Fig. 1. Nanomedicine can prevent the progression of autoimmune diseases. Autoimmune disease stems from self-reactive lymphocytes escaping checkpoints of central tolerance in primary lymphoid organs. After recognizing self-antigens, the self-reactive lymphocyte act in concert with other immune cells to propagate the inflammatory cascade. Depending on the disease, this propagation can be local or systemic. Current therapies in the clinic, including small molecules, corticosteroids, and monoclonal antibodies, are able to combat inflammation by broadly suppressing the immune system. On the other hand, nanomedicine-based therapies have the potential to act before the inflammatory cascade has taken effect, reverse autoimmune disease phenotype and restore immune homeostasis at the fundamental level.

Table 1

Overview of current FDA-approved therapies for prevalent autoimmune diseases. Table includes the names and trade names of common therapies, the class or type of therapy, the implicated immunological target and pathway, and the autoimmune disease that the therapy is prescribed for.

Therapy	Class	Implicated Immune Target/ Pathway	Autoimmune Disease Indication
Adalimumab (Humira) Infliximab (Remicade) Certolizumab (Cimzia)	Antibody	TNF-alpha	Crohn's Disease, Plaque Psoriasis, Psoriatic Arthritis, Ankylosing Spondylitis, Rheumatoid Arthritis [22,209,210]
Ustekinumab (Stelara)		IL-12 and IL-23	Crohn's Disease, Plaque Psoriasis,
Risankizumab-rzaa (Skyrizi)		IL-23	Psoriatic Arthritis 211,[212]
Secukinumab (Cosentyx)		IL-17	Plaque Psoriasis, Psoriatic Arthritis, Ankylosing Spondylitis [213]
Ixekizumab (Taltz)			Psoriatic Arthritis, Ankylosing Spondyloarthritis [214]
Tocilizumab (Actemra) Sarilumab (Kevzara)		IL-6	Rheumatoid Arthritis [215]
Belimumab (Benlysta)		B-Lymphocyte Stimulator	Lupus, Lupus Nephritis [216]
Anifrolumab-fnia (Saphnelo)		Type I Interferon Receptor	Lupus [199]
Ofatumumab (Kesimpta)		CD20	Multiple Sclerosis [217]
Etanercept (Enbrel)	Fusion Protein	TNF-alpha	Ankylosing Spondylitis, Plaque Psoriasis, Psoriatic Arthritis, Rheumatoid Arthritis [200]
Interferon beta-1b (Extavia/ Betaseron)	Cytokine	Broad (T and B cell function, MHC-I expression)	Multiple Sclerosis [201]
Anakinra (Kineret)	Synthetic Protein	IL-1 Receptor	Rheumatoid Arthritis [202]
Apremilast (Otezla)	Small Molecule	PDE4/cAMP	Plaque Psoriasis, Psoriatic Arthritis [203]
Baricitinib (Olumiant)		JAK	Rheumatoid Arthritis [218]
Upadacitinib (RINVOQ)			Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease [219]
Tofacitinib (Xeljanz)			Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis [220]
Methimazole		Thyroid Stimulating Immunoglobulin	Graves' Disease [204]
Methotrexate		Adenosine signaling pathway	Rheumatoid Arthritis, Psoriasis, Lupus [6]
Methotrexate		NF-kB, ATIC	Broad inflammation [6]
Glucocorticoids (Prednisone, Betamethasone, Dexamethasone, etc)		Glucocorticoid receptor, AP-1, NF-kB	Broad inflammation [221]
Retinoids (Tazarotene, Acitretin, Tretinoin, etc)		Nuclear retinoid receptors, MRP-8, AP-1 (in epidermal	Plaque Psoriasis [205]

Table 1 (*continued*)

Therapy	Class	Implicated Immune Target/ Pathway	Autoimmune Disease Indication
		keratinocytes)	
Azathioprine (Imuran)		Purine synthesis (DNA, RNA, protein synthesis)	Rheumatoid Arthritis [222]
Sulfasalazine		NF-kB, Broad (T and B cell function)	Rheumatoid Arthritis [206]

example, the TNFα-targeting mAbs infliximab and adalimumab (trade names Remicade and Humira) sequester the pro-inflammatory cytokine TNFα [22,23]. mAbs against lymphocyte receptors such as teplizumab (anti-CD3) and rituximab (anti-CD20) have also proven beneficial for autoimmune disease [24–26]. Teplizumab blocks inflammatory T cell receptor signaling to delay the progression of new onset type 1 diabetes (T1D). Rituximab, which was initially used to treat lymphomas, acts by depleting B cells and improves outcomes in a myriad of autoimmune diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and vasculitis [26].

Although the FDA-approved therapies have seen clinical success, they have major drawbacks stemming from their delivery route and mechanisms of action. Small molecules and corticosteroids are generally administered orally, resulting in a sharp decrease in bioavailability due to first pass metabolism and other gastrointestinal barriers [7]. Furthermore, these therapies are extremely non-specific and result in systemic immunosuppression [6,7]. Though advantageous in suppressing autoimmune pathologies, this systemic suppression can leave the body susceptible to other ailments, including bacterial infections, viral infections, allergies, and even cancer. mAbs are inherently more specific; however, systemic administration of mAbs results in the systemic inhibition of specific cell–cell or cell-cytokine interactions, leading to similar concerns of systemic immunosuppression [27]. Furthermore, all of these therapies require frequent dosing, which has proven to be costly and problematic in cases where patients have developed immune responses against the administered agents.

With the goal of overcoming these longstanding limitations, the development of next-generation autoimmunity therapies has been focused on three main objectives: (1) targeting specific cells/organs to avoid systemic suppression; (2) balancing the interactions with the immune system; and (3) utilizing multi-faceted and multiplexed approaches to improve therapeutic outcomes. In this review, we outline how nanomedicine-based strategies can be leveraged to develop next-generation autoimmunity therapies. We highlight how nanomedicine is advantageous in that nanoparticles are large enough to incorporate multiple functionalities such as tissue targeting and protecting encapsulated cargo for controlled release at the desired site of action while remaining small enough to traverse biological barriers. Furthermore, we discuss how the physical properties of nanoparticles can be engineered to elicit biological responses that act synergistically with that of the therapeutic cargo. Finally, we provide future directions and perspectives on the field and how nanomedicine fits into the larger narrative of autoimmunity therapies.

2. Considerations in nanomedicine for autoimmune diseases

The ideal nanomedicine for autoimmune disease will promote immune homeostasis by reducing inflammation and subsequent tissue destruction without the need for systemic immunosuppression. Current autoimmunity therapies fail to achieve these goals in part due to poor bioavailability stemming from drug properties including size, charge, and hydrophobicity [27,6,7]. Consequently, these drugs are cleared rapidly and require high and frequent dosing to achieve therapeutic effects [7,27]. Nanomedicine offers unique advantages to overcome these challenges because of their ability to incorporate multiple

functionalities through rational combination of core biomaterial, architecture, active pharmaceutical ingredients and routes of administration. The size, shape, surface chemistry, and degradation of nanoparticles are readily tunable to encapsulate and release cargo spanning a wide range of chemical structures and to interact with desired cell types [28,29]. These advantages not only improve the bioavailability and pharmacological activity of drugs, but they can also decrease off-target toxicity and alleviate systemic effects by enabling spatiotemporal control over drug release. Here, we will discuss how nanoparticle properties can be leveraged to improve the activity of existing therapeutics, modulate inflammation, and enable the delivery of new drug classes for autoimmune disease. While existing literature provides in-depth commentary on nanomedicine for broad therapeutic applications, this review will highlight research that has successfully applied technology across the nano- and microscale to animal models of autoimmune disease and may therefore enable future implementation of next-generation interventions for autoimmune disease [30–32]. It is important to note that although we will isolate individual characteristics of nanomedicines (used interchangeably with nanoparticles) for discussion, these properties are highly interconnected and dependent on each other. For more in-depth discussion about individual characteristics, we refer readers to other published works [29,33–37].

2.1. Physical characteristics of nanoparticles determine their utility for treating autoimmune diseases

2.1.1. Size

Nanomedicine can be engineered over a wide range of sizes to elicit specific cellular interactions, control the release of encapsulated drug, or ensure their retention in a physiological depot [29,30]. Therapies for autoimmune disease require drug or biologic delivery to cells of the innate and adaptive immune system present in lymphoid tissues, such as the spleen and lymph nodes [38,39]. Larger particles (0.5-2 μm) generally remain localized at the site of injection and associate with dendritic cells (DCs), whereas smaller particles (20–200 nm) effectively drain to lymph nodes and interact with lymph node-resident dendritic cells and macrophages [29,40]. Within the 20–200 nm size range, one study found that ultra-small polymeric (polypropylene sulfide) nanoparticles infused into the tip of mouse tail skin drain more efficiently through lymphatic capillaries and undergo uptake by ∼ 50 % of lymph node-resident dendritic cells, whereas under the same conditions, 100 nm nanoparticles are found within only 6 % of dendritic cells [41]. Moreover, the ultra-small nanoparticles were retained within the lymph node for at least 120 h after injection, while the 100 nm particles were cleared within 24 h [41]. To highlight the interdependence of nanoparticle properties on biological outcomes, a study investigating the delivery of gold nanoparticles to dendritic cells and their subsequent clearance reported the opposite: 50–100 nm gold nanoparticles were retained by follicular dendritic cell networks for over 5 weeks, while 5–15 nm gold nanoparticles were cleared within 48 h [42].

In addition to determining biodistribution and cellular uptake, nanoparticle size also influences the resulting immune response. A study using antigen-coated nanoparticles to elicit immune responses found that 40–50 nm particles induced primarily type 1 responses as evidenced by IFN-γ production, while 90–120 nm particles favored a type 2 response characterized by IL-4 [43]. Nanoparticle size also influences the magnitude of the resulting immune response, where ∼ 200 nm nanoparticles were found to induce greater antigen presentation and antibody responses in mice than smaller nanoparticles [44,45]. Notably, one study found that all lipid nanoparticles ranged ∼ 50–150 nm induced comparable prophylactic vaccine responses in non-human primates, while another study shows that the ideal particle size for intravenous RNA delivery to non-human primates (50–60 nm) may actually be smaller than the ideal size for rodents (70–80 nm), suggesting that the ideal nanoparticle size may further depend on species-specific physiology [44,46].

2.1.2. Charge

It is widely accepted that cationic biomaterials can be immunogenic and inflammatory [33,34,47]. Numerous studies associate this toxicity with the adsorption of serum proteins and the activation of toll-like receptor 4 (TLR4), leading to an increased production of inflammatory cytokines [48–50]. In contrast, negatively charged nanoparticles are of great interest for their ability to blunt inflammatory signaling, a property that appears to hold for anionic biomaterials of diverse classes [51,52]. The past several years have yielded an increased interest in how nanoparticles incorporating anionic materials can selectively deliver cargo to macrophages and dendritic cells, particularly in the spleen [53–59]. Moreover, this trend appears to hold for nanoparticles containing cationic components but with an overall negative charge. Specific examples of how charge manipulation results in altered tropism are discussed in the section below on physicochemical targeting. While negative charge is a property common to many biomaterials useful for combatting inflammation, the mechanisms governing this response remain poorly understood. One proposed mechanism is that anionic materials mimic apoptosis, which is inherently tolerogenic [60]. This is discussed further in the section below on liposomes and lipid nanoparticles. Interestingly, anti-inflammatory and tolerizing responses have also been attributed to negatively charged nanoparticles without obvious apoptotic mimicry, such as gold and silica nanoparticles [61,62]. Alkyl-terminated gold nanoparticles have been shown to possess self-therapeutic properties and reduce psoriatic symptoms [61]. The nanoparticles were shown to deliver to keratinocytes when topically administered, and the gold core of the nanoparticles was shown to be the source of therapeutic effect [61].

2.1.3. Surface chemistry

Nanoparticles can be readily functionalized with chemical and bioactive groups that can render their surfaces hydrophilic or hydrophobic, with a range of immunological outcomes [35,63]. For nanoparticles injected into the bloodstream, it is well understood that hydrophilic nanoparticles exhibit increased circulation times and are therefore more likely to reach extrahepatic target cells, such as immune cells [28]. Perhaps the most popular strategy to achieve this is PEGylation, or coating the surface of nanoparticles with the hydrophilic polymer polyethylene glycol (PEG) [64,65]. The conformation of PEG on nanoparticle surfaces depends on its density, with highly dense PEG layers exhibiting a "brush-like" conformation and sparse PEG layers exhibiting a "mushroom-like" conformation [66]. PEG provides stability to nanoparticles in physiological environments by preventing aggregation and reducing the passive adsorption of proteins. Of particular relevance to immune cell targeting, nanoparticles with dense PEG layers traffic most efficiently across lymphatic endothelial cells to reach immune cells within lymph nodes [67]. However, PEG can also decrease the ability of nanoparticles to interact with cells, indicating that the degree of PEG functionalization needs to be carefully tuned to elicit the desired biological response [68].

PEG is widely regarded as immunologically inert, though this has recently been called into question, reviewed elsewhere [69]. There are several PEGylated protein, small molecule, nucleotide, and nanoparticle drugs already in clinical use, including the PEGylated protein drugs Cimzia (anti-TNFα Fab) and Plegridy (IFN-β 1a) for RA and multiple sclerosis (MS), respectively [70–72]. This indicates the safety and efficacy of PEGylated therapeutics in treating autoimmune diseases. However, some individuals who have never received PEGylated therapeutics have anti-PEG antibodies in systemic circulation, possibly due to the presence of PEG in hygiene and cosmetic products, and many others who receive PEGylated drugs develop anti-PEG antibodies [73]. These antibodies are predominantly IgM and IgE isotypes, which tend to exist at higher levels in individuals with autoimmune diseases, though their precise roles in diverse autoimmune contexts remain to be elucidated [74,75]. Nonetheless, as anti-PEG antibodies can facilitate accelerated blood clearance, complement activation, and hypersensitivity reactions,

it is critical that research continues to investigate the immunological implications of PEGylated nanomedicine in autoimmune disease.

Finally, hydrophobicity also contributes to the immunological activity of nanoparticles, though this appears to depend on the source of the hydrophobicity. For example, hydrophobic nanoparticles have been leveraged as vaccine carriers for their endogenous inflammatory adjuvant activity [76]. However, a growing number of reports indicate that nanoparticles decorated with hydrophobic peptides are capable of blocking TLR signaling to reduce inflammation [77,78].

2.2. Leveraging biomaterials with tolerogenic properties

In nanomedicine, the core biomaterial often serves as a scaffold to encapsulate, conjugate, or adsorb small molecule drugs and biologics with pharmacologic activity. However, these biomaterials also interact with the immune system and are capable of eliciting diverse immunological outcomes [56,79]. Because autoimmune diseases are characterized by aberrant inflammation, it is critical to choose biomaterials that are immunologically inert or exhibit inherent tolerogenic properties to avoid exacerbating pre-existing inflammation. Although a multitude of biomaterials have been developed as nanomaterials, this section will focus on major biomaterials with known tolerogenic properties that may be particularly useful for autoimmunity therapies.

2.2.1. Poly(D,L-lactide-co-glycolide) (PLGA)
PLGA is an aliphatic polyester that has been widely investigated and FDA-approved for drug delivery because of its excellent degradability and safety profile [52,80,81]. It is especially well-suited for encapsulating diverse therapeutic cargo because the porosity and degradation rate of the matrix can be tuned via the molecular weight and lactide:glycolide copolymer ratio [80]. In physiological environments, PLGA degrades by bulk erosion as water diffuses into the matrix and hydrolyzes ester bonds until the polymer dissolves into its original lactic acid and glycolic acid monomers, which are naturally-occurring metabolic by-products [82]. Numerous preclinical studies have successfully used PLGA nano- and microparticles as vehicles for autoantigens and immunoregulatory cues, indicating that it may have innate tolerogenic properties [58,83–85]. One study that exemplifies this demonstrated that drug-free PLGA particles without any active pharmaceutical ingredient or targeting ligand reduced clinical scores in experimental autoimmune encephalomyelitis (EAE), a mouse model of MS [86]. This effect was greatest for particles containing high molecular weight PLGA. A T1D study reported a similar finding: while PLGA microparticles encapsulating insulin peptide best delayed hyperglycemia onset in nonobese diabetic (NOD) mice, PLGA microparticles alone also significantly delayed disease onset [87]. While the exact relationship remains controversial, many studies have found that the size of PLGA particles greatly influences immune outcomes [82]. Immune responses to PLGA may further depend on the lactide:glycolide copolymer ratio. While the aforementioned EAE and T1D studies both employed 50:50 PLGA (the most commonly used ratio), two studies found that 75:25 PLGA induces maturation in cultured dendritic cells, which indicates a propensity for a pro-inflammatory response [88,89]. Thus, PLGA NPs have the ability to be anti- or pro-inflammatory depending upon their specific composition, and thus are suitable or unsuitable, respectively, for autoimmunity therapies.

2.2.2. Lipids
Lipid-based delivery systems, including liposomes and lipid nanoparticles (LNPs), are among the most widely investigated nanoparticle classes for drug delivery [90–92]. From the FDA approval of liposomal doxorubicin (Doxil) in the 1990s to the more recent approval of mRNA LNP vaccines during the SARS-CoV-2 pandemic, they are also the most clinically advanced [93–96]. Liposomes and LNPs are composed of mixtures of lipids that are structurally similar to those in the cell membrane. These lipids generally include cholesterol and phospholipid,

which provide structure, rigidity and fluidity to the nanoparticle [90,97,98]. Liposomes consist of a single aqueous core surrounded by a lipid bilayer, while LNPs contain a solid lipid core with smaller hydrophilic compartments [99]. The immunological activity of liposomes and LNPs is extremely tunable depending on the specific lipid composition [99,100]. Cationic and ionizable cationic lipids produce liposomes and LNPs with potent and inflammatory adjuvant activity, while negatively charged lipids impart these particles with tolerogenic properties [101,53,54,57]. In particular, phosphatidylserine and phosphoglycerol have been widely studied as tolerogenic lipid components [56]. Phosphatidylserine is thought to induce tolerogenic activity through apoptotic mimicry [102,56,57,60]. During apoptosis, phosphatidylserine is exposed on the outer leaflet of the cell membrane, presenting an "eat me" signal to the immune system [60]. Phosphatidylserine presentation triggers efferocytosis, the process by which phagocytes clear apoptotic cells. Phagocytes release anti-inflammatory cytokines such as IL-10 and TGF-β during engulfment to resolve local inflammation and promote tissue repair [103]. Antigens contained within the phagocytosed, apoptotic cells are in turn processed and presented on MHC complexes to T cells, which induce a tolerizing response in the presence of anti-inflammatory cytokines [57,102,104]. Phosphatidylserine has been incorporated into liposomes and LNPs delivering antigen to induce antigen-specific immune tolerance in animal models of MS, T1D, RA, and myasthenia gravis [101,102,105–108]. Phosphoglycerol-containing lipids have also been exploited to induce similar anti-inflammatory effects in a mouse model of atherosclerosis [101]. This study showed a tolerizing mechanism similar to that of phosphatidylserine; it identified the complement protein C1q as a critical component of the protein corona bound to phosphoglycerol-containing liposomes, which in turn also binds to phosphatidylserine exposed on apoptotic cells [101,109].

3. Avoiding systemic suppression via tissue targeting and controlled drug release

Systemic immunosuppression is the standard of care in autoimmune disorders, which increases the risk of the body acquiring other immunological disorders such as bacterial infections, viruses, and can even lead to the formation of tumors [110]. This is partially because although pathological cell and tissue types in autoimmune disease have been identified, specifically targeting these cells and tissues with current therapies without observing off-target effects is extremely difficult [110]. Additionally, the common cell types implicated across various autoimmune etiologies are immune cells such as macrophages, dendritic cells, neutrophils, T cells and B cells, all of which have multi-faceted physiological functions [110]. Maintaining the physiological function while hindering the pathological function of these cells upon therapeutic delivery is an important consideration. Thus, lack of specificity remains a major challenge in the development of autoimmunity therapies.

Though nanomedicines result in the efficient intracellular delivery of therapeutic cargo, achieving this delivery in specific cell populations can be challenging. Most nanomedicines that are administered intravenously are susceptible to hepatic clearance [30,111]. As blood is filtered by the liver, nanoparticles in the blood are filtered into the liver as well [111,112]. The fenestrated epithelium of the liver facilitates this as well by reducing physiological barriers to nanoparticle uptake by hepatocytes [112]. This decreases the potential therapeutic benefit of nanomedicines in extrahepatic tissues. To overcome this challenge and achieve cell-specific targeting of nanomedicines, several strategies can be employed. Targeting can be achieved by modulating the physicochemical properties of nanomedicines to dictate tropism or through molecular targeting accomplished by modifying the surfaces of nanomedicines with ligands such as peptides, proteins, or mAbs that target specific molecular receptors on cells and tissues [113,114,53]. These strategies, when synergized with a specific route of nanoparticle administration (e.g., intravenous, intraperitoneal, intramuscular), can result in extrahepatic tropism and fine control over cell- and tissue-

specific delivery [53].

3.1. Physicochemical targeting

Nanomedicines are highly modular and tunable, allowing for changes to their physicochemical properties such as size, charge and composition. This modularity allows for control of tissue tropism and delivery to specific cell types (Fig. 2A) [115]. For example, lipoplexes and LNPs containing cationic lipids enable efficient nucleic acid delivery to the lung endothelium and epithelium [53,116]. In contrast, LNPs including anionic lipids effectively deliver cargoes to the spleen instead, underscoring the importance of charge modification in dictating organ tropism of nanomedicines [53,54,56]. As splenocytes are primarily either immune cells or support cells involved in maintaining peripheral tolerance, spleen-tropic LNPs hold great promise in being utilized for autoimmunity therapies. Modulating the charge of nanoparticles can also enable control over drug release within a specific cell or tissue target of interest. For example, nanoparticles constructed through layer-by-layer (LbL) assembly of oppositely charged polymers, lipids, metals or other materials of interest exhibit multi-faceted control over cargo delivery: the outer layer can dictate which cell type the nanoparticle is delivered to, and the inner layers can control the release of the encapsulated drug upon delivery to the cell of interest [117,118]. LbL nanoparticles with anionic outer layers have been shown to effectively accumulate and deliver cargo to ovarian cancer cells both *in vitro* and *in*

vivo [119]. Thus, utilizing charge to dictate nanoparticle tropism could be a viable strategy in autoimmunity therapies as well.

Interestingly, the specific material composition of nanoparticles can also dictate physicochemical targeting. For example, ferritin-nanoparticles have been shown to target APCs in secondary lymphoid tissues. These ferritin-nanoparticles, composed of self-assembling Spy-Tag-ferritin and SpyCatcher-antigen components, have been utilized to deliver the pre-S1 antigen to dendritic cells and macrophages as a vaccine strategy against hepatitis B virus (HBV) [120]. As a result, these nanoparticles could potentially be used for tolerizing vaccines in the context of autoimmune disorders. The tissue tropism of lipid-based nanomedicine can be determined by the structure of ionizable lipids—the primary excipient that becomes charged in cellular endosomes and allows for endosomal escape and release of cargo within cells. LNPs with different ionizable lipids demonstrate differing tissue tropism and delivery efficacy both *in vivo* and *in vitro* [121,122,97]. Depending on the ionizable lipid, LNPs differentially transfect T cells, liver cells, pancreatic cells, placental cells, splenic cells and peripheral blood mononuclear cells, resulting in the use of different LNP formulations for specific applications [121,122,97]. Modifying the other excipient lipids—cholesterol, helper lipid, and PEG-lipid—also alters tissue tropism and delivery efficacy [100,122–124]. For example, optimizing LNP excipients using a design of experiments (DoE) approach led to the identification of top-performing LNPs that resulted in a significant improvement in mRNA delivery to placental cells *in vitro* and also
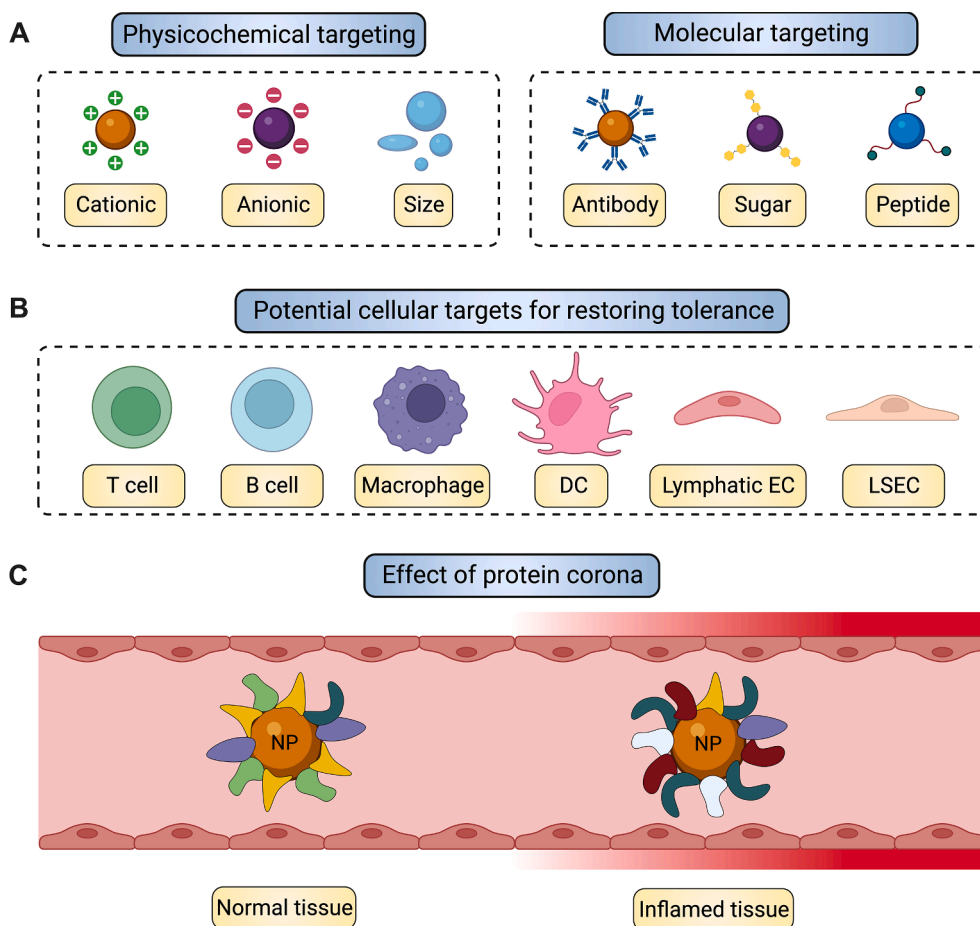

Fig. 2. Modulating characteristics of nanomedicines to achieve cell- or organ-targeting. (A) Strategies for altering the physicochemical properties as well as the surface chemistry of nanomedicines to achieve cell- or organ-specific delivery. (B) Several cellular targets, including immune and non-immune cells, that nano-medicines can engineer for therapeutic applications. These cells not only have the potential to reduce inflammation but can also maintain and propagate peripheral tolerance, leading to a more durable autoimmune disease therapy. (C) Differential formation of the protein corona around intravenously administered nanoparticles (NPs) in normal versus inflamed conditions. The altered protein corona has the power to redirect nanoparticle tropism and alter expected therapeutic outcomes. DC, dendritic cell; EC, endothelial cell; LSEC, liver sinusoidal endothelial cell.

enhanced extrahepatic delivery to the placenta *in vivo* [122,125,126]. The DoE approach for optimizing formulations has also been shown to increase LNP delivery efficacy in immune cells, establishing potential for this strategy to be utilized in nanomedicine-based autoimmunity therapies [100]. Thus, the specific nanoparticle composition along with the biomaterial of choice can control tropism and delivery efficacy of nanoparticles in physiological systems.

3.2. Molecular targeting

Molecular targeting can also be used to target specific cell types by functionalizing nanoparticles with bioactive components (i.e., a sugar, peptide, protein or antibody) that bind specific cell surface receptors (Fig. 2A) [127]. This heightened specificity from the receptor-ligand interaction results in more 'active' control of cell and tissue tropism [127]. Targeting ligands can be conjugated to the surface of nanomedicines using various conjugation chemistries, including but not limited to maleimide-thiol, gold-thiol, DBCO/BCN/alkyne-azide, biotin-streptavidin, and EDC/NHS [113,114,61]. The conjugation technique can be chosen based on choice of biomaterial, encapsulated cargo, and intended biological application.

One of the most crucial advantages of molecular targeting is the ability to increase organ-specific accumulation and delivery of nanomedicine and their cargoes. For example, intercellular adhesion molecule 1 (ICAM)-targeted nanoparticles resulted in increased delivery of lipid-based and polymer-based nanoparticles to the lungs and brain in a mouse model of acute brain inflammation [128]. Within organs, molecular targeting can also allow for control of cell-specific delivery – an important advantage because different cell types are therapeutically relevant across different diseases. A prime example highlighting the importance of this is cell-specific delivery within the liver. Intravenous administration of nanomedicines generally results in delivery and accumulation in hepatocytes [112]. However, liver sinusoidal endothelial cells (LSECs) have emerged as an important cell type in generating and maintaining peripheral tolerance. LSECs, which play a role in the scavenger clearance system, have also been found to function as tolerogenic APCs and interact with and promote T_{reg} cell expansion (Fig. 2B) [129,130]. To achieve preferential delivery to LSECs over hepatocytes, mannose ligand-decorated nanoparticles have been employed [130,131]. These mannose ligand-decorated nanoparticles were used to deliver peanut allergen-encoding mRNA to LSECs, thereby sensitizing the system to the allergen and resulting in reduced symptoms of anaphylaxis when challenged with crude peanut allergen extract [130]. Similarly, LSECs could be targeted using nanomedicine for inducing tolerogenic responses in autoimmunity therapies.

Besides specific cell types in the liver, targeting immune cells as well as neighboring cells that provide signals to propagate the inflammatory cascade is crucial [132,133]. Fortunately, several nanomedicine-based approaches to actively target these cell types have been established. For example, mRNA LNPs have been functionalized with anti-CD4 as well as anti-CD5 or anti-CD7 mAb fragments using thiol-maleimide chemistry to specifically target CD4^{+} T cells or T cells in general, respectively (Fig. 2B) [113,134,135]. LNPs have also been functionalized with anti-podoplanin mAbs using azide-DBCO chemistry to target lymphatic endothelial cells—an important and understudied cell type in maintaining immune homeostasis—to achieve siRNA delivery [114]. On the polymeric side, alginate-based nanoparticles have been functionalized with tuftsin protein to specifically target macrophages with the objective of repolarizing them from pro-inflammatory M1 to anti-inflammatory M2 macrophages in RA [136]. The nanoparticles were loaded with plasmids encoding IL-10, which is a known cytokine that facilitates macrophage repolarization and induces T_{reg} cell responses [136]. Interestingly, a polymer-lipid hybrid nanoparticle decorated with CD22L—a B cell inhibitory co-receptor—was used to specifically suppress B cell activation and antigen recognition in a mouse model of RA [137]. Therefore, targeting the various immune cells that act in concert

with one another using molecular targeting strategies can be a viable strategy in tackling autoimmune diseases.

3.3. Emerging prospect: protein corona

An interesting challenge that both physicochemical and molecular targeting approaches face is the formation of the protein corona around nanomedicines (Fig. 2C) [138]. When nanomedicines are intravenously administered in physiological systems, they are immediately enveloped by various plasma proteins that adsorb to nanoparticle surface based on nanoparticle physicochemical characteristics (e.g., size, charge, curvature, biomaterial), protein characteristics (e.g., structure, size, charge, affinity), and physiological conditions (e.g., pH, ionic strength, concentration) [139]. This envelope around nanoparticles, termed the 'protein corona', has been shown to strongly influence cell/tissue tropism. For example, several LNP studies demonstrate that the adsorption of Apolipoprotein E (ApoE) to LNP surfaces results in enhanced delivery to the liver, especially in the case of nanoparticles administered intravenously [140,141]. These results have been corroborated by supplemental studies using ApoE knockout mice, highlighting that LNP delivery to the liver was significantly reduced when ApoE was not present [140,141].

The protein corona around nanoparticles also largely dictates extrahepatic tropism. As mentioned previously, lipid-based nanoparticles with charge alterations can result in extrahepatic delivery; specifically, nanoparticles with cationic lipids tend to accumulate in the lungs in healthy mice [53,142]. An interesting corollary to this study found that lipid-based nanoparticles accumulated in the lungs primarily due to the altered protein corona formed around them [54]. Another recent study showed that fibrinogen in the bloodstream adsorbed to cationic LNPs and initiated clotting, leading to thrombosis and severe lung toxicity in mice [143]. This effect was exacerbated in the presence of pre-existing inflammation [143]. Thus, nanoparticles with permanently cationic components may cause severe toxicity and potential worsening of any existing inflammation in an autoimmune disease state. In summary, the design of nanomedicine for autoimmunity therapies must account for the protein corona forming around nanoparticles to create the most clinically translational and useful nanomedicine-based therapies.

4. Establishing balance between immune interaction and evasion

The acute and chronic inflammation found in autoimmune disorders results in aberrant changes in the immunological landscape of the body. As a result, therapies for autoimmune disorders can become ineffective due to interactions with the patient's altered immune system [109,144]. For example, in several cases where mAbs are administered, B cells generate antibodies against these therapies, causing their clearance and potentially leading to complement activation and increased inflammatory cytokines [27]. The occurrence and severity of these adverse reactions also depends on route of mAb administration (e.g., local vs systemic delivery), source and clone of mAb (e.g., mouse vs human) and frequency of treatment [145]. Overactive inflammatory macrophages—stemming from a generally overactive mononuclear phagocytic system (MPS)—may also result in the excessive clearance of any administered therapies, including nanomedicines [146].

A key challenge when designing nanomedicines for autoimmune disease is that nanomedicines are often inherently inflammatory [147]. When nanomedicines are taken up by cells through various endocytic pathways, they must escape the endosome to avoid degradation and release their contents intracellularly to achieve their therapeutic effect [148]. However, endosomal damage triggers activation of TLRs and other receptors that propagate the inflammatory cascade and result in the heightened immunogenicity that is observed for nanomedicine-based approaches [149]. In applications for cancer immunotherapy or

vaccines where adjuvant activity to boost immune responses is necessary, this property of nanomedicines is highly beneficial. However, this can quickly become detrimental in the context of pre-existing inflammation, such as in autoimmune diseases. For example, systemically administered LNPs were shown to drastically worsen inflammation in a mouse model of systemic LPS-induced inflammation compared to a non-inflamed system [143,150]. Therefore, nanomedicines must balance the interaction with and evasion of the immune system by delivering their cargo while simultaneously avoiding immune cell activation (Fig. 3).

4.1. Immune evasive and anti-inflammatory nanomedicine

Autoimmunity therapies can be excessively cleared or be hindered by immune responses against the therapies themselves. Therefore, using immune evasive or anti-inflammatory nanomedicine-based therapies in autoimmune diseases is key. As discussed previously, one popular strategy to disguise nanomedicines from the immune system is coating them with PEG, a strategy also employed by several mAbs used in the clinic (Fig. 3) [69,71]. One potential drawback is the generation of anti-PEG antibodies by the body that may lead to accelerated clearance and, in extreme cases, anaphylaxis [73]. While this presents challenges for any PEG-containing drug, it is especially crucial to consider anti-PEG antibodies when developing nanomedicines for conditions characterized by pre-existing inflammation. Another strategy to develop immune evasive nanoparticles is to coat nanoparticles with cell membrane-derived or exosome membrane-derived coatings [151–154]. The outer layer of the nanoparticles is naturally derived from cells or cell products; as a result, the outer layer contains 'self' markers, preventing immediate clearance by the MPS [151,154]. Macrophage membrane-coated or

Fig. 3. Avenues for controlling interactions of nanomedicines with the immune system. Nanomedicines can be engineered to be anti-inflammatory by incorporating tolerogenic or anti-inflammatory materials into their composition. Nanomedicines can also be coated with PEG, self-markers, or even cell membrane-derived coatings, prolonging their circulation time to allow them to reach the cell type of interest. Finally, nanomedicines can also be employed in *ex vivo* cell engineering applications to generate adoptive cell therapies such as CAR T$_{reg}$ cells or anti-inflammatory monocytes. Importantly, all three strategies can be used to engineer tolerogenic vaccines for combatting autoimmune diseases.

macrophage-derived nanoparticles can target sites of RA by leveraging ligand-specific macrophage binding to inflamed synovial tissue [155]. Engineered, macrophage-derived extracellular vesicles loaded with exogenous pDNA encoding the anti-inflammatory cytokine IL-10 or with tacrolimus-containing PLGA nanoparticles can reduce inflammation in a mouse model of collagen-induced arthritis [156,157]. Thus, this strategy not only achieves the same cloaking benefits as PEG, but can further specifically target inflamed tissue using a naturally derived coating.

Rather than evading the immune system altogether, nanoparticles can also be engineered to be anti-inflammatory and actively suppress the immune system. In addition to leveraging anti-inflammatory or tolerogenic biomaterials (as described previously), anti-inflammatory nanoparticles can enable tissue-specific delivery of immunosuppressants (Fig. 3) [158,159]. Nanoparticle encapsulation has the advantage of enhancing the delivery of immunosuppressants to the relevant inflamed tissues while simultaneously reducing their systemic delivery, which can be toxic [158,159]. For example, dexamethasone and rapamycin-loaded nanoparticles have been widely investigated for alleviating inflammation and inducing antigen-specific tolerance in models of RA, MS, and T1D [158,160,161]. Further, LNPs containing dexamethasone can both enhance mRNA delivery relative to LNPs without dexamethasone and reduce inflammatory cytokine levels in mice [162]. Extrapolating this idea, several other nanomedicine-based approaches could be used to deliver other anti-inflammatory drugs such as DMARDs and other corticosteroids in a more controlled fashion. Thus, nanomedicines can be rationally designed based on the chosen biomaterial and encapsulated cargo to evade or antagonize the immune system.

4.2. Tolerogenic vaccines

Tolerogenic vaccination has become a promising therapeutic strategy for autoimmunity therapies [163,164]. Tolerogenic vaccines bypass the need for global immunosuppression and directly address the need for restoring physiological tolerance. While traditional vaccines require immune stimulation and propagation of the inflammatory cascade for therapeutic effect, tolerogenic vaccines aim to target autoantigen-specific pathology while leaving the rest of the immune system intact [163]. Although the immune pathways of antigen presentation and subsequent adaptive immune system induction are common between traditional and tolerogenic vaccines, tolerogenic vaccines rely on the presence of suppressive or anti-inflammatory cues to skew the development of APCs towards a tolerogenic state [165]. These tolerogenic APCs allow for the generation of antigen-specific Treg cells that are able to induce peripheral tolerance, similar to a normal immune homeostatic state.

Tolerogenic vaccines have explored the use of autoantigen peptides as well as DNA and mRNA encoding autoantigens to achieve vaccination [166–169]. To control the tropism, release profile and delivery efficacy of these autoantigens, nanomedicine-based strategies have been utilized. For example, mesoporous silica nanoparticles (MSNs) encapsulating MOG autoantigen demonstrated reversal of autoimmune phenotype in EAE mice [166]. Intravenous delivery of autoantigen resulted in induction of peripheral tolerance in the spleen, indicated by the increase in Treg cells, as well as prevented inflammatory dendritic cells from migrating into the central nervous system to propagate demyelination [166]. In another study, autoantigen conjugated to a glycosylated polymer (pGal) was shown to result in similar induction of tolerance via delivery to liver sinusoidal endothelial cells in an EAE mouse model as well as an antigen-specific non-human primate (NHP) model [167]. This study also demonstrated that the administration of pGal resulted in the upregulation of co-inhibitory receptors (PD-1, CTLA-4) on tolerized T cells, indicating that the tolerized T cells were capable of inducing anergy in autoantigen-specific pathogenic T cells [167]. Thus, nanomedicine-based tolerogenic vaccines for autoimmune disease show great potential in addressing the root problem of autoimmune diseases.
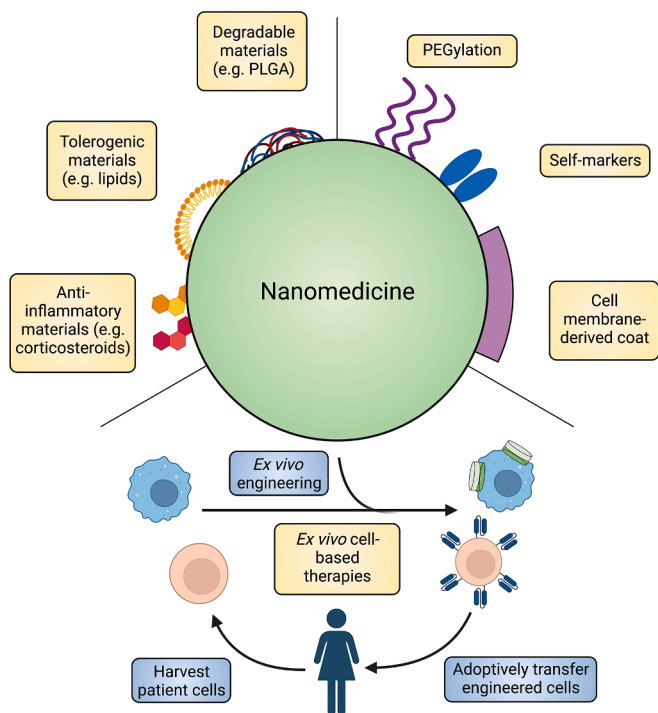
4.3. Adoptive cell therapies

Adoptive cell therapies also hold great promise for treating autoimmune diseases (Fig. 3). Cells for adoptive transfer therapies are typically engineered *ex vivo* using retroviral vectors [170]. However, because viral vectors are limited in DNA cargo capacity, batch-to-batch variability, and increased regulatory requirements, nanoparticle-based cell engineering is becoming increasingly popular [97,170–172]. Further, by engineering immune cells in an *ex vivo* setting, the interaction between nanomedicine and immune cells can be carefully controlled, and the risk of systemic inflammation exacerbation is greatly reduced. For example, PLGA and PVA-heparin nanodiscs or 'backpacks' containing dexamethasone and IL-4 were conjugated to monocytes *ex vivo* to generate a myeloid cell-based therapy for MS [173]. Dexamethasone and IL-4 served as agents to maintain the monocytes in a suppressive rather than inflammatory state—similar to the anti-inflammatory cues needed for tolerogenic DC generation—resulting in improved CNS-related symptoms in an EAE mouse model [173].

Immune cells can also be engineered to be antigen-specific in an *ex vivo* setting. For example, chimeric antigen receptor (CAR)-functionalized immune cells have demonstrated high antigen specificity and great clinical efficacy in the context of cancer [97,100]. Although traditionally done through viral vectors, inducing CAR expression in immune cells can also be achieved through nanomedicine. Using nanomedicine to induce CAR expression avoids the potential genotoxicity and cytotoxicity associated with viral vectors and allows for safer outcomes [97,100]. For example, LNPs have been explored to deliver mRNA to T cells and generate chimeric antigen receptor (CAR) T cells *ex vivo* [97]. These CAR T cells strongly express anti-CD19 CAR and demonstrate specific killing of cancer cells expressing CD19. Interestingly, these cancer therapies are being explored in autoimmune disease with several anti-CD19 and anti-BCMA CAR T cell therapies targeting B cells in clinical trials to treat SLE [174].

The idea of antigen-specific immune cells—specifically antigen-specific T_{reg} cells—can be further applied in the context of autoimmune diseases. For example, biodegradable microparticles loaded with rapamycin and functionalized with an IL-2 fusion protein were employed to expand T_{reg} cells that had an MHC loaded with a myelin peptide [175]. Expanding these myelin-specific T_{reg} cells allowed for generation of a high number of antigen-specific T_{reg} cells, which when administered *in vivo* were able to reverse the MS phenotype in EAE mice [175]. This approach aimed at restoring tolerance through harnessing the innate tolerogenic potential of Treg cells – a strategy that has quickly become an emerging prospect.

4.4. Emerging prospect: CAR T_{reg} cells

Borrowing from the cancer research space, tolerogenic T_{reg} cells can also be endowed with CARs to improve their honing ability to specific cells and induce antigen-specific immunosuppression [176,177]. For example, CAR T_{reg} cells were engineered *ex vivo* to recognize the alloantigen Bw6 and were adoptively transferred into a non-human primate with a Bw6+ allograft. These CAR T_{reg} cells demonstrated increased trafficking to the graft site and exhibited an immunosuppressive phenotype, which prevented rejection of the transplanted graft [177]. Extrapolating this idea, CAR T_{reg} cells could be engineered using nanomedicines to be antigen-specific to autoimmune disease-related antigens (e.g., myelin peptide in MS) and achieve therapeutic effect.

Since 2018, several biotechnology companies have turned their attention to engineering T_{reg} cells for applications in organ transplantation, allergies, and, importantly, autoimmune disorders [178]. Excitingly, nanomedicine has already demonstrated success in delivering a plethora of cargoes to achieve efficient *ex vivo* immune cell engineering. Thus, the combination of nanomedicines and T_{reg} cells provides a promising next step in the development of next-generation cell-based therapies for autoimmunity. Furthermore, other immune cells, such as tolerogenic dendritic cells, B cells or monocytes, could also be engineered in a similar fashion to create a wide variety of immune cell-based therapies to tackle different types of autoimmune diseases.

5. Elevated delivery platforms for challenging cargoes

Current therapies for autoimmune disease, such as mAbs or corticosteroids, focus on mitigating one specific step in the inflammatory cascade. However, the complexity of autoimmune disorders results in pathologies that, oftentimes, cannot be solved by such a linear approach [2]. Thus, therapies for autoimmune disorders necessitate strategic approaches that further existing therapies to elevate the current standard of care while tackling more than one autoimmune disease pathology.

5.1. Direct delivery of peptides, proteins and mAbs

One strategy is to use nanomedicine to facilitate the delivery of complex cargoes such as peptides, proteins, and mAbs, which cannot easily traverse the cell membrane to achieve an intracellular effect (Fig. 4A) [179–181]. In cancer immunotherapy, delivery of proteins and mAbs can be used to target 'undruggable' targets or even metastasizing tumors. For example, LNPs encapsulating designed ankyrin repeat proteins (DARPins) that inhibit mutated RAS proteins were shown to improve intracellular DARPin delivery and subsequently reduce tumor burden in an HTVI-induced mouse model when compared to freely administered DARPins [180]. This strategy can be used to deliver autoantigen peptides as well as full proteins in the context of tolerogenic vaccines. Another study encapsulated the mAb Rituximab within a zwitterionic polymer nanoparticle to allow for its sustained release and improve delivery to metastasized tumor in the CNS by tenfold when compared to free antibody [182]. This is especially useful in autoimmune disorders where currently FDA-approved antibody-based therapies can be packaged into delivery vehicles to improve the safety and circulation time of these therapies.

In the context of controlling inflammation, complex cargo delivery can result in desirable modulation of the local physiological microenvironment. For example, intraocular delivery of Connexin43 mimetic peptide (Cx43 MP) using hyaluronic acid-coated albumin nanoparticles showed reduced retinal damage in a rat model of retinal ischemia [183]. The sustained release of Cx43 MP reduced retinal thinning and was able to suppress nearby inflammation, resulting in preservation of the retinal vasculature [183]. These strategies to directly deliver proteins, mAbs and peptides could be leveraged to address inflammation in autoimmunity therapies as well.

5.2. Co-delivery of therapeutics

Another strategy to combat the several facets of autoimmune disease is to co-deliver two or more therapeutics. There are several considerations when combining therapeutics, including dosage, timing, interactions of the therapeutics, and potential side effects resulting from the combined therapy [184,185]. Fortunately, nanomedicine can be used to co-deliver therapeutics in a synergistic fashion (Fig. 4B). Nucleic acids such as messenger RNA (mRNA), small interfering RNA (siRNA), single guide RNA (sgRNA), plasmid DNA (pDNA) and single-stranded DNA (ssDNA) have been co-delivered using various types of nanomedicines [184,185]. mRNA and siRNA, for example, have been co-delivered using LNPs and have demonstrated synergistic effects in the functionality of both. In T cells, co-delivery of CAR mRNA and PD-1 siRNA led to improved expression of CAR and greater knockdown of PD-1, respectively, resulting in CAR T cells that were highly functional and also resisted exhaustion [184]. This finding is beneficial to autoimmunity therapies, as CAR T cells are now also being explored to achieve B cell depletion in the context of autoantibody-mediated autoimmune disorders.

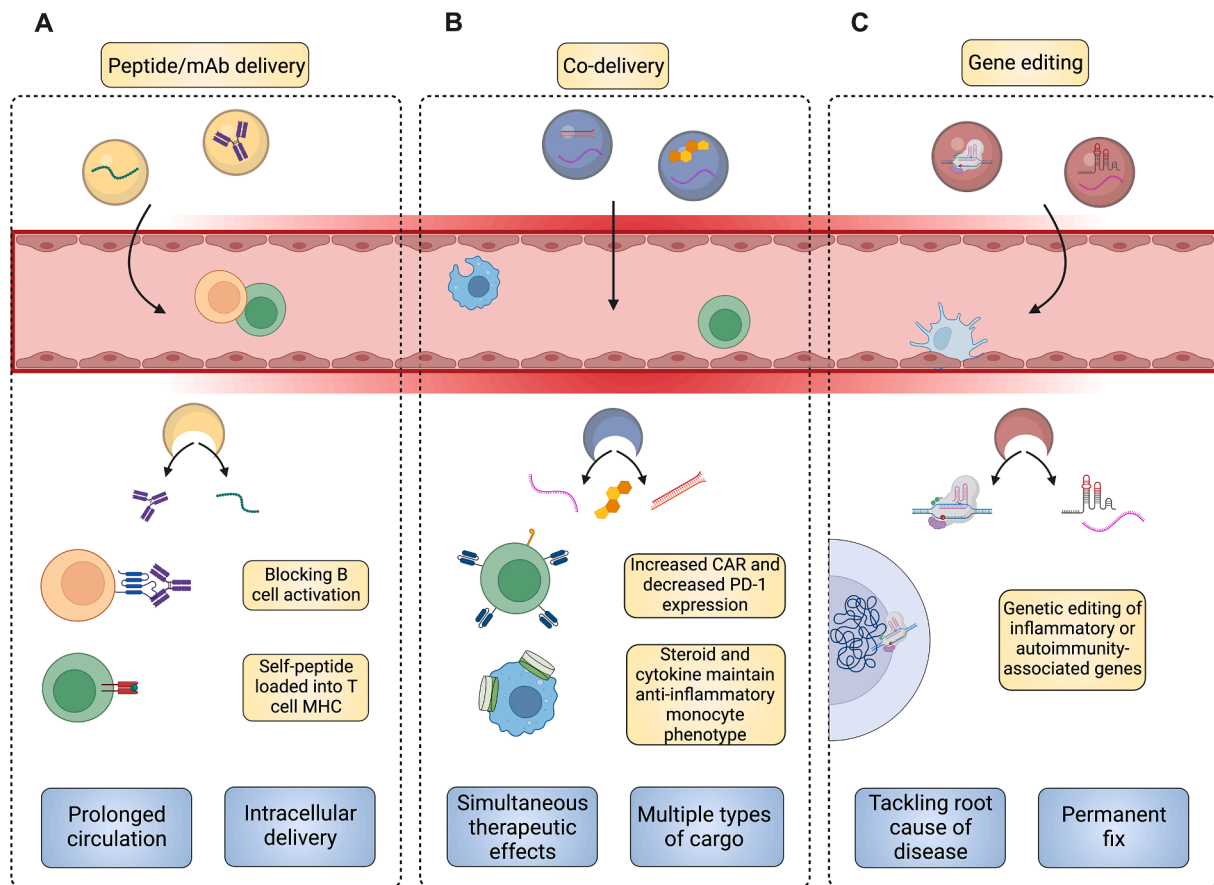Nanomedicines can also be used to co-deliver different types of

Fig. 4. Employing nanomedicine-based platforms for delivery of complex cargoes. (A) Peptides, proteins and monoclonal antibodies, which do not cross the cell membrane readily and are easily cleared by the scavenger system, can be packaged inside nanomedicines to prolong their circulation time and achieve intracellular delivery. (B) Different types of cargoes can be co-encapsulated inside nanoparticles to achieve a simultaneous and synergistic therapeutic effect. Cargoes like mRNA and siRNA or even mRNA and corticosteroids can be packaged into nanoparticles and be co-delivered. (C) Gene editing technologies that are able to tackle the genetic basis of autoimmune disease can also be elevated using nanomedicine. Next-generation autoimmunity therapies can focus on using nanoparticles to dictate tropism to specific cell types and deliver the gene editing machinery intracellularly, enabling the editing of autoimmunity-associated genes and addressing the biological basis of disease.

cargoes simultaneously. Emulsions made from incomplete Freund's adjuvant were used to co-deliver dexamethasone (corticosteroid) and proteolipid protein autoantigen (antigen) in an EAE mouse model, resulting in increased humoral responses and a shift away from inflammation [186]. Similarly, PLGA and PVA-heparin nanodiscs or 'backpacks' containing dexamethasone (corticosteroid) and IL-4 (cytokine) were latched onto monocytes *ex vivo* to generate a cell-based therapy for MS [173]. The backpacks resulted in co-delivery of dexamethasone and IL-4, which induced anti-inflammatory phenotypes in monocytes [173]. Upon adoptive transfer, the monocytes were able to retain their anti-inflammatory properties due to the combined effect of both cargoes and were able to improve neurologic symptoms in an EAE mouse model. Thus, the ability of nanomedicines to co-encapsulate and co-deliver different cargoes simultaneously is an important benefit that can be leveraged in the realm of autoimmunity.

5.3. Emerging prospect: gene editing

Since the early 2000s, genetic engineering using gene editing technologies such as base editors and CRISPR-based systems has revolutionized therapeutic avenues across a plethora of diseases [173,187]. These strategies can target genetic defects that lead to disease pathology and thus address the root cause of the disease with permanent genome editing. Autoimmune diseases have been known to arise from an interplay between genetic predisposition as well as environmental factors [2,188]. Thus, the associated genetic changes can be visualized and

analyzed using several sequencing techniques, including single cell RNA-seq (scRNA-seq), high-depth RNA-seq, ATAC-seq, ChIP-seq, and One-seq. [189,207,208] With these gene editing and sequencing tools established, tackling the genetic arm of autoimmune diseases is a promising therapeutic avenue for the reversal of these disease phenotypes. However, achieving precise, timely and functional delivery of complex gene editing machinery presents a major challenge.

Nanomedicines have been widely explored to deliver gene editing cargoes to a variety of different cell types (Fig. 4C). Specifically, LNPs have been explored to deliver mRNA encoding base editors or even sgRNA and mRNA encoding SpCas9 in applications for congenital brain disease, cardiovascular disease, and even organ transplant applications [189–191]. For example, LNPs encapsulating an adenine base editor targeting PCSK9 were delivered in nonhuman primates to lower cholesterol levels, reducing the risk of cardiovascular disease [189]. Similarly, genes that are known to be mutated in autoimmune and autoinflammatory disorders could be corrected using nanomedicine-based gene editing technology. For example, the NLRP3 gene is known to be mutated in neonatal-onset multisystem inflammatory disease, which is a condition that causes damage in the skin, joints and nervous system [192]. Gene editing machinery can be used to correct NLRP3 gene and the subsequent protein cryopyrin, resulting in proper assembly and control of the inflammasome [192,193]. On the other hand, gene editing technology can be used to engineer therapies with utility in autoimmune disorders *ex vivo*. CAR T cells as well as chimeric autoantibody receptor (CAAR) T cells are currently being explored for

achieving B cell depletion in autoantibody-mediated autoimmune disorders [5,194]. One major limitation of this approach is that the patient could have adverse reactions to the adoptively transferred T cells due to HLA mismatch [195]. By going one step further in the CAR or CAAR engineering process, T cell membrane proteins such as beta-2 microglobulin (B2M), endogenous T cell receptor (TCR) and PD-1 can be knocked out using gene editing to make these cells allogeneic and resistant to exhaustion [196,197].

One of the major concerns with gene editing technologies is editing in off-target cells and tissues as well as off-target editing in on-target tissues, which could result in unpredictable adverse events [198]. Targeting strategies for nanomedicines discussed previously can be employed to mitigate off-target effects and result in more on-target delivery of gene editing cargoes. For example, poly(beta-amino ester) (PBAE) polymeric nanoparticles coated in a macrophage-derived membrane encapsulating pDNA encoding for destabilized Cas9 (dsCas9) protein and sgRNA were used to induce editing [153]. The cell membrane coating on the nanoparticle allowed for preferential tropism towards sites of inflammation. Additionally, the outer layer of the nanoparticle was functionalized with a reactive oxygen species (ROS)-responsive component that, upon exposure to ROS in an inflamed environment, resulted in cleavage from the nanoparticle surface and stabilized the expressed dsCas9 protein. The combination of ROS-responsive moieties as well as dsCas9 that only edited upon stabilization resulted in editing only at sites of inflammation [153]. Overall, nanomedicines can be combined with gene editing technologies to tackle the multi-faceted nature of autoimmune disorders and develop next-generation therapies for autoimmune diseases.

6. Future outlook and perspective

Autoimmune diseases represent a massive burden on global healthcare, with numbers rising every day. Furthermore, chronic autoimmune conditions require regular and frequent therapy administration, resulting in patients also facing an immense economic burden. These issues persist because current autoimmunity therapies simply mitigate inflammation systemically and target components of the inflammatory cascade. The development of next-generation autoimmunity therapies should focus on restoring immune homeostasis rather than ameliorating downstream inflammation – a strategy that works well with the application of nanomedicines.

Unfortunately, current nanomedicine-based approaches face challenges that hinder their rapid clinical translation. Polymer-based NPs, lipid-based NPs and cell membrane-coated or derived NPs have issues relating to stability in solution over time as well as premature cargo release and cargo degradation. Polymeric NPs such as PLGA NPs have hydrophobic cores, which limit their utility to primarily hydrophobic cargoes. Thus, depending on the cargo of choice, either the polymers themselves or the cargoes must be engineered. For lipid-based systems, including cationic components in the formulation increases delivery efficacy but can exacerbate toxicity. LNPs tend to have innate adjuvant activity; therefore, utilizing them for autoimmunity therapies is challenging. Finally, cell membrane-coated or derived particles are limited by the availability of cells, the heterogenous expression of membrane proteins and the amount of membrane that can be derived from the cells at once.

While there are limitations pertaining to individual classes of nanomedicines, nanomedicines broadly pose several advantages in terms of restoring tolerance in autoimmune diseases. Nanomedicines have tunable physicochemical and surface modification properties that can be modulated to result in cell- and tissue-specific delivery. This property can be leveraged to specifically deliver auto-antigens to regulatory T cells and tolerogenic dendritic cells, which are cells that are capable of propagating peripheral tolerance. Nanomedicines can also be carefully engineered to control their interactions with the immune system and generate therapies suited for the inflamed physiological

environment found in autoimmune diseases. This property can be employed to avoid the inflammation exacerbation that accompanies nanomedicine-based therapies. Moreover, nanomedicines can tackle autoimmune disease pathologies on multiple fronts, resulting in holistic and multi-faceted therapeutic avenues. This property can be utilized to multiplex novel nanomedicine-based approaches with currently FDA-approved therapies, potentially expediting clinical translation.

Besides the physiological advantages, one pivotal advantage of nanomedicine-based therapies is the relative ease with which they can be scaled up to achieve clinical translation and impact. The most pertinent example is the scale up of the mRNA LNP COVID-19 vaccines developed by Moderna and Pfizer BioNTech [93–95]. When vaccines were in dire need to prevent the global spread of COVID-19 in 2020–2021, the production of the LNP vaccines was immensely scaled up. More importantly, this unprecedented scale up demonstrated consistent physicochemical properties and delivery efficacy of LNPs with low batch-to-batch variability, resulting in a reliable and rapid distribution of vaccines worldwide. Thus, the scalability along with other physiological advantages make nanomedicines an attractive platform to be used in next-generation autoimmunity therapies.

Despite the benefits outweighing the limitations, nanomedicines are severely underutilized in autoimmunity therapies. This is primarily due to nanomedicines being extremely understudied in the context of autoimmune disease conditions, causing a broad lack of scientific confidence in the medical community. As such, more resources must be given to fund autoimmune disease research, specifically fundamental autoimmunity research, to identify pathogenic antigens that can be leveraged to develop nanomedicine-based antigen-specific autoimmunity therapies. Better animal models closely mimicking human autoimmune disease pathogenesis are needed to improve preclinical evaluation of nanomedicine-based therapies. Further research must also be conducted to elucidate the structure–function relationships of nanomedicine-based therapies across the varied pathologies of autoimmune diseases. Additionally, more light must be shed on the mechanisms governing nanoparticle delivery to immune cells and inflamed tissues. By employing the aforementioned strategies, nanomedicines can substantially reduce the global healthcare burden and revolutionize the development of next-generation autoimmunity therapies.

Author contributions

All authors conceived the outline and wrote the manuscript. A.S.T designed all the figures in Biorender. All authors edited the manuscript and approved the final version for submission.

CRediT authorship contribution statement

Ajay S. Thatte: Conceptualization, Writing – original draft, Writing – review and editing, Visualization, Validation, Software. **Margaret M. Billingsley:** Conceptualization, Writing – original draft, Writing – review and editing. **Drew Weissman:** Funding acquisition, Writing – review and editing, Supervision, Resources. **Jilian R. Melamed:** Conceptualization, Writing – original draft, Writing – review and editing, Supervision, Project administration. **Michael J. Mitchell:** Conceptualization, Funding acquisition, Writing – review and editing, Supervision, Resources, Project administration, Software.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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References

[1] F.W. Miller, L. Alfredsson, K.H. Costenbader, D.L. Kamen, L.M. Nelson, J. M. Norris, A.J. De Roos, Epidemiology of environmental exposures and human autoimmune diseases: findings from a national institute of environmental health sciences expert panel workshop, J. Autoimmun. 39 (4) (2012) 259–271, https://doi.org/10.1016/j.jaut.2012.05.002.

[2] D.S. Pisetsky, Pathogenesis of autoimmune disease, Nat. Rev. Nephrol. 19 (8) (2023) 509–524, https://doi.org/10.1038/s41581-023-00720-1.

[3] P. Marrack, J. Kappler, B.L. Kotzin, Autoimmune disease: why and where it occurs, Nat. Med. 7 (8) (2001) 899–905, https://doi.org/10.1038/90935.

[4] L. Fugger, L.T. Jensen, J. Rossjohn, Challenges, progress, and prospects of developing therapies to treat autoimmune diseases, Cell 181 (1) (2020) 63–80, https://doi.org/10.1016/j.cell.2020.03.007.

[5] D.S.W. Lee, O.L. Rojas, J.L. Gommerman, B cell depletion therapies in autoimmune disease: advances and mechanistic insights, Nat. Rev. Drug Discov. 20 (3) (2021) 179–199, https://doi.org/10.1038/s41573-020-00092-2.

[6] B.N. Cronstein, T.M. Aune, Methotrexate and its mechanisms of action in inflammatory arthritis, Nat. Rev. Rheumatol. 16 (3) (2020) 145–154, https://doi.org/10.1038/s41584-020-0373-9.

[7] A.S. Fauci, Corticosteroids in autoimmune disease, Hosp. Pract. 18 (10) (1983) 99–114, https://doi.org/10.1080/21548331.1983.11702661.

[8] H. Li, Y. Gao, L. Xie, R. Wang, R. Duan, Z. Li, B. Chen, L. Zhu, X. Wang, W. Su, Prednisone reprograms the transcriptional immune cell landscape in CNS autoimmune disease, Front. Immunol. 12 (2021) 739605, https://doi.org/10.3389/fimmu.2021.739605.

[9] E.M. El-Shebiny, E.S. Zahran, S.A. Shoeib, E.S. Habib, Bridging autoinflammatory and autoimmune diseases, Egypt J Intern Med 33 (1) (2021) 11, https://doi.org/10.1186/s43162-021-00040-5.

[10] Z. Szekanecz, I.B. McInnes, G. Schett, S. Szamosi, S. Benkő, G. Szűcs, Autoinflammation and autoimmunity across rheumatic and musculoskeletal diseases, Nat. Rev. Rheumatol. 17 (10) (2021) 585–595, https://doi.org/10.1038/s41584-021-00652-9.

[11] M. Wahren-Herlenius, T. Dörner, Immunopathogenic mechanisms of systemic autoimmune disease, Lancet 382 (9894) (2013) 819–831, https://doi.org/10.1016/S0140-6736(13)60954-X.

[12] B. Kyewski, L. Klein, A central role for central tolerance, Annu. Rev. Immunol. 24 (1) (2006) 571–606, https://doi.org/10.1146/annurev.immunol.23.021704.115601.

[13] D.M. Richards, B. Kyewski, M. Feuerer, Re-examining the nature and function of self-reactive T cells, Trends Immunol. 37 (2) (2016) 114–125, https://doi.org/10.1016/j.it.2015.12.005.

[14] A.N. Theofilopoulos, D.H. Kono, R. Baccala, The multiple pathways to autoimmunity, Nat. Immunol. 18 (7) (2017) 716–724, https://doi.org/10.1038/ni.3731.

[15] S.H. Venkatesha, M. Durai, K.D. Moudgil, Epitope spreading in autoimmune diseases, in: Infection and Autoimmunity, Elsevier, 2024, pp. 61–89, https://doi.org/10.1016/B978-0-323-99130-8.00038-6.

[16] S. Dong, K.J. Hiam-Galvez, C.T. Mowery, K.C. Herold, S.E. Gitelman, J. H. Esensten, W. Liu, A.P. Lares, A.S. Leinbach, M. Lee, V. Nguyen, S.J. Tamaki, W. Tamaki, C.M. Tamaki, M. Mehdizadeh, A.L. Putnam, M.H. Spitzer, C.J. Ye, Q. Tang, J.A. Bluestone, The effect of low-dose IL-2 and treg adoptive cell therapy in patients with type 1 diabetes, JCI Insight 6 (18) (2021) e147474.

[17] A. Schmidt, N. Oberle, P.H. Krammer, Molecular mechanisms of treg-mediated T cell suppression, Front. Immun. 3 (2012), https://doi.org/10.3389/fimmu.2012.00051.

[18] P. Cipriani, P. Ruscitti, F. Carubbi, V. Liakouli, R. Giacomelli, Methotrexate: an old new drug in autoimmune disease, Expert Rev. Clin. Immunol. 10 (11) (2014) 1519–1530, https://doi.org/10.1586/1744666X.2014.962996.

[19] T. Aoki, N. Noma, I. Takajo, J.-I. Yamaga, M. Otsuka, H. Yuchi, N. Ishikawa, H. Inatsu, J.-I. Sakata, Y. Asada, T. Eto, Protein-losing gastropathy associated with autoimmune disease: successful treatment with prednisolone, J. Gastroenterol. 37 (3) (2002) 204–209, https://doi.org/10.1007/s005350200022.

[20] U. Hafeez, H.K. Gan, A.M. Scott, Monoclonal antibodies as immunomodulatory therapy against cancer and autoimmune diseases, Curr. Opin. Pharmacol. 41 (2018) 114–121, https://doi.org/10.1016/j.coph.2018.05.010.

[21] J. Osbourn, L. Jermutus, A. Duncan, Current methods for the generation of human antibodies for the treatment of autoimmune diseases, Drug Discov. Today 8 (18) (2003) 845–851, https://doi.org/10.1016/S1359-6446(03)02803-4.

[22] R. Melsheimer, A. Geldhof, I. Apaolaza, T. Schaible, Remicade® (Infliximab): 20 years of contributions to science and medicine, BTT 13 (2019) 139–178, https://doi.org/10.2147/BTT.S207246.

[23] M.H. Schiff, Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis, Ann. Rheum. Dis. 65 (7) (2005) 889–894, https://doi.org/10.1136/ard.2005.043166.

[24] F. Waldron-Lynch, O. Henegariu, S. Deng, P. Preston-Hurlburt, J. Tooley, R. Flavell, K.C. Herold, Teplizumab induces human gut-tropic regulatory cells in humanized mice and patients, Sci. Transl. Med. 4 (118) (2012), https://doi.org/10.1126/scitranslmed.3003401.

[25] E.K. Sims, B.N. Bundy, K. Stier, E. Serti, N. Lim, S.A. Long, S.M. Geyer, A. Moran, C.J. Greenbaum, C. Evans-Molina, K.C. Herold, Type 1 Diabetes TrialNet Study Group, L.A. DiMeglio, S.E. Gitelman, P.A. Gottlieb, J.B. Marks, W. Moore, H. Rodriguez, W.E. Russell, D. Schatz, E. Tsalikian, D.K. Wherrett, A.-G. Ziegler, Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals, Sci. Transl. Med. 13 (583) (2021) eabc8980, https://doi.org/10.1126/scitranslmed.abc8980.

[26] K.L. Randall, Rituximab in autoimmune diseases, Aust. Prescr. 39 (4) (2016) 131–134, https://doi.org/10.18773/austprescr.2016.053.

[27] T.T. Hansel, H. Kropshofer, T. Singer, J.A. Mitchell, A.J.T. George, The safety and side effects of monoclonal antibodies, Nat. Rev. Drug Discov. 9 (4) (2010) 325–338, https://doi.org/10.1038/nrd3003.

[28] X. Duan, Y. Li, Physicochemical characteristics of nanoparticles affect circulation, biodistribution, cellular internalization, and trafficking, Small 9 (9–10) (2013) 1521–1532, https://doi.org/10.1002/smll.201201390.

[29] A. Albanese, P.S. Tang, W.C.W. Chan, The effect of nanoparticle size, shape, and surface chemistry on biological systems, Annu. Rev. Biomed. Eng. 14 (1) (2012) 1–16, https://doi.org/10.1146/annurev-bioeng-071811-150124.

[30] M.J. Mitchell, M.M. Billingsley, R.M. Haley, M.E. Wechsler, N.A. Peppas, R. Langer, Engineering precision nanoparticles for drug delivery, Nat. Rev. Drug Discov. 20 (2) (2021) 101–124, https://doi.org/10.1038/s41573-020-0090-8.

[31] E.R. Brannon, M.V. Guevara, N.J. Pacifici, J.K. Lee, J.S. Lewis, O. Eniola-Adefeso, Polymeric particle-based therapies for acute inflammatory diseases, Nat. Rev. Mater. 7 (10) (2022) 796–813, https://doi.org/10.1038/s41578-022-00458-5.

[32] K.L. Swingle, A.S. Ricciardi, W.H. Peranteau, M.J. Mitchell, Delivery technologies for women's health applications, Nat Rev Bioeng 1 (6) (2023) 408–425, https://doi.org/10.1038/s44222-023-00040-w.

[33] K. Xiao, Y. Li, J. Luo, J.S. Lee, W. Xiao, A.M. Gonik, R.G. Agarwal, K.S. Lam, The effect of surface charge on in vivo biodistribution of PEG-oligocholic acid based micellar nanoparticles, Biomaterials 32 (13) (2011) 3435–3446, https://doi.org/10.1016/j.biomaterials.2011.01.021.

[34] C.R. Miller, B. Bondurant, S.D. McLean, K.A. McGovern, D.F. O'Brien, Liposome−cell interactions in vitro: effect of liposome surface charge on the binding and endocytosis of conventional and sterically stabilized liposomes, Biochemistry 37 (37) (1998) 12875–12883, https://doi.org/10.1021/bi980096y.

[35] J.S. Suk, Q. Xu, N. Kim, J. Hanes, L.M. Ensign, PEGylation as a strategy for improving nanoparticle-based drug and gene delivery, Adv. Drug Deliv. Rev. 99 (2016) 28–51, https://doi.org/10.1016/j.addr.2015.09.012.

[36] C.J. Cheng, G.T. Tietjen, J.K. Saucier-Sawyer, W.M. Saltzman, A holistic approach to targeting disease with polymeric nanoparticles, Nat. Rev. Drug Discov. 14 (4) (2015) 239–247, https://doi.org/10.1038/nrd4503.

[37] M.A. Ackun-Farmmer, C.M. Jewell, Delivery route considerations for designing antigen-specific biomaterial strategies to combat autoimmunity, Adv. NanoBiomed Res. 3 (3) (2023) 2200135, https://doi.org/10.1002/anbr.202200135.

[38] A. Schudel, D.M. Francis, S.N. Thomas, Material design for lymph node drug delivery, Nat. Rev. Mater. 4 (6) (2019) 415–428, https://doi.org/10.1038/s41578-019-0110-7.

[39] S. Kaur, S.M. Allan, Z.S. Al-Ahmady, Re-directing nanomedicines to the spleen: a potential technology for peripheral immunomodulation, J. Control. Release 350 (2022) 60–79, https://doi.org/10.1016/j.jconrel.2022.04.005.

[40] V. Manolova, A. Flace, M. Bauer, K. Schwarz, P. Saudan, M.F. Bachmann, Nanoparticles target distinct dendritic cell populations according to their size, Eur. J. Immunol. 38 (5) (2008) 1404–1413, https://doi.org/10.1002/eji.200737984.

[41] S.T. Reddy, A.J. Van Der Vlies, E. Simeoni, V. Angeli, G.J. Randolph, C.P. O'Neil, L.K. Lee, M.A. Swartz, J.A. Hubbell, Exploiting lymphatic transport and complement activation in nanoparticle vaccines, Nat. Biotechnol. 25 (10) (2007) 1159–1164, https://doi.org/10.1038/nbt1332.

[42] Y.-N. Zhang, J. Lazarovits, W. Poon, B. Ouyang, L.N.M. Nguyen, B.R. Kingston, W. C.W. Chan, Nanoparticle size influences antigen retention and presentation in lymph node follicles for humoral immunity, Nano Lett. 19 (10) (2019) 7226–7235, https://doi.org/10.1021/acs.nanolett.9b02834.

[43] P.L. Mottram, D. Leong, B. Crimeen-Irwin, S. Gloster, S.D. Xiang, J. Meanger, R. Ghildyal, N. Vardaxis, M. Plebanski, Type 1 and 2 immunity following vaccination is influenced by nanoparticle size: formulation of a model vaccine for respiratory syncytial virus, Mol. Pharm. 4 (1) (2007) 73–84, https://doi.org/10.1021/mp060096p.

[44] K.J. Hassett, J. Higgins, A. Woods, B. Levy, Y. Xia, C.J. Hsiao, E. Acosta, Ö. Almarsson, M.J. Moore, L.A. Brito, Impact of lipid nanoparticle size on mRNA

vaccine immunogenicity, J. Control. Release 335 (2021) 237–246, https://doi.org/10.1016/j.jconrel.2021.05.021.

[45] A. Stano, C. Nembrini, M.A. Swartz, J.A. Hubbell, E. Simeoni, Nanoparticle size influences the magnitude and quality of mucosal immune responses after intranasal immunization, Vaccine 30 (52) (2012) 7541–7546, https://doi.org/10.1016/j.vaccine.2012.10.050.

[46] K. Lam, P. Schreiner, A. Leung, P. Stainton, S. Reid, E. Yaworski, P. Lutwyche, J. Heyes, Optimizing lipid nanoparticles for delivery in primates, Adv. Mater. 35 (26) (2023) 2211420, https://doi.org/10.1002/adma.202211420.

[47] A.E. Nel, L. Mädler, D. Velegol, T. Xia, E.M.V. Hoek, P. Somasundaran, F. Klaessig, V. Castranova, M. Thompson, Understanding biophysicochemical interactions at the nano-bio interface, Nat. Mater. 8 (7) (2009) 543–557, https://doi.org/10.1038/nmat2442.

[48] R. Kedmi, N. Ben-Arie, D. Peer, The systemic toxicity of positively charged lipid nanoparticles and the role of toll-like receptor 4 in immune activation, Biomaterials 31 (26) (2010) 6867–6875, https://doi.org/10.1016/j.biomaterials.2010.05.027.

[49] Q. Wei, Y. Su, H. Xin, L. Zhang, J. Ding, X. Chen, Immunologically effective biomaterials, ACS Appl. Mater. Interfaces 13 (48) (2021) 56719–56724, https://doi.org/10.1021/acsami.1c14781.

[50] A.I.S. Van Den Berg, C.-O. Yun, R.M. Schiffelers, W.E. Hennink, Polymeric delivery systems for nucleic acid therapeutics: approaching the clinic, J. Control. Release 331 (2021) 121–141, https://doi.org/10.1016/j.jconrel.2021.01.014.

[51] Z. Tu, Y. Zhong, H. Hu, D. Shao, R. Haag, M. Schirner, J. Lee, B. Sullenger, K. W. Leong, Design of therapeutic biomaterials to control inflammation, Nat. Rev. Mater. 7 (7) (2022) 557–574, https://doi.org/10.1038/s41578-022-00426-z.

[52] N. Benne, D. Ter Braake, A.J. Stoppelenburg, F. Broere, Nanoparticles for inducing antigen-specific T cell tolerance in autoimmune diseases, Front. Immunol. 13 (2022) 864403, https://doi.org/10.3389/fimmu.2022.864403.

[53] Q. Cheng, T. Wei, L. Farbiak, L.T. Johnson, S.A. Dilliard, D.J. Siegwart, Selective organ targeting (SORT) nanoparticles for tissue-specific mRNA delivery and CRISPR–cas gene editing, Nat. Nanotechnol. 15 (4) (2020) 313–320, https://doi.org/10.1038/s41565-020-0669-6.

[54] S.A. Dilliard, Q. Cheng, D.J. Siegwart, On the mechanism of tissue-specific mRNA delivery by selective organ targeting nanoparticles, PNAS 118 (52) (2021), https://doi.org/10.1073/pnas.2109256118.

[55] S.T. LoPresti, M.L. Arral, N. Chaudhary, K.A. Whitehead, The replacement of helper lipids with charged alternatives in lipid nanoparticles facilitates targeted mRNA delivery to the spleen and lungs, J. Control. Release 345 (2022) 819–831, https://doi.org/10.1016/j.jconrel.2022.03.046.

[56] S. Luozhong, Z. Yuan, T. Sarmiento, Y. Chen, W. Gu, C. McCurdy, W. Gao, R. Li, S. Wilkens, S. Jiang, Phosphatidylserine lipid nanoparticles promote systemic RNA delivery to secondary lymphoid organs, Nano Lett. 22 (20) (2022) 8304–8311, https://doi.org/10.1021/acs.nanolett.2c03234.

[57] H. Hosseini, Y. Li, P. Kanellakis, C. Tay, A. Cao, P. Tipping, A. Bobik, B.-H. Toh, T. Kyaw, Phosphatidylserine liposomes mimic apoptotic cells to attenuate atherosclerosis by expanding polyreactive IgM producing B1a lymphocytes, Cardiovasc. Res. 106 (3) (2015) 443–452, https://doi.org/10.1093/cvr/cvv037.

[58] Z. Hunter, D.P. McCarthy, W.T. Yap, C.T. Harp, D.R. Getts, L.D. Shea, S.D. Miller, A biodegradable nanoparticle platform for the induction of antigen-specific immune tolerance for treatment of autoimmune disease, ACS Nano 8 (3) (2014) 2148–2160, https://doi.org/10.1021/nn405033r.

[59] D.P. McCarthy, J.-W.-T. Yap, C.T. Harp, W.K. Song, J. Chen, R.M. Pearson, S. D. Miller, L.D. Shea, An antigen-encapsulating nanoparticle platform for TH1/17 immune tolerance therapy, Nanomed. Nanotechnol. Biol. Med. 13 (1) (2017) 191–200, https://doi.org/10.1016/j.nano.2016.09.007.

[60] G.C. Ramos, D. Fernandes, C.T. Charão, D.G. Souza, M.M. Teixeira, J. Assreuy, Apoptotic mimicry: phosphatidylserine liposomes reduce inflammation through activation of peroxisome proliferator-activated receptors (PPARs) in vivo, Brit. J. Pharmacol. 151 (6) (2007) 844–850, https://doi.org/10.1038/sj.bjp.0707302.

[61] R. Han, L.W.C. Ho, Q. Bai, C.K.W. Chan, L.K.C. Lee, P.-C.-L. Choi, C.H.J. Choi, Alkyl-terminated gold nanoparticles as a self-therapeutic treatment for psoriasis, Nano Lett. 21 (20) (2021) 8723–8733, https://doi.org/10.1021/acs.nanolett.1c02899.

[62] H. Li, A. Granados, E. Fernández, R. Pleixats, A. Vallribera, Anti-inflammatory cotton fabrics and silica nanoparticles with potential topical medical applications, ACS Appl. Mater. Interfaces 12 (23) (2020) 25658–25675, https://doi.org/10.1021/acsami.0c06629.

[63] C. Zylberberg, K. Gaskill, S. Pasley, S. Matosevic, Engineering liposomal nanoparticles for targeted gene therapy, Gene Ther. 24 (8) (2017) 441–452, https://doi.org/10.1038/gt.2017.41.

[64] J.M. Harris, R.B. Chess, Effect of pegylation on pharmaceuticals, Nat. Rev. Drug Discov. 2 (3) (2003) 214–221, https://doi.org/10.1038/nrd1033.

[65] P.Y. Li, F. Bearoff, P. Zhu, Z. Fan, Y. Zhu, M. Fan, L. Cort, T. Kambayashi, E. P. Blankenhorn, H. Cheng, PEGylation enables subcutaneously administered nanoparticles to induce antigen-specific immune tolerance, J. Control. Release 331 (2021) 164–175, https://doi.org/10.1016/j.jconrel.2021.01.013.

[66] L. Shi, J. Zhang, M. Zhao, S. Tang, X. Cheng, W. Zhang, W. Li, X. Liu, H. Peng, Q. Wang, Effects of polyethylene glycol on the surface of nanoparticles for targeted drug delivery, Nanoscale 13 (24) (2021) 10748–10764, https://doi.org/10.1039/D1NR02065J.

[67] J. McCright, C. Skeen, J. Yarmovsky, K. Maisel, Nanoparticles with dense poly (ethylene glycol) coatings with near neutral charge are maximally transported across lymphatics and to the lymph nodes, Acta Biomater. 145 (2022) 146–158, https://doi.org/10.1016/j.actbio.2022.03.054.

[68] M. Li, S. Jiang, J. Simon, D. Paßlick, M.-L. Frey, M. Wagner, V. Mailänder, D. Crespy, K. Landfester, Brush conformation of polyethylene glycol determines the stealth effect of nanocarriers in the low protein adsorption regime, Nano Lett. 21 (4) (2021) 1591–1598, https://doi.org/10.1021/acs.nanolett.0c03756.

[69] D. Shi, D. Beasock, A. Fessler, J. Szebeni, J.Y. Ljubimova, K.A. Afonin, M. A. Dobrovolskaia, To PEGylate or not to PEGylate: immunological properties of nanomedicine's most popular component, polyethylene glycol and its alternatives, Adv. Drug Deliv. Rev. 180 (2022) 114079, https://doi.org/10.1016/j.addr.2021.114079.

[70] B.-M. Chen, T.-L. Cheng, S.R. Roffler, Polyethylene glycol immunogenicity: theoretical, clinical, and practical aspects of anti-polyethylene glycol antibodies, ACS Nano 15 (9) (2021) 14022–14048, https://doi.org/10.1021/acsnano.1c05922.

[71] Y. Joshi, M. Joshi, Z. Zhao, S. Mitragotri, PEGylated therapeutics in the clinic, Bioeng. Transl. Med. (2023) btm2.10600, https://doi.org/10.1002/btm2.10600.

[72] P.L. Turecek, M.J. Bossard, F. Schoetens, I.A. Ivens, PEGylation of biopharmaceuticals: a review of chemistry and nonclinical safety information of approved drugs, J. Pharm. Sci. 105 (2) (2016) 460–475, https://doi.org/10.1016/j.xphs.2015.11.015.

[73] J.K. Armstrong, The occurrence, induction, specificity and potential effect of antibodies against poly(ethylene glycol), in: F.M. Veronese, (Ed.), PEGylated Protein Drugs: Basic Science and Clinical Applications, Birkhäuser Basel, Basel, 2009, pp 147–168. Doi:10.1007/978-3-7643-8679-5_9.

[74] M.A. Sanjuan, D. Sagar, R. Kolbeck, Role of IgE in autoimmunity, J. Allergy Clin. Immunol. 137 (6) (2016) 1651–1661, https://doi.org/10.1016/j.jaci.2016.04.007.

[75] C. Duarte-Rey, D.P. Bogdanos, P.S.C. Leung, J.-M. Anaya, M.E. Gershwin, IgM predominance in autoimmune disease: genetics and gender, Autoimmun. Rev. 11 (6–7) (2012) A404–A412, https://doi.org/10.1016/j.autrev.2011.12.001.

[76] A. Azuar, Z. Li, M.A. Shibu, L. Zhao, Y. Luo, A.O. Shalash, Z.G. Khalil, R.J. Capon, W.M. Hussein, I. Toth, M. Skwarczynski, Poly(hydrophobic amino acid)-based self-adjuvanting nanoparticles for Group A streptococcus vaccine delivery, J. Med. Chem. 64 (5) (2021) 2648–2658, https://doi.org/10.1021/acs.jmedchem.0c01660.

[77] H. Yang, S.-Y. Fung, S. Xu, D.P. Sutherland, T.R. Kollmann, M. Liu, S.E. Turvey, Amino acid-dependent attenuation of toll-like receptor signaling by peptide-gold nanoparticle hybrids, ACS Nano 9 (7) (2015) 6774–6784, https://doi.org/10.1021/nn505634h.

[78] H. Yang, L. Kozicky, A. Saferali, S.-Y. Fung, N. Afacan, B. Cai, R. Falsafi, E. Gill, M. Liu, T.R. Kollmann, R.E.W. Hancock, L.M. Sly, S.E. Turvey, Endosomal pH modulation by peptide-gold nanoparticle hybrids enables potent anti-inflammatory activity in phagocytic immune cells, Biomaterials 111 (2016) 90–102, https://doi.org/10.1016/j.biomaterials.2016.09.032.

[79] J. Heyes, L. Palmer, K. Bremner, I. MacLachlan, Cationic lipid saturation influences intracellular delivery of encapsulated nucleic acids, J. Control. Release 107 (2) (2005) 276–287, https://doi.org/10.1016/j.jconrel.2005.06.014.

[80] R.A. Jain, The manufacturing techniques of various drug loaded biodegradable poly(lactide-co-glycolide) (PLGA) devices, Biomaterials 21 (23) (2000) 2475–2490, https://doi.org/10.1016/S0142-9612(00)00115-0.

[81] T.K. Kishimoto, R.A. Maldonado, Nanoparticles for the induction of antigen-specific immunological tolerance, Front. Immunol. 9 (2018) 230, https://doi.org/10.3389/fimmu.2018.00230.

[82] A.L. Silva, P.C. Soema, B. Slütter, F. Ossendorp, W. Jiskoot, PLGA particulate delivery systems for subunit vaccines: linking particle properties to immunogenicity, Hum. Vaccin. Immunother. 12 (4) (2016) 1056–1069, https://doi.org/10.1080/21645515.2015.1117714.

[83] J.S. Lewis, N.V. Dolgova, Y. Zhang, C.Q. Xia, C.H. Wasserfall, M.A. Atkinson, M. J. Clare-Salzler, B.G. Keselowsky, A combination dual-sized microparticle system modulates dendritic cells and prevents type 1 diabetes in prediabetic NOD mice, Clin. Immunol. 160 (1) (2015) 90–102, https://doi.org/10.1016/j.clim.2015.03.023.

[84] Y.M. Yoon, J.S. Lewis, M.R. Carstens, M. Campbell-Thompson, C.H. Wasserfall, M.A. Atkinson, B.G. Keselowsky, A combination hydrogel microparticle-based vaccine prevents type 1 diabetes in non-obese diabetic mice, Sci. Rep. 5 (1) (2015) 13155, https://doi.org/10.1038/srep13155.

[85] J.M. Gammon, S.T. Carey, V. Saxena, H.B. Eppler, S.J. Tsai, C. Paluskievicz, Y. Xiong, L. Li, M. Ackun-Farmmer, L.H. Tostanoski, E.A. Gosselin, A.A. Yanes, X. Zeng, R.S. Oakes, J.S. Bromberg, C.M. Jewell, Engineering the lymph node environment promotes antigen-specific efficacy in type 1 diabetes and islet transplantation, Nat. Commun. 14 (1) (2023) 681, https://doi.org/10.1038/s41467-023-36225-5.

[86] E. Saito, R. Kuo, R.M. Pearson, N. Gohel, B. Cheung, N.J.C. King, S.D. Miller, L. D. Shea, Designing drug-free biodegradable nanoparticles to modulate inflammatory monocytes and neutrophils for ameliorating inflammation, J. Control. Release 300 (2019) 185–196, https://doi.org/10.1016/j.jconrel.2019.02.025.

[87] M. Liu, D. Feng, X. Liang, M. Li, J. Yang, H. Wang, L. Pang, Z. Zhou, Z. Yang, D. Kong, C. Li, Old dog new tricks: PLGA microparticles as an adjuvant for insulin peptide fragment-induced immune tolerance against type 1 diabetes, Mol. Pharm. 17 (9) (2020) 3513–3525, https://doi.org/10.1021/acs.molpharmaceut.0c00525.

[88] J. Park, J.E. Babensee, Differential functional effects of biomaterials on dendritic cell maturation, Acta Biomater. 8 (10) (2012) 3606–3617, https://doi.org/10.1016/j.actbio.2012.06.006.

[89] M. Yoshida, J.E. Babensee, Poly(lactic- co -glycolic acid) enhances maturation of human monocyte-derived dendritic cells, J. Biomed. Mater. Res. 71A (1) (2004) 45–54, https://doi.org/10.1002/jbm.a.30131.

[90] X. Hou, T. Zaks, R. Langer, Y. Dong, Lipid nanoparticles for mRNA delivery, Nat. Rev. Mater. 6 (12) (2021) 1078–1094, https://doi.org/10.1038/s41578-021-00358-0.

[91] R.M. Pearson, L.M. Casey, K.R. Hughes, S.D. Miller, L.D. Shea, In vivo reprogramming of immune cells: technologies for induction of antigen-specific tolerance, Adv. Drug Deliv. Rev. 114 (2017) 240–255, https://doi.org/10.1016/j.addr.2017.04.005.

[92] N.A. Nagy, A.M. De Haas, T.B.H. Geijtenbeek, R. Van Ree, S.W. Tas, Y. Van Kooyk, E.C. De Jong, Therapeutic liposomal vaccines for dendritic cell activation or tolerance, Front. Immunol. 12 (2021) 674048, https://doi.org/10.3389/fimmu.2021.674048.

[93] A.B. Vogel, I. Kanevsky, Y. Che, K.A. Swanson, A. Muik, M. Vormehr, L.M. Kranz, K.C. Walzer, S. Hein, A. Güler, J. Loschko, M.S. Maddur, A. Ota-Setlik, K. Tompkins, J. Cole, B.G. Lui, T. Ziegenhals, A. Plaschke, D. Eisel, S.C. Dany, S. Fesser, S. Erbar, F. Bates, D. Schneider, B. Jesionek, B. Sänger, A.-K. Wallisch, Y. Feuchter, H. Junginger, S.A. Krumm, A.P. Heinen, P. Adams-Quack, J. Schlereth, S. Schille, C. Kröner, D.e. La Caridad, R. Güimil Garcia, T. Hiller, L. Fischer, R.S. Sellers, S. Choudhary, O. Gonzalez, F. Vascotto, M.R. Gutman, J. A. Fontenot, S. Hall-Ursone, K. Brasky, M.C. Griffor, S. Han, A.A.H. Su, J.A. Lees, N.L. Nedoma, E.H. Mashalidis, P.V. Sahasrabudhe, C.Y. Tan, D. Pavliakova, G. Singh, C. Fontes-Garfias, M. Pride, I.L. Scully, T. Ciolino, J. Obregon, M. Gazi, R. Carrion, K.J. Alfson, W.V. Kalina, D. Kaushal, P.-Y. Shi, T. Klamp, C. Rosenbaum, A.N. Kuhn, Ö. Türeci, P.R. Dormitzer, K.U. Jansen, U. Sahin, BNT162b vaccines protect rhesus macaques from SARS-CoV-2, Nature 592 (7853) (2021) 283–289, https://doi.org/10.1038/s41586-021-03275-y.

[94] L.A. Jackson, E.J. Anderson, N.G. Rouphael, P.C. Roberts, M. Makhene, R. N. Coler, M.P. McCullough, J.D. Chappell, M.R. Denison, L.J. Stevens, A. J. Pruijssers, A. McDermott, B. Flach, N.A. Doria-Rose, K.S. Corbett, K. M. Morabito, S. O'Dell, S.D. Schmidt, P.A. Swanson, M. Padilla, J.R. Mascola, K. M. Neuzil, H. Bennett, W. Sun, E. Peters, M. Makowski, J. Albert, K. Cross, W. Buchanan, R. Pikaart-Tautges, J.E. Ledgerwood, B.S. Graham, J.H. Beigel, An mRNA vaccine against SARS-CoV-2—preliminary report, N. Engl. J. Med. 383 (20) (2020) 1920–1931, https://doi.org/10.1056/NEJMoa2022483.

[95] E. Cavalcanti, M.A. Isgrò, D. Rea, L. Di Capua, G. Trillò, L. Russo, G. Botti, L. Miscio, F.M. Buonaguro, A.A.M. Bianchi, Vaccination strategy and anti - SARS-CoV-2 S titers in healthcare workers of the INT – IRCCS "Fondazione Pascale" Cancer Center (Naples, Italy), Infect Agents Cancer 16 (1) (2021) 32, https://doi.org/10.1186/s13027-021-00375-2.

[96] P. Tardi, N. Boman, P. Cullis, Liposomal doxorubicin, J. Drug Target. 4 (3) (1996) 129–140, https://doi.org/10.3109/10611869609015970.

[97] M.M. Billingsley, N. Singh, P. Ravikumar, R. Zhang, C.H. June, M.J. Mitchell, Ionizable lipid nanoparticle-mediated mRNA delivery for human CAR T cell engineering, Nano Lett. 20 (3) (2020) 1578–1589, https://doi.org/10.1021/acs.nanolett.9b04246.

[98] K.J. Kauffman, J.R. Dorkin, J.H. Yang, M.W. Heartlein, F. DeRosa, F.F. Mir, O. S. Fenton, D.G. Anderson, Optimization of lipid nanoparticle formulations for mRNA delivery in vivo with fractional factorial and definitive screening designs, Nano Lett. 15 (11) (2015) 7300–7306, https://doi.org/10.1021/acs.nanolett.5b02497.

[99] A. Akbarzadeh, R. Rezaei-Sadabady, S. Davaran, S.W. Joo, N. Zarghami, Y. Hanifehpour, M. Samiei, M. Kouhi, K. Nejati-Koshki, Liposome: classification, preparation, and applications, Nanoscale Res. Lett. 8 (1) (2013) 102, https://doi.org/10.1186/1556-276X-8-102.

[100] M.M. Billingsley, A.G. Hamilton, D. Mai, S.K. Patel, K.L. Swingle, N.C. Sheppard, C.H. June, M.J. Mitchell, Orthogonal design of experiments for optimization of lipid nanoparticles for mRNA engineering of CAR T cells, Nano Lett. 22 (1) (2022) 533–542, https://doi.org/10.1021/acs.nanolett.1c02503.

[101] N. Benne, J. Van Duijn, F. Lozano Vigario, R.J.T. Leboux, P. Van Veelen, J. Kuiper, W. Jiskoot, B. Slütter, Anionic 1,2-distearoyl-Sn-glycero-3-phosphoglycerol (DSPG) liposomes induce antigen-specific regulatory T cells and prevent atherosclerosis in mice, J. Control. Release 291 (2018) 135–146, https://doi.org/10.1016/j.jconrel.2018.10.028.

[102] S. Rodriguez-Fernandez, I. Pujol-Autonell, F. Brianso, D. Perna-Barrull, M. Cano-Sarabia, S. Garcia-Jimeno, A. Villalba, A. Sanchez, E. Aguilera, F. Vazquez, J. Verdaguer, D. Maspoch, M. Vives-Pi, Phosphatidylserine-liposomes promote tolerogenic features on dendritic cells in human type 1 diabetes by apoptotic mimicry, Front. Immunol. 9 (2018) 253, https://doi.org/10.3389/fimmu.2018.00253.

[103] M.R. Elliott, K.M. Koster, P.S. Murphy, Efferocytosis signaling in the regulation of macrophage inflammatory responses, J. Immunol. 198 (4) (2017) 1387–1394, https://doi.org/10.4049/jimmunol.1601520.

[104] D. Dudziak, A.O. Kamphorst, G.F. Heidkamp, V.R. Buchholz, C. Trumpfheller, S. Yamazaki, C. Cheong, K. Liu, H.-W. Lee, C.G. Park, R.M. Steinman, M. C. Nussenzweig, Differential antigen processing by dendritic cell subsets in vivo, Science 315 (5808) (2007) 107–111, https://doi.org/10.1126/science.1136080.

[105] I. Pujol-Autonell, M.-J. Mansilla, S. Rodriguez-Fernandez, M. Cano-Sarabia, J. Navarro-Barriuso, R.-M. Ampudia, A. Rius, S. Garcia-Jimeno, D. Perna-Barrull, E. Martinez-Caceres, D. Maspoch, M. Vives-Pi, Liposome-based immunotherapy against autoimmune diseases: therapeutic effect on multiple sclerosis, Nanomedicine 12 (11) (2017) 1231–1242, https://doi.org/10.2217/nnm-2016-0410.

[106] R.A. Roberts, T.K. Eitas, J.D. Byrne, B.M. Johnson, P.J. Short, K.P. McKinnon, S. Reisdorf, J.C. Luft, J.M. DeSimone, J.P. Ting, Towards programming immune tolerance through geometric manipulation of phosphatidylserine, Biomaterials 72 (2015) 1–10, https://doi.org/10.1016/j.biomaterials.2015.08.040.

[107] M. Gomi, Y. Nakayama, Y. Sakurai, R. Oyama, K. Iwasaki, M. Doi, Y. Liu, M. Hori, H. Watanabe, K. Hashimoto, H. Tanaka, K. Tange, Y. Nakai, H. Akita, Tolerogenic lipid nanoparticles for delivering self-antigen mRNA for the treatment of experimental autoimmune encephalomyelitis, Pharmaceuticals 16 (9) (2023) 1270, https://doi.org/10.3390/ph16091270.

[108] I. Pujol-Autonell, A. Serracant-Prat, M. Cano-Sarabia, R.M. Ampudia, S. Rodriguez-Fernandez, A. Sanchez, C. Izquierdo, T. Stratmann, M. Puig-Domingo, D. Maspoch, J. Verdaguer, M. Vives-Pi, Use of autoantigen-loaded phosphatidylserine-liposomes to arrest autoimmunity in type 1 diabetes, PLoS One 10 (6) (2015) e0127057.

[109] N.S. Merle, S.E. Church, V. Fremeaux-Bacchi, L.T. Roumenina, Complement system Part I – molecular mechanisms of activation and regulation, Front. Immunol. 6 (2015), https://doi.org/10.3389/fimmu.2015.00262.

[110] D. Niethammer, J. Kümmerle-Deschner, G.E. Dannecker, Side-effects of long-term immunosuppression versus morbidity in autologous stem cell rescue: striking the balance, Rheumatology 38 (8) (1999) 747–750, https://doi.org/10.1093/rheumatology/38.8.747.

[111] T. Nakamura, Y. Sato, Y. Yamada, M.M. Abd Elwakil, S. Kimura, M.A. Younis, H. Harashima, Extrahepatic targeting of lipid nanoparticles in vivo with intracellular targeting for future nanomedicines, Adv. Drug Deliv. Rev. 188 (2022) 114417, https://doi.org/10.1016/j.addr.2022.114417.

[112] S.M. Moghimi, R. McCullough, D. Simberg, Revisiting nanoparticle transendothelial migration in the liver, Mol. Ther. 31 (3) (2023) 605–606, https://doi.org/10.1016/j.ymthe.2023.01.024.

[113] I. Tombácz, D. Laczkó, H. Shahnawaz, H. Muramatsu, A. Natesan, A. Yadegari, T. E. Papp, M.-G. Alameh, V. Shuvaev, B.L. Mui, Y.K. Tam, V. Muzykantov, N. Pardi, D. Weissman, H. Parhiz, Highly efficient CD4+ T cell targeting and genetic recombination using engineered CD4+ cell-homing mRNA-LNPs, Mol. Ther. 29 (11) (2021) 3293–3304, https://doi.org/10.1016/j.ymthe.2021.06.004.

[114] Y. Sakurai, N. Abe, K. Yoshikawa, R. Oyama, S. Ogasawara, T. Murata, Y. Nakai, K. Tange, H. Tanaka, H. Akita, Targeted delivery of lipid nanoparticle to lymphatic endothelial cells via anti-podoplanin antibody, J. Control. Release 349 (2022) 379–387, https://doi.org/10.1016/j.jconrel.2022.06.052.

[115] Y. Xu, X. Han, Y. Li, H. Min, X. Zhao, Y. Zhang, Y. Qi, J. Shi, S. Qi, Y. Bao, G. Nie, Sulforaphane mediates glutathione depletion via polymeric nanoparticles to restore cisplatin chemosensitivity, ACS Nano 13 (11) (2019) 13445–13455, https://doi.org/10.1021/acsnano.9b07032.

[116] V. Fehring, U. Schaeper, K. Ahrens, A. Santel, O. Keil, M. Eisermann, K. Giese, J. Kaufmann, Delivery of therapeutic siRNA to the lung endothelium via novel lipoplex formulation DACC, Mol. Ther. 22 (4) (2014) 811–820, https://doi.org/10.1038/mt.2013.291.

[117] P.T. Hammond, Building biomedical materials layer-by-layer, Mater. Today 15 (5) (2012) 196–206, https://doi.org/10.1016/S1369-7021(12)70090-1.

[118] D. Alkekhia, P.T. Hammond, A. Shukla, Layer-by-layer biomaterials for drug delivery, Annu. Rev. Biomed. Eng. 22 (1) (2020) 1–24, https://doi.org/10.1146/annurev-bioeng-060418-052350.

[119] S. Correa, N. Boehnke, A.E. Barberio, E. Deiss-Yehiely, A. Shi, B. Oberlton, S. G. Smith, I. Zervantonakis, E.C. Dreaden, P.T. Hammond, Tuning nanoparticle interactions with ovarian cancer through layer-by-layer modification of surface chemistry, ACS Nano 14 (2) (2020) 2224–2237, https://doi.org/10.1021/acsnano.9b09213.

[120] W. Wang, X. Zhou, Y. Bian, S. Wang, Q. Chai, Z. Guo, Z. Wang, P. Zhu, H. Peng, X. Yan, W. Li, Y.-X. Fu, M. Zhu, Dual-targeting nanoparticle vaccine elicits a therapeutic antibody response against chronic hepatitis B, Nat. Nanotechnol. 15 (5) (2020) 406–416, https://doi.org/10.1038/s41565-020-0648-y.

[121] J.R. Melamed, S.S. Yerneni, M.L. Arral, S.T. LoPresti, N. Chaudhary, A. Sehrawat, H. Muramatsu, M.-G. Alameh, N. Pardi, D. Weissman, G.K. Gittes, K. A. Whitehead, Ionizable lipid nanoparticles deliver mRNA to pancreatic β cells via macrophage-mediated gene transfer, Sci. Adv. 9 (4) (2023) eade1444, https://doi.org/10.1126/sciadv.ade1444.

[122] K.L. Swingle, H.C. Safford, H.C. Geisler, A.G. Hamilton, A.S. Thatte, M. B. Billingsley, R.A. Joseph, K. Mrksich, M.S. Padilla, A.A. Ghalsasi, M.-G. Alameh, D. Weissman, M.J. Mitchell, Ionizable lipid nanoparticles for *In Vivo* mRNA delivery to the placenta during pregnancy, J. Am. Chem. Soc. 145 (8) (2023) 4691–4706, https://doi.org/10.1021/jacs.2c12893.

[123] S.K. Patel, M.M. Billingsley, C. Frazee, X. Han, K.L. Swingle, J. Qin, M.-G. Alameh, K. Wang, D. Weissman, M.J. Mitchell, Hydroxycholesterol substitution in ionizable lipid nanoparticles for mRNA delivery to T cells, J. Control. Release 347 (2022) 521–532, https://doi.org/10.1016/j.jconrel.2022.05.020.

[124] R.E. Young, K.M. Nelson, S.I. Hofbauer, T. Vijayakumar, M.-G. Alameh, D. Weissman, C. Papachristou, J.P. Gleghorn, R.S. Riley, Lipid nanoparticle composition drives mRNA delivery to the placenta, Bioengineering (2022), https://doi.org/10.1101/2022.12.22.521490 preprint.

[125] H.C. Safford, K.L. Swingle, H.C. Geisler, A.G. Hamilton, A.S. Thatte, A.A. Ghalsasi, M.M. Billingsley, M. Alameh, D. Weissman, M.J. Mitchell, Orthogonal design of experiments for engineering of lipid nanoparticles for mRNA delivery to the placenta, Small (2023) 2303568, https://doi.org/10.1002/smll.202303568.

[126] R.E. Young, K.M. Nelson, S.I. Hofbauer, T. Vijayakumar, M.-G. Alameh, D. Weissman, C. Papachristou, J.P. Gleghorn, R.S. Riley, Systematic development of ionizable lipid nanoparticles for placental mRNA delivery using a design of experiments approach, Bioact. Mater. 34 (2024) 125–137, https://doi.org/10.1016/j.bioactmat.2023.11.014.

[127] J. Yoo, C. Park, G. Yi, D. Lee, H. Koo, Active targeting strategies using biological ligands for nanoparticle drug delivery systems, Cancers 11 (5) (2019) 640, https://doi.org/10.3390/cancers11050640.

[128] J. Nong, P.M. Glassman, J.W. Myerson, V. Zuluaga-Ramirez, A. Rodriguez-Garcia, A. Mukalel, S. Omo-Lamai, L.R. Walsh, M.E. Zamora, X. Gong, Z. Wang, K. Bhamidipati, R.Y. Kiseleva, C.H. Villa, C.F. Greineder, S.E. Kasner, D. Weissman, M.J. Mitchell, S. Muro, Y. Persidsky, J.S. Brenner, V. R. Muzykantov, O.A. Marcos-Contreras, Targeted nanocarriers co-opting pulmonary intravascular leukocytes for drug delivery to the injured brain, ACS Nano 17 (14) (2023) 13121–13136, https://doi.org/10.1021/acsnano.2c08275.

[129] S. Shetty, P.F. Lalor, D.H. Adams, Liver sinusoidal endothelial cells—gatekeepers of hepatic immunity, Nat. Rev. Gastroenterol. Hepatol. 15 (9) (2018) 555–567, https://doi.org/10.1038/s41575-018-0020-y.

[130] X. Xu, X. Wang, Y.-P. Liao, L. Luo, T. Xia, A.E. Nel, Use of a liver-targeting immune-tolerogenic mRNA lipid nanoparticle platform to treat peanut-induced anaphylaxis by single- and multiple-epitope nucleotide sequence delivery, ACS Nano 17 (5) (2023) 4942–4957, https://doi.org/10.1021/acsnano.2c12420.

[131] M. Kim, M. Jeong, S. Hur, Y. Cho, J. Park, H. Jung, Y. Seo, H.A. Woo, K.T. Nam, K. Lee, H. Lee, Engineered ionizable lipid nanoparticles for targeted delivery of RNA therapeutics into different types of cells in the liver, Sci. Adv. 7 (9) (2021) eabf4398, https://doi.org/10.1126/sciadv.abf4398.

[132] K. Ley, C. Laudanna, M.I. Cybulsky, S. Nourshargh, Getting to the site of inflammation: the leukocyte adhesion cascade updated, Nat. Rev. Immunol. 7 (9) (2007) 678–689, https://doi.org/10.1038/nri2156.

[133] S. Schwager, M. Detmar, Inflammation and lymphatic function, Front. Immunol. 10 (2019) 308, https://doi.org/10.3389/fimmu.2019.00308.

[134] J.G. Rurik, I. Tombácz, A. Yadegari, P.O. Méndez Fernández, S.V. Shewale, L. Li, T. Kimura, O.Y. Soliman, T.E. Papp, Y.K. Tam, B.L. Mui, S.M. Albelda, E. Puré, C. H. June, H. Aghajanian, D. Weissman, H. Parhiz, J.A. Epstein, CAR T cells produced in vivo to treat cardiac injury, Science 375 (6576) (2022) 91–96, https://doi.org/10.1126/science.abm0594.

[135] M.M. Billingsley, N. Gong, A.J. Mukalel, A.S. Thatte, R. El-Mayta, S.K. Patel, A. E. Metzloff, K.L. Swingle, X. Han, L. Xue, A.G. Hamilton, H.C. Safford, M. Alameh, T.E. Papp, H. Parhiz, D. Weissman, M.J. Mitchell, In vivo mRNA CAR T cell engineering via targeted ionizable lipid nanoparticles with extrahepatic tropism, Small (2023) 2304378, https://doi.org/10.1002/smll.202304378.

[136] S. Jain, T.-H. Tran, M. Amiji, Macrophage repolarization with targeted alginate nanoparticles containing IL-10 plasmid DNA for the treatment of experimental arthritis, Biomaterials 61 (2015) 162–177, https://doi.org/10.1016/j.biomaterials.2015.05.028.

[137] K.A. Brzezicka, B.M. Arlian, S. Wang, M. Olmer, M. Lotz, J.C. Paulson, Suppression of autoimmune rheumatoid arthritis with hybrid nanoparticles that induce B and T cell tolerance to self-antigen, ACS Nano 16 (12) (2022) 20206–20221, https://doi.org/10.1021/acsnano.2c05643.

[138] W. Richtering, I. Alberg, R. Zentel, Nanoparticles in the biological context: surface morphology and protein corona formation, Small 16 (39) (2020) 2002162, https://doi.org/10.1002/smll.202002162.

[139] G. Bashiri, M.S. Padilla, K.L. Swingle, S.J. Shepherd, M.J. Mitchell, K. Wang, Nanoparticle protein corona: from structure and function to therapeutic targeting, Lab Chip 23 (6) (2023) 1432–1466, https://doi.org/10.1039/D2LC00799A.

[140] A. Akinc, W. Querbes, S. De, J. Qin, M. Frank-Kamenetsky, K.N. Jayaprakash, M. Jayaraman, K.G. Rajeev, W.L. Cantley, J.R. Dorkin, J.S. Butler, L. Qin, T. Racie, A. Sprague, E. Fava, A. Zeigerer, M.J. Hope, M. Zerial, D.W. Sah, K. Fitzgerald, M.A. Tracy, M. Manoharan, V. Koteliansky, A.D. Fougerolles, M. A. Maier, Targeted delivery of RNAi therapeutics with endogenous and exogenous ligand-based mechanisms, Mol. Ther. 18 (7) (2010) 1357–1364, https://doi.org/10.1038/mt.2010.85.

[141] K. Paunovska, A.J. Da Silva Sanchez, M.P. Lokugamage, D. Loughrey, E. S. Echeverri, A. Cristian, M.Z.C. Hatit, P.J. Santangelo, K. Zhao, J.E. Dahlman, The extent to which lipid nanoparticles require apolipoprotein E and low-density lipoprotein receptor for delivery changes with ionizable lipid structure, Nano Lett. 22 (24) (2022) 10025–10033, https://doi.org/10.1021/acs.nanolett.2c03741.

[142] L.M. Kranz, M. Diken, H. Haas, S. Kreiter, C. Loquai, K.C. Reuter, M. Meng, D. Fritz, F. Vascotto, H. Hefesha, C. Grunwitz, M. Vormehr, Y. Hüsemann, A. Selmi, A.N. Kuhn, J. Buck, E. Derhovanessian, R. Rae, S. Attig, J. Diekmann, R. A. Jabulowsky, S. Heesch, J. Hassel, P. Langguth, S. Grabbe, C. Huber, Ö. Türeci, U. Sahin, Systemic RNA delivery to dendritic cells exploits antiviral defence for cancer immunotherapy, Nature 534 (7607) (2016) 396–401, https://doi.org/10.1038/nature18300.

[143] S. Omo-Lamai, M.E. Zamora, M.N. Patel, J. Wu, J. Nong, Z. Wang, A. Peshkova, L. S. Chase, E.-O. Essien, V. Muzykantov, O. Marcos-Contreras, J.W. Myerson, J. S. Brenner, Physicochemical targeting of lipid nanoparticles to the lungs induces clotting: mechanisms and solutions, Bioengineering (2023) https://doi.org/10.1101/2023.07.21.550260, preprint.

[144] J.M. Thurman, R. Yapa, Complement therapeutics in autoimmune disease, Front. Immunol. 10 (2019) 672, https://doi.org/10.3389/fimmu.2019.00672.

[145] S.J. Lee, A. Kavanaugh, Adverse reactions to biologic agents: focus on autoimmune disease therapies, J. Allergy Clin. Immunol. 116 (4) (2005) 900–905, https://doi.org/10.1016/j.jaci.2005.03.028.

[146] N.M. La-Beck, A.A. Gabizon, Nanoparticle interactions with the immune system: clinical implications for liposome-based cancer chemotherapy, Front. Immunol. 8 (2017), https://doi.org/10.3389/fimmu.2017.00416.

[147] M.-G. Alameh, I. Tombácz, E. Bettini, K. Lederer, S. Ndeupen, C. Sittplangkoon, J. R. Wilmore, B.T. Gaudette, O.Y. Soliman, M. Pine, P. Hicks, T.B. Manzoni, J. J. Knox, J.L. Johnson, D. Laczkó, H. Muramatsu, B. Davis, W. Meng, A. M. Rosenfeld, S. Strohmeier, P.J.C. Lin, B.L. Mui, Y.K. Tam, K. Karikó, A. Jacquet,

F. Krammer, P. Bates, M.P. Cancro, D. Weissman, E.T. Luning Prak, D. Allman, B. Z. Igyártó, M. Locci, N. Pardi, Lipid nanoparticles enhance the efficacy of mRNA and protein subunit vaccines by inducing robust T follicular helper cell and humoral responses, Immunity 54 (12) (2021) 2877–2892.e7, https://doi.org/10.1016/j.immuni.2021.11.001.

[148] S. Patel, J. Kim, M. Herrera, A. Mukherjee, A.V. Kabanov, G. Sahay, Brief update on endocytosis of nanomedicines, Adv. Drug Deliv. Rev. 144 (2019) 90–111, https://doi.org/10.1016/j.addr.2019.08.004.

[149] K. Miyake, T. Shibata, R. Fukui, R. Sato, S.-I. Saitoh, Y. Murakami, Nucleic acid sensing by toll-like receptors in the endosomal compartment, Front. Immunol. 13 (2022) 941931, https://doi.org/10.3389/fimmu.2022.941931.

[150] H. Parhiz, J.S. Brenner, P.N. Patel, T.E. Papp, H. Shahnawaz, Q. Li, R. Shi, M. E. Zamora, A. Yadegari, O.A. Marcos-Contreras, A. Natesan, N. Pardi, V. V. Shuvaev, R. Kiseleva, J.W. Myerson, T. Uhler, R.S. Riley, X. Han, M.J. Mitchell, K. Lam, J. Heyes, D. Weissman, V.R. Muzykantov, Added to pre-existing inflammation, mRNA-lipid nanoparticles induce inflammation exacerbation (IE), J. Control. Release 344 (2022) 50–61, https://doi.org/10.1016/j.jconrel.2021.12.027.

[151] J.C. Harris, M.A. Scully, E.S. Day, Cancer cell membrane-coated nanoparticles for cancer management, Cancers 11 (12) (2019) 1836, https://doi.org/10.3390/cancers11121836.

[152] C. Liu, W. Zhang, Y. Li, J. Chang, F. Tian, F. Zhao, Y. Ma, J. Sun, Microfluidic sonication to assemble exosome membrane-coated nanoparticles for immune evasion-mediated targeting, Nano Lett. 19 (11) (2019) 7836–7844, https://doi.org/10.1021/acs.nanolett.9b02841.

[153] X. Yan, Q. Pan, H. Xin, Y. Chen, Y. Ping, Genome-editing prodrug: targeted delivery and conditional stabilization of CRISPR-Cas9 for precision therapy of inflammatory disease, Sci. Adv. 7 (50) (2021) eabj0624, https://doi.org/10.1126/sciadv.abj0624.

[154] X. Huang, H. Guo, L. Wang, Z. Zhang, W. Zhang, Biomimetic cell membrane-coated nanocarriers for targeted siRNA delivery in cancer therapy, Drug Discov. Today 28 (4) (2023) 103514, https://doi.org/10.1016/j.drudis.2023.103514.

[155] Y. Wu, S. Wan, S. Yang, H. Hu, C. Zhang, J. Lai, J. Zhou, W. Chen, X. Tang, J. Luo, X. Zhou, L. Yu, L. Wang, A. Wu, Q. Fan, J. Wu, Macrophage cell membrane-based nanoparticles: a new promising biomimetic platform for targeted delivery and treatment, J. Nanobiotechnol. 20 (1) (2022) 542, https://doi.org/10.1186/s12951-022-01746-6.

[156] H. Li, Y. Feng, X. Zheng, M. Jia, Z. Mei, Y. Wang, Z. Zhang, M. Zhou, C. Li, M2-type exosomes nanoparticles for rheumatoid arthritis therapy via macrophage re-polarization, J. Control. Release 341 (2022) 16–30, https://doi.org/10.1016/j.jconrel.2021.11.019.

[157] R. Li, Y. He, Y. Zhu, L. Jiang, S. Zhang, J. Qin, Q. Wu, W. Dai, S. Shen, Z. Pang, J. Wang, Route to rheumatoid arthritis by macrophage-derived microvesicle-coated nanoparticles, Nano Lett. 19 (1) (2019) 124–134, https://doi.org/10.1021/acs.nanolett.8b03439.

[158] J.M. Gammon, C.M. Jewell, Engineering immune tolerance with biomaterials, Adv. Healthcare Mater. 8 (4) (2019) 1801419, https://doi.org/10.1002/adhm.201801419.

[159] Y. Rui, H.B. Eppler, A.A. Yanes, C.M. Jewell, Tissue-targeted drug delivery strategies to promote antigen-specific immune tolerance, Adv. Healthcare Mater. 12 (6) (2023) 2202238, https://doi.org/10.1002/adhm.202202238.

[160] M. Lorscheider, N. Tsapis, M. ur-Rehman, F. Gaudin, J. Stolfa, S. Abreu, S. Mura, P. Chaminade, M. Espeli, E. Fattal, Dexamethasone palmitate nanoparticles: an efficient treatment for rheumatoid arthritis, J. Control. Release 296 (2019) 179–189, https://doi.org/10.1016/j.jconrel.2019.01.015.

[161] N. Chen, K.J. Peine, M.A. Collier, S. Gautam, K.A. Jablonski, M. Guerau-de-Arellano, K.M. Ainslie, E.M. Bachelder, Co-delivery of disease associated peptide and rapamycin via acetalated dextran microparticles for treatment of multiple sclerosis, Adv. Biosys. 1 (3) (2017) 1700022, https://doi.org/10.1002/adbi.201700022.

[162] H. Zhang, X. Han, M.-G. Alameh, S.J. Shepherd, M.S. Padilla, L. Xue, K. Butowska, D. Weissman, M.J. Mitchell, Rational design of anti-inflammatory lipid nanoparticles for mRNA delivery, J. Biomed. Mater. Res. A 110 (5) (2022) 1101–1108, https://doi.org/10.1002/jbm.a.37356.

[163] C.D. Moorman, S.J. Sohn, H. Phee, Emerging therapeutics for immune tolerance: tolerogenic vaccines, T cell therapy, and IL-2 therapy, Front. Immunol. 12 (2021) 657768, https://doi.org/10.3389/fimmu.2021.657768.

[164] J.E. Kenison, N.A. Stevens, F.J. Quintana, Therapeutic induction of antigen-specific immune tolerance, Nat. Rev. Immunol. (2023), https://doi.org/10.1038/s41577-023-00970-x.

[165] O. Morante-Palacios, F. Fondelli, E. Ballestar, E.M. Martínez-Cáceres, Tolerogenic dendritic cells in autoimmunity and inflammatory diseases, Trends Immunol. 42 (1) (2021) 59–75, https://doi.org/10.1016/j.it.2020.11.001.

[166] T.L. Nguyen, Y. Choi, J. Im, H. Shin, N.M. Phan, M.K. Kim, S.W. Choi, J. Kim, Immunosuppressive biomaterial-based therapeutic vaccine to treat multiple sclerosis via re-establishing immune tolerance, Nat. Commun. 13 (1) (2022) 7449, https://doi.org/10.1038/s41467-022-35263-9.

[167] A.C. Tremain, R.P. Wallace, K.M. Lorentz, T.B. Thornley, J.T. Antane, M.R. Raczy, J.W. Reda, A.T. Alpar, A.J. Slezak, E.A. Watkins, C.D. Maulloo, E. Budina, A. Solanki, M. Nguyen, D.J. Bischoff, J.L. Harrington, R. Mishra, G.P. Conley, R. Marlin, N. Dereuddre-Bosquet, A.-S. Gallouët, R. LeGrand, D.S. Wilson, S. Kontos, J.A. Hubbell, Synthetically glycosylated antigens for the antigen-specific suppression of established immune responses, Nat. Biomed. Eng. 7 (9) (2023) 1142–1155, https://doi.org/10.1038/s41551-023-01086-2.

[168] C. Krienke, L. Kolb, E. Diken, M. Streuber, S. Kirchhoff, T. Bukur, Ö. Akilli-Öztürk, L.M. Kranz, H. Berger, J. Petschenka, M. Diken, S. Kreiter, N. Yogev, A. Waisman,

K. Karikó, Ö. Türeci, U. Sahin, A noninflammatory mRNA vaccine for treatment of experimental autoimmune encephalomyelitis, Science 371 (6525) (2021) 145–153, https://doi.org/10.1126/science.aay3638.

[169] J. Postigo-Fernandez, R.J. Creusot, A multi-epitope DNA vaccine enables a broad engagement of diabetogenic T cells for tolerance in type 1 diabetes, J. Autoimmun. 98 (2019) 13–23, https://doi.org/10.1016/j.jaut.2018.11.003.

[170] X. Wang, I. Rivière, Clinical manufacturing of CAR T cells: foundation of a promising therapy, Mol. Ther. Oncolytics 3 (2016) 16015, https://doi.org/10.1038/mto.2016.15.

[171] S. Douka, L.E. Brandenburg, C. Casadidio, J. Walther, B.B.M. Garcia, J. Spanholtz, M. Raimo, W.E. Hennink, E. Mastrobattista, M. Caiazzo, Lipid nanoparticle-mediated messenger RNA delivery for ex vivo engineering of natural killer cells, J. Control. Release 361 (2023) 455–469, https://doi.org/10.1016/j.jconrel.2023.08.014.

[172] A.S. Thatte, A.G. Hamilton, B.E. Nachod, A.J. Mukalel, M.M. Billingsley, R. Palanki, K.L. Swingle, M.J. Mitchell, mRNA lipid nanoparticles for *Ex Vivo* engineering of immunosuppressive T cells for autoimmunity therapies, Nano Lett. 23 (22) (2023) 10179–10188, https://doi.org/10.1021/acs.nanolett.3c02573.

[173] N. Kapate, M. Dunne, N. Kumbhojkar, S. Prakash, L.-L.-W. Wang, A. Graveline, K. S. Park, V. Chandran Suja, J. Goyal, J.R. Clegg, S. Mitragotri, A Backpack-based myeloid cell therapy for multiple sclerosis, PNAS 120 (17) (2023), https://doi.org/10.1073/pnas.2221535120.

[174] A. Mullard, CAR T cell therapies raise hopes—and questions—for lupus and autoimmune disease, Nat. Rev. Drug Discov. (2023) d41573-023-00166–x. doi: 10.1038/d41573-023-00166-x.

[175] K.R. Rhodes, S.Y. Tzeng, M. Iglesias, D. Lee, K. Storm, S.Y. Neshat, D. VanDyke, S. M. Lowmaster, J.B. Spangler, G. Raimondi, J.J. Green, Bioengineered particles expand myelin-specific regulatory T cells and reverse autoreactivity in a mouse model of multiple sclerosis, Sci. Adv. 9 (22) (2023) eadd8693, https://doi.org/10.1126/sciadv.add8693.

[176] M. Dall'Era, M.L. Pauli, K. Remedios, K. Taravati, P.M. Sandova, A.L. Putnam, A. Lares, A. Haemel, Q. Tang, M. Hellerstein, M. Fitch, J. McNamara, B. Welch, J. A. Bluestone, D. Wofsy, M.D. Rosenblum, The autoimmunity centers of excellence. adoptive treg cell therapy in a patient with systemic lupus erythematosus, Arthritis Rheumatol. 71 (3) (2019) 431–440, https://doi.org/10.1002/art.40737.

[177] G.I. Ellis, K.E. Coker, D.W. Winn, M.Z. Deng, D. Shukla, V. Bhoj, M.C. Milone, W. Wang, C. Liu, A. Naji, R. Duran-Struuck, J.L. Riley, Trafficking and persistence of alloantigen-specific chimeric antigen receptor regulatory T cells in cynomolgus macaque, Cell Rep. Med. 3 (5) (2022) 100614, https://doi.org/10.1016/j.xcrm.2022.100614.

[178] E. Dolgin, Treg engineers take aim at autoimmunity, Nat. Biotechnol. 39 (11) (2021) 1317–1319, https://doi.org/10.1038/s41587-021-01115-y.

[179] J.E. Chung, S. Tan, S.J. Gao, N. Yongvongsoontorn, S.H. Kim, J.H. Lee, H.S. Choi, H. Yano, L. Zhuo, M. Kurisawa, J.Y. Ying, Self-assembled micellar nanocomplexes comprising green tea catechin derivatives and protein drugs for cancer therapy, Nat. Nanotech. 9 (11) (2014) 907–912, https://doi.org/10.1038/nnano.2014.208.

[180] R.M. Haley, A. Chan, M.M. Billingsley, N. Gong, M.S. Padilla, E.H. Kim, H. Wang, D. Yin, K.J. Wangensteen, A. Tsourkas, M.J. Mitchell, Lipid nanoparticle delivery of small proteins for potent *in vivo* RAS inhibition, ACS Appl. Mater. Interfaces 15 (18) (2023) 21877–21892, https://doi.org/10.1021/acsami.3c01501.

[181] M. Durán-Lobato, A.M. López-Estévez, A.S. Cordeiro, T.G. Dacoba, J. Crecente-Campo, D. Torres, M.J. Alonso, Nanotechnologies for the delivery of biologicals: historical perspective and current landscape, Adv. Drug Deliv. Rev. 176 (2021) 113899, https://doi.org/10.1016/j.addr.2021.113899.

[182] J. Wen, D. Wu, M. Qin, C. Liu, L. Wang, D. Xu, H.V. Vinters, Y. Liu, E. Kranz, X. Guan, G. Sun, X. Sun, Y. Lee, O. Martinez-Maza, D. Widney, Y. Lu, I.S.Y. Chen, M. Kamata, Sustained delivery and molecular targeting of a therapeutic monoclonal antibody to metastases in the central nervous system of mice, Nat. Biomed. Eng. 3 (9) (2019) 706–716, https://doi.org/10.1038/s41551-019-0434-z.

[183] D. Huang, Y.-S. Chen, C.R. Green, I.D. Rupenthal, Hyaluronic acid coated albumin nanoparticles for targeted peptide delivery in the treatment of retinal ischaemia, Biomaterials 168 (2018) 10–23, https://doi.org/10.1016/j.biomaterials.2018.03.034.

[184] A.G. Hamilton, K.L. Swingle, R.A. Joseph, D. Mai, N. Gong, M.M. Billingsley, M.-G. Alameh, D. Weissman, N.C. Sheppard, C.H. June, M.J. Mitchell, Ionizable lipid nanoparticles with integrated immune checkpoint inhibition for mRNA CAR T cell engineering, Adv. Healthcare Mater. n/a (n/a) 2301515. Doi:10.1002/adhm.202301515.

[185] R.L. Ball, K.A. Hajj, J. Vizelman, P. Bajaj, K.A. Whitehead, Lipid nanoparticle formulations for enhanced co-delivery of siRNA and mRNA, Nano Lett. 18 (6) (2018) 3814–3822, https://doi.org/10.1021/acs.nanolett.8b01101.

[186] L. Northrup, J.D. Griffin, M.A. Christopher, L.R. Antunez, B.L. Hartwell, C. J. Pickens, C. Berkland, Co-delivery of autoantigen and dexamethasone in incomplete freund's adjuvant ameliorates experimental autoimmune encephalomyelitis, J. Control. Release 266 (2017) 156–165, https://doi.org/10.1016/j.jconrel.2017.09.034.

[187] S. Randhawa, S. Sengar, The evolution and history of gene editing technologies, in: Progress in Molecular Biology and Translational Science, Elsevier, 2021, pp. 1–62, https://doi.org/10.1016/bs.pmbts.2021.01.002.

[188] M. Gutierrez-Arcelus, Y. Baglaenko, J. Arora, S. Hannes, Y. Luo, T. Amariuta, N. Teslovich, D.A. Rao, J. Ermann, A.H. Jonsson, NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium, C. Navarrete, S.S. Rich, K.D. Taylor, J. I. Rotter, P.K. Gregersen, T. Esko, M.B. Brenner, S. Raychaudhuri, Allele-specific expression changes dynamically during T cell activation in HLA and other autoimmune loci, Nat Genet 52 (3) (2020) 247–253, https://doi.org/10.1038/s41588-020-0579-4.

[189] K. Musunuru, A.C. Chadwick, T. Mizoguchi, S.P. Garcia, J.E. DeNizio, C.W. Reiss, K. Wang, S. Iyer, C. Dutta, V. Clendaniel, M. Amaonye, A. Beach, K. Berth, S. Biswas, M.C. Braun, H.-M. Chen, T.V. Colace, J.D. Ganey, S.A. Gangopadhyay, R. Garrity, L.N. Kasiewicz, J. Lavoie, J.A. Madsen, Y. Matsumoto, A.M. Mazzola, Y.S. Nasrullah, J. Nneji, H. Ren, A. Sanjeev, M. Shay, M.R. Stahley, S.H.Y. Fan, Y. K. Tam, N.M. Gaudelli, G. Ciaramella, L.E. Stolz, P. Malyala, C.J. Cheng, K. G. Rajeev, E. Rohde, A.M. Bellinger, S. Kathiresan, In vivo CRISPR base editing of PCSK9 durably lowers cholesterol in primates, Nature 593 (7859) (2021) 429–434, https://doi.org/10.1038/s41586-021-03534-y.

[190] R. Palanki, S.K. Bose, A. Dave, B.M. White, C. Berkowitz, V. Luks, F. Yaqoob, E. Han, K.L. Swingle, P. Menon, E. Hodgson, A. Biswas, M.M. Billingsley, L. Li, F. Yiping, M. Carpenter, A. Trokhan, J. Yeo, N. Johana, T.Y. Wan, M.-G. Alameh, F.C. Bennett, P.B. Storm, R. Jain, J. Chan, D. Weissman, M.J. Mitchell, W. H. Peranteau, Ionizable lipid nanoparticles for therapeutic base editing of congenital brain disease, ACS Nano 17 (14) (2023) 13594–13610, https://doi.org/10.1021/acsnano.2c02268.

[191] Y. Zhang, S. Shen, G. Zhao, C.-F. Xu, H.-B. Zhang, Y.-L. Luo, Z.-T. Cao, J. Shi, Z.-B. Zhao, Z.-X. Lian, J. Wang, In situ repurposing of dendritic cells with CRISPR/Cas9-based nanomedicine to induce transplant tolerance, Biomaterials 217 (2019) 119302, https://doi.org/10.1016/j.biomaterials.2019.119302.

[192] J.B. Kuemmerle-Deschner, D. Verma, T. Endres, L. Broderick, A.A. De Jesus, F. Hofer, N. Blank, K. Krause, C. Rietschel, G. Horneff, I. Aksentijevich, P. Lohse, R. Goldbach-Mansky, H.M. Hoffman, S.M. Benseler, Brief report: clinical and molecular phenotypes of low-penetrance variants of NLRP 3: diagnostic and therapeutic challenges, Arthritis Rheumatol. 69 (11) (2017) 2233–2240, https://doi.org/10.1002/art.40208.

[193] D.T. Ewart, E.J. Peterson, C.J. Steer, Gene editing for inflammatory disorders, Ann. Rheum. Dis. 78 (1) (2019) 6–15, https://doi.org/10.1136/annrheumdis-2018-213454.

[194] C.T. Ellebrecht, V.G. Bhoj, A. Nace, E.J. Choi, X. Mao, M.J. Cho, G. Di Zenzo, A. Lanzavecchia, J.T. Seykora, G. Cotsarelis, M.C. Milone, A.S. Payne, Reengineering chimeric antigen receptor T cells for targeted therapy of autoimmune disease, Science 353 (6295) (2016) 179–184, https://doi.org/10.1126/science.aaf6756.

[195] S. Rafiq, C.S. Hackett, R.J. Brentjens, Engineering strategies to overcome the current roadblocks in CAR T cell therapy, Nat. Rev. Clin. Oncol. 17 (3) (2020) 147–167, https://doi.org/10.1038/s41571-019-0297-y.

[196] J.R. Hamilton, E. Chen, B.S. Perez, C.R. Sandoval Espinoza, M.H. Kang, M. Trinidad, W. Ngo, J.A. Doudna, In vivo human T cell engineering with enveloped delivery vehicles, Nat. Biotechnol. (2024), https://doi.org/10.1038/s41587-023-02085-z.

[197] J. Ren, X. Liu, C. Fang, S. Jiang, C.H. June, Y. Zhao, Multiplex genome editing to generate universal CAR T cells resistant to PD1 inhibition, Clin. Cancer Res. 23 (9) (2017) 2255–2266, https://doi.org/10.1158/1078-0432.CCR-16-1300.

[198] M. Naeem, S. Majeed, M.Z. Hoque, I. Ahmad, Latest developed strategies to minimize the off-target effects in CRISPR-Cas-mediated genome editing, Cells 9 (7) (2020) 1608, https://doi.org/10.3390/cells9071608.

[199] E.F. Morand, R. Furie, Y. Tanaka, I.N. Bruce, A.D. Askanase, C. Richez, S.-C. Bae, P.Z. Brohawn, L. Pineda, A. Berglind, R. Tummala, Trial of anifrolumab in active systemic lupus erythematosus, N. Engl. J. Med. 382 (3) (2020) 211–221, https://doi.org/10.1056/NEJMoa1912196.

[200] W.-M. Wang, H.-Z. Jin, Biologics in the treatment of pustular psoriasis, Expert Opin. Drug Saf. 19 (8) (2020) 969–980, https://doi.org/10.1080/14740338.2020.1785427.

[201] C. Madsen, The innovative development in interferon beta treatments of relapsing-remitting multiple sclerosis, Brain Behav. 7 (6) (2017) e00696.

[202] Y. Jiang, H.K. Genant, I. Watt, M. Cobby, B. Bresnihan, R. Aitchison, D. McCabe, A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of genant and Larsen scores, Arthritis Rheum. 43 (5) (2000) 1001, https://doi.org/10.1002/1529-0131(200005)43:5<1001::AID-ANR7>3.0.CO;2-P.

[203] P.H. Schafer, P. Chen, L. Fang, A. Wang, R. Chopra, The pharmacodynamic impact of apremilast, an oral phosphodiesterase 4 inhibitor, on circulating levels of inflammatory biomarkers in patients with psoriatic arthritis: substudy results from a phase III, randomized, placebo-controlled trial (PALACE 1), J. Immunol. Res. 2015 (2015) 1–10, https://doi.org/10.1155/2015/906349.

[204] B.L. Furman, Methimazole, in: xPharm: The Comprehensive Pharmacology Reference, Elsevier, 2007, pp. 1–4, https://doi.org/10.1016/B978-008055232-3.62148-8.

[205] P.C.M. Van De Kerkhof, Update on retinoid therapy of psoriasis in: an update on the use of retinoids in dermatology, Dermatol. Ther. 19(5) (2006) 252–263. Doi: 10.1111/j.1529-8019.2006.00082.x.

[206] J. Choi, A. Fenando, Sulfasalazine. StatPearls, StatPearls Publishing, Treasure Island (FL), 2023.

[207] J. Yang, A. McGovern, P. Martin, K. Duffus, X. Ge, P. Zarrineh, A.P. Morris, A. Adamson, P. Fraser, M. Rattray, S. Eyre, Analysis of Chromatin Organization and Gene Expression in T Cells Identifies Functional Genes for Rheumatoid Arthritis, Nat Commun 11 (1) (2020) 4402, https://doi.org/10.1038/s41467-020-18180-7.

[208] J.-M. Yang, Y. Ren, A. Kumar, X. Xiong, J.K. Das, H.-Y. Peng, L. Wang, X. Ren, Y. Zhang, C. Ji, Y. Cheng, L. Zhang, R.C. Alaniz, P. De Figueiredo, D. Fang, H. Zhou, X. Liu, J. Wang, J. Song, NAC1 Modulates Autoimmunity by Suppressing

Regulatory T Cell–Mediated Tolerance, Sci. Adv. 8 (26) (2022) eabo0183, https://doi.org/10.1126/sciadv.abo0183.

[209] Scheinfeld, N. Adalimumab: A Review of Side Effects. *Expert Opinion on Drug Safety* **2005**, *4* (4), 637–641. https://doi.org/10.1517/14740338.4.4.637.

[210] G.Y. Melmed, S.R. Targan, U. Yasothan, D. Hanicq, P. Kirkpatrick, Certolizumab Pegol. Nat Rev Drug Discov 7 (8) (2008) 641–642, https://doi.org/10.1038/nrd2654.

[211] Scherl, E. J.; Kumar, S.; Warren, R. U. Review of the Safety and Efficacy of Ustekinumab. *Therap Adv Gastroenterol* **2010**, *3* (5), 321–328. https://doi.org/10.1177/1756283X10374216.

[212] Pang, Y.; D'Cunha, R.; Winzenborg, I.; Veldman, G.; Pivorunas, V.; Wallace, K. Risankizumab: Mechanism of Action, Clinical and Translational Science. *Clinical Translational Sci* **2024**, *17* (1), e13706. https://doi.org/10.1111/cts.13706.

[213] A. Mahmood, A. Ali, H. Haider, B. Zulfiqar, Long-Term Efficacy and Safety of Secukinumab in Patients with Psoriatic Arthritis, European Journal of Internal Medicine 118 (2023) 152–154, https://doi.org/10.1016/j.ejim.2023.08.023.

[214] G. Caldarola, A. Chiricozzi, M. Megna, P. Dapavo, A. Giunta, M. Burlando, P. Malagoli, V. Dini, M. Mariani, G. Fabbrocini, P. Quaglino, L. Bianchi, A. Parodi, K. Peris, C. De Simone, Real-Life Experience with Ixekizumab in Plaque Psoriasis: A Multi-Center, Retrospective, 3-Year Study, Expert Opinion on Biological Therapy 23 (4) (2023) 365–370, https://doi.org/10.1080/14712598.2023.2193288.

[215] M. Harigai, T. Miyamae, H. Hashimoto, A. Yoshida, K. Yamashita, Y. Nakaoka, A Multicentre, Large-Scale, Observational Study of Tocilizumab in Patients with Takayasu Arteritis in Japan: The ACTEMRA® (ACT)-Bridge Study, Modern Rheumatology 33 (5) (2023) 998–1006, https://doi.org/10.1093/mr/roac099.

[216] R. Kneeland, D. Montes, J. Endo, B. Shields, C.M. Bartels, S. Garg, Improvement in Cutaneous Lupus Erythematosus After Twenty Weeks of Belimumab Use: A Systematic Review and Meta-Analysis, Arthritis Care & Research 75 (8) (2023) 1838–1848, https://doi.org/10.1002/acr.25058.

[217] S.L. Hauser, L. Kappos, A. Bar-Or, H. Wiendl, D. Paling, M. Williams, R. Gold, A. Chan, R. Milo, A. Das Gupta, G. Karlsson, R. Sullivan, G. Graham, M. Merschhemke, D.A. Häring, P. Vermersch, The Development of Ofatumumab, a Fully Human Anti-CD20 Monoclonal Antibody for Practical Use in Relapsing Multiple Sclerosis Treatment, Neurol Ther 12 (5) (2023) 1491–1515, https://doi.org/10.1007/s40120-023-00518-0.

[218] A.R. Allam, M.S. Alhateem, A.M. Mahmoud, Efficacy and Safety of Baricitinib in Treatment of Systemic Lupus Erythematosus: A Systematic Review and Meta-Analysis, BMC Rheumatol 7 (1) (2023) 40, https://doi.org/10.1186/s41927-023-00363-6.

[219] Boyce, E. G.; Rogan, E. L.; C. Lui, M. Upadacitinib for the Treatment of Rheumatoid Arthritis: An Extensive Review. *Ann Pharmacother* **2023**, *57* (4), 450–462. https://doi.org/10.1177/10600280221113092.

[220] R. Harrington, P. Harkins, R. Conway, Janus Kinase Inhibitors in Rheumatoid Arthritis: An Update on the Efficacy and Safety of Tofacitinib, Baricitinib and Upadacitinib, JCM 12 (20) (2023) 6690, https://doi.org/10.3390/jcm12206690.

[221] A. Palmowski, S.M. Nielsen, Z. Boyadzhieva, A. Schneider, A. Pankow, L. Hartman, Da Silva, J. Kirwan, S. Wassenberg, C. Dejaco, R. Christensen, M. Boers, F. Buttgereit, Safety and Efficacy Associated with Long-Term Low-Dose Glucocorticoids in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis, Rheumatology 62 (8) (2023) 2652–2660, https://doi.org/10.1093/rheumatology/kead088.

[222] Matson, S. M.; Baqir, M.; Moua, T.; Marll, M.; Kent, J.; Iannazzo, N. S.; Boente, R. D.; Donatelli, J. M.; Dai, J.; Diaz, F. J.; Demoruelle, M. K.; Hamblin, M. B.; Mathai, S. K.; Ryu, J. H.; Pope, K.; Walker, C. M.; Lee, J. S. Treatment Outcomes for Rheumatoid Arthritis-Associated Interstitial Lung Disease. *Chest* **2023**, *163* (4), 861–869. https://doi.org/10.1016/j.chest.2022.11.035.