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Targeted modulation of immune cells and tissues using engineered biomaterials

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Abstract

Therapies modulating the immune system offer the prospect of treating a wide range of conditions including infectious diseases, cancer and autoimmunity. Biomaterials can promote specific targeting of immune cell subsets in peripheral or lymphoid tissues and modulate the dosage, timing and location of stimulation, thereby improving safety and efficacy of vaccines and immunotherapies. Here we review recent advances in biomaterials-based strategies, focusing on targeting of lymphoid tissues, circulating leukocytes, tissue-resident immune cells and immune cells at disease sites. These approaches can improve the potency and efficacy of immunotherapies by promoting immunity or tolerance against different diseases.

Short Summary

This Review discusses biomaterials that promote therapeutic targeting of immune cells by modulating the dosage, timing and location of stimulation, thereby improving the safety and efficacy of vaccines and immunotherapies.

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Author contributions

The manuscript was drafted and revised by PY, KN, and DJI.

Competing interests

DJ is an inventor on patents related to “albumin hitchhiking” discussed under lymph node targeting, nanoparticle modification of T cells discussed under “Backpacking adoptively transferred cells” and alum-binding cytokines discussed under “Intratumoural delivery of biomaterials”. These patents have been licensed to Elicio Therapeutics, Repertoire Immune Medicines and Ankyra Therapeutics, respectively, and DJI holds equity in these companies. The remaining authors declare no competing interests.

Introduction

Modulating the immune system is a pivotal treatment strategy of modern medicine. In 2021, seven of the top 10 drugs by sales act on the immune system, including, notably, the messenger RNA (mRNA)-based vaccines for COVID-19[1]. Beyond its established role in vaccine development, immunomodulation holds therapeutic potential against different conditions including autoimmunity and cancer, as well as inflammatory, fibrotic and infectious diseases. However, immunomodulation is a two-edged sword, as most clearly demonstrated in the field of cancer immunotherapy, where despite inducing substantial anti-tumour immunity, systemic administration of many immunotherapy drugs has resulted in immune-related adverse events distal to tumour sites[2]. Therefore, delivering precise dosages of immunomodulatory drugs with spatiotemporal control to specific cells and tissues, while avoiding unwanted off-target stimulation, is essential to ensure a safe and effective immune response.

Targeting of immune cells can be achieved using traditional protein engineering strategies, employing monoclonal antibodies, engineered binding proteins or recombinant native ligands for immune cell surface receptors. These approaches are at various stages of clinical development, with mono- and multi-specific antibodies being the most advanced[3–7]. However, the only cell surface protein that truly defines a lymphocyte as disease relevant is its antigen receptor, making highly specific targeting challenging. In addition, simply linking an antibody domain to an immunomodulatory drug is not always sufficient to achieve effective targeting, as the therapeutic payload may dominate the biodistribution of such fusions[8]. [8] Engineered biomaterials can introduce additional functionality beyond simple binding to target cells by concentrating immunotherapy agents in specific tissue sites, controlling their release kinetics and their intracellular localization.

The immune system consists of well-defined regional control centres (lymphoid organs), important tissue-resident cell populations (especially at barrier tissues such as mucosal surfaces) and mobile cell populations that constantly recirculate through the blood and tissues, providing both challenges and opportunities as a therapeutic target (Fig. 1a). Here we review recent advances of biomaterials-enabled therapeutic strategies for in vivo targeted modulation of the immune system. We focus on approaches targeting immune cells and lymphoid organs, excluding direct targeting of pathogens such as viruses or bacteria, followed by a discussion on prospects and challenges for future developments in this area.

Lymphoid organs as target

Lymphoid organs coordinate the maturation and migration of immune cells while organizing and regulating immune responses (Fig. 1a). Primary lymphoid organs in adults include the bone marrow and thymus, which serve as niches for lymphocyte development. Secondary lymphoid organs, which include 600–800 lymph nodes (LNs) distributed across the body, the spleen and mucosa-associated lymphoid tissue, house and organize T cells, B cells and antigen presenting cells (APCs). These organs serve as command centres of adaptive immunity by activating naïve B and T lymphocytes (Fig. 1a–b), and are thus natural targets for vaccines and immunotherapies.

Principles of lymph node targeting

Passive targeting of therapeutics to lymphatic vessels.—LNs interface with peripheral tissues through lymphatic vessels, which drain lymph fluid from all tissues and provide a conduit for immune cell trafficking. Drugs and vaccines can be targeted to LNs through lymphatic uptake following parenteral injection. A major factor influencing lymphatic targeting is the physical size of the injected agents: following injection into tissue (including tumours), particles larger than 50–100 nm in diameter become trapped in the extracellular matrix (ECM), whereas particles in the size range of 5–50 nm convect with lymph into the lymphatic vessels, and flow to draining LNs (dLNs). By contrast, particles smaller than 5 nm partition preferentially into the blood rather than the lymph (Fig. 2a)[9,10]. These are approximate size ranges that depend on the tissue site of injection (which can vary in ECM and lymphatic composition) and factors such as injection volume and rate (which can cause mechanical expansion of flaps mediating entry into lymphatic vessels), especially in small animal models. Furthermore, particle shape, charge and surface chemistry can also play a role by promoting or hindering convection through the tissue and lymphatic entry[11]. Notably, capturing particles at the downstream dLN is a less-studied but equally important prerequisite for LN modulation, as evidenced by data showing that proteins[12] and small hydrophilic nanoparticles (NPs)[13] can pass through the entire lymphatic chain, reach the thoracic duct and enter the systemic circulation following a parenteral injection. In this regard, using adjuvants that promote compound entry into LNs[14], or designing carriers that stimulate recognition by macrophages lining the subcapsular and medullary sinuses can prove useful[15].

Protein NPs with surface-arrayed antigens and a size optimized for efficient lymphatic uptake enhance the immunogenicity of vaccines[16–20]. Protein NP vaccines are currently in clinical trials for human immunodeficiency virus (HIV), SARS-CoV-2 and influenza, and have been shown to be safe and elicit potent neutralizing antibody responses in humans[21,22] (Table 1). Lipid nanodiscs and block copolymer micelles smaller than 50 nm also efficiently traffic and deliver compounds into lymphatics [23,24]. Cage-like NPs formed by the self-assembly of saponin and lipids (termed ISCOMs) are potent vaccine adjuvants with an ideal size (~40 nm) for LN targeting, and recently received emergency use approval in the US against SARS-CoV-2 (EudraCT: 2020–004123-16)[25]. Another strategy to promote lymphatic uptake is to exploit albumin and lipoproteins that naturally traffic from blood to lymph. Amphiphilic conjugates consisting of peptides, proteins or small molecules linked to an albumin-binding lipid tail through a hydrophilic poly(ethylene glycol) (PEG) spacer (amph-vaccines), bind to endogenous albumin in the tissue following parenteral injection, improving LN targeting[26–29]. In one example, conjugation of an albumin-binding lipid tail to a CpG oligonucleotide adjuvant resulted in a 12-fold greater area-under-the-curve for total LN exposure following subcutaneous immunization in mice, compared with unmodified CpG[26]. This approach is currently being tested in the clinic for LN targeting of a cancer vaccine (NCT04853017; Table 1)[30]. LN-targeting NPs are also being used to deliver latency-reverting drugs in HIV cure strategies[31] and to induce immunological tolerance[32–35]. NPs composed of self-assembled proteins, synthetic bioresorbable polymers or lipid assemblies, have different in vivo lifetimes and stabilities that can impact their functionality. For

example, proteolysis of protein NPs vaccines could lead to particle disassembly and loss of antigen multimerization. However, such effects have received limited attention to date.

Targeting lymph node-bound migratory immune cells in peripheral tissues.— Complementary to the strategy of direct lymphatic targeting, this approach leverages the natural process by which immune cells, including dendritic cells (DCs), monocytes and neutrophils, internalize antigens in peripheral tissues and transport them to LNs as part of their constitutive immune surveillance (Fig. 2b). For example, subcutaneously-implanted porous polymer scaffolds releasing the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) attract and differentiate monocytes into the DC lineage. When such scaffolds also carry molecular adjuvants and tumour antigens, these are taken up by the recruited cells and transported to dLNs (Fig. 2b)[36,37]. This approach improved anti-tumour immunity, eliciting ~50% complete responses in an aggressive mouse model of melanoma, and leading to a first-in-humans clinical trial of this technology (NCT01753089; Table 1). Data from this trial are not yet published, but should provide important insights into the safety of generating a strong localized inflammatory reaction at the implant site, an approach that could be extended to applications beyond cancer. To avoid implantation, injectable polymeric hydrogels[38] or suspensions of biodegradable silica particles[39] have been employed, resulting in both cellular and humoral immune responses against cancer or microbial antigens[40]. Similarly, microparticles loaded with tumour lysates as antigen and adenosine triphosphate (ATP) as a chemotaxis-inducing ‘find-me’ signal promoted recruitment of DCs and increased levels of mature DCs migrating to tumour dLNs, resulting in reduced tumour growth.[41]

DC-attracting biomaterials are also being developed to program tolerance rather than immunity. Dual-sized poly(lactide-*co*-glycolide) (PLGA) particles consisting of small (0.5–2.5 μm diam.) phagocytosable microparticles loaded with the tolerogenic metabolite vitamin D3 and autoantigens, combined with large (10–65 μm diam.) non-phagocytosable microparticles designed to release extracellular transforming growth factor-beta (TGF-β) and GM-CSF, prevented hyperglycemia in a mouse model of type 1 diabetes[42] and induced antigen-specific tolerance in mouse models of multiple sclerosis (MS) and collagen-induced arthritis[43,44]. This example highlights the potential of DCs-attracting approaches not only to modulate immunity, but also to program tolerance.

Targeting niches within lymph nodes

Organization of lymph nodes.—LNs are highly organized organs with defined compartments enriched in different immune cell subsets. Afferent lymph enters the subcapsular sinus (SCS) of the LN, a fluid space between the LN capsule and the LN parenchyma, lined by lymphatic endothelial cells and macrophages (Fig. 1b). Within the parenchyma, many of the key cell populations regulating adaptive immunity have specific niches; B cells and follicular DCs reside in follicles arrayed around the exterior of the node, whereas T cells are localized deeper in the LN paracortex (Fig. 1b)[45,46]. This physical segregation plays an important role in orchestrating sequential steps in the immune response, therefore, targeting distinct niches in the LN could offer valuable therapeutic opportunities.

Entry into lymph nodes.—Under physiological conditions, substances in the lymph can pass into the parenchyma through narrow collagen conduits, or be captured and transferred into the LN interior by subcapsular sinus (SCS) macrophages (Fig. 1b)[47–49]. The conduits exclude globular proteins larger than ~70 kDa[49,50], although evidence suggests that this size limit can change in the presence of a live infection[51]. Vaccine adjuvants such as oil-in-water nanoemulsions and saponin NPs have been used to boost entry of compounds into LNs by inducing rapid death of SCS macrophages (Fig. 3a)[14,52,53]. Similarly, liposomal formulations of clodronate, widely used to deplete SCS macrophages, improve antigen entry into LNs[54]. In another strategy, a two-stage delivery system was developed, in which CpG oligonucleotides were coupled to ~30 nm poly(propylene sulfide) (PPS) NPs through cleavable oxanorbornadiene linkers and then injected intradermally in a murine model of lymphoma[55]. The NPs efficiently trafficked from the injection site to dLNs, but were largely trapped in the sinuses after 24 hr. By tuning the chemistry of the oxanorbornadiene linker, the CpG adjuvant payload remained bound to the NPs during trafficking to the dLN, and were later released deep into the LN parenchyma (Fig. 3b).

Targeting specific cells and niches within the lymph node.—To facilitate intra-nodal delivery, specific cell populations can be targeted within the LN parenchyma, in particular DCs and macrophages. For example, oral or systemic administration of rapamycin promotes tolerance by acting on DCs and myeloid cells (for example, in organ transplants); however, with considerable systemic side effects [56]. Subcutaneous injection of rapamycin encapsulated in PEG-b-PPS polymer vesicles (~100 nm diam.) efficiently targeted the LNs in a diabetic mouse model, where it was preferentially phagocytosed by DCs and other myeloid cells and induced a regulatory DC phenotype enabling allogeneic pancreatic islet transplants to be maintained over 100 days, without side effects[57]. To drive antigen-specific tolerance, LN DCs were targeted using liposomes co-delivering a tolerance-driving aryl hydrocarbon receptor agonist drug together with a multiple sclerosis (MS)-related peptide in a murine MS model[58]. Cancer neoantigens linked to hydrophobic peptides bearing toll-like receptor-7 (TLR7) agonists were developed to self-assemble into ~20 nm micelles, which efficiently trafficked from s.c. injection sites to dLNs, achieving uptake in 80% of LN DCs, leading to anti-tumour immunity in multiple murine tumor models[59]. DC targeting has also been achieved by targeting specific receptors expressed by these cells. Following intradermal vaccination, polymer chains functionalized with antigens, TLR7 agonists and mannose moieties to target mannose receptor$^+$ DCs improved uptake of antigens in LNs (Fig. 3c), generating antigen-specific CD8$^+$ T cell responses and increasing serum antibody concentrations (1.7- and 3.6-fold compared to potent alternative adjuvant formulations AS01EL and poly(I:C), respectively)[60]. These studies highlight the potential of co-delivering antigens and adjuvant compounds to the same cell through physical conjugation or encapsulation within the polymer carrier, an already widely-adopted strategy[59,61,62]. Moreover, the physical chemistry of antigen and adjuvant compounds, together with a selective design of NPs carriers that enable release into DCs upon arrival in the LNs, are important parameters to consider to ensure optimal T cell priming and functional polarization[62–64]. For example, autoimmune-related peptide antigens coupled to ~10 nm quantum dots (QDs) trafficked from s.c. injection sites to dLNs, where they accumulated in macrophage receptor with collagenous structure (MARCO)$^+$ macrophages[65].

These cells have been associated with immune tolerance, and expanded regulatory T cells (Tregs) contributing to disease control in a mouse model of MS[65]. Therefore, targeting both of these LN APC populations appears promising for promoting both immunity and tolerance. Of note, in this work QDs were used owing to their bright fluorescent properties, but are known to release toxic metals over time[66]. In general, an important question to address with any polymer or NP-based DC targeting strategy is whether the material is effectively captured in the draining lymph node chain following injection, or whether they it passes through the thoracic duct and enters the systemic circulation[67], raising potential toxicity concerns, in particular for potent immunostimulants.

B cell follicles are another important niche regulating humoral immune responses. NPs engineered to activate the complement system can target antigens or therapeutics to B cell follicles. For example, NPs bearing a high density of mannose-containing glycans are recognized by the innate immune protein mannose-binding lectin, which triggers complement deposition on the particles. Upon arrival to the LNs, SCS macrophages transfer complement-decorated particles to migratory B cells in the LN parenchyma, which in turn pass the particle to follicular DCs (FDCs) (Fig. 3d)[53,68]. For vaccines, this strategy is glycan density-dependent, amplifies germinal centre and serum antibody responses and can be engineered into synthetic particles to promote follicle localization[68,69]. A protein nanoparticle vaccine that triggers the FDC targeting process completed a phase I trial (NCT03547245) and demonstrated 97% efficacy in initiating broadly-neutralizing antibody B cell lineages in humans[70]. In principle, particles triggering complement activation through natural immunoglobulin M (IgM) or the alternative pathway should also be capable of such FDC localization. However, this trafficking is size dependent; complement-decorated particles smaller than 15 nm were internalized and cleared by FDCs, whereas particles 50 nm or larger were retained on FDC dendrites for several weeks, resulting in improved antibody responses[71]. An important parameter to consider when designing carriers targeting B cells, is that rigid particles carrying multivalent copies of an antigen are more effective than flexible polymers in triggering B cell activation[72].

T cells are another key cell type in LNs, which are located in the paracortex and interfollicular regions (Fig. 1b). Polymer NPs coated with DC-derived plasma membrane fragments and conjugated with anti-CD3 antibodies showed efficient accumulation in dLNs, activated and expanded $CD8^+$ T cells, and, in combination with anti-programmed cell death protein 1 (PD-1) therapy, eliciting antitumor immunity[73]. To provide vaccine-like stimulation of chimeric antigen receptor (CAR) T cells in LNs, albumin-binding ‘amph-vaccine’ molecules were designed carrying CAR ligands. The lipid tails of these conjugates inserted into cell membranes of DCs and macrophages in the dLN, enabling activation of CAR T cells in the LN and improving anti-tumor activity (Fig. 3e)[74].

Targeting lymph nodes, spleen and liver

Unlike live infections, current vaccines fail to elicit high-magnitude CD8 T cell responses in humans, which has motivated the field to explore new ways to prime cellular immunity[75]. Vaccines commonly act locally on a chain of LNs draining at the injection site such as the muscle[76]. However, this means that reacting immune cells are confined to a few LNs,

resulting in competition for a limited resources (for example cytokines or antigens), which theoretically might restrain the eventual systemic immune response. One hypothesis is that systemic administration of antigens to several LNs could alleviate such resource constraints and enable more potent immune priming. A key consideration is that adjuvant and antigen signals need to be delivered together to ensure that immunity, rather than tolerance, is elicited. Moreover, intravenously (i.v.) administered materials are rapidly opsonized and captured by macrophages in the liver, spleen and bone marrow, in particular for particles larger than 100 nm. By contrast, particles smaller than 5 nm are rapidly cleared through the kidneys[77]. Therefore, to systemically target lymphoid organs, opsonization-resistant (e.g., PEGylated) particles in the range of 5–100 nm would be ideal, although this size dependency could be altered if circulating immune cells take up the particles and actively transport them into systemic lymph nodes. For example, i.v. administration of negatively charged interferon-inducing lipid nanoparticles (LNPs) carrying antigen-encoding mRNA efficiently targeted DCs in the spleen and peripheral LNs as well as myeloid cells in the liver and bone marrow, resulting in a substantial antigen-specific T cells response (30–60% of the total $CD8^+$ T cell compartment specific for the targeted antigens), and consequent tumour rejection in aggressive murine tumour models[78] (Fig. 4). These findings spurred ongoing clinical trials of mRNA LNPs in multiple cancers, with promising interim results including objective response rates in 6 out of 17 patients with advanced melanoma[79,80] (NCT04534205, NCT03418480 and NCT02410733; Table 1). Similarly, i.v. vaccination with self-assembled polymer NPs carrying cancer neoantigen peptides and small molecule TLR-7/8 agonists primed a larger $TCF\text{-}1^+$ stem-like antigen-specific T cell population compared to parenteral vaccination with the same material, leading to improved anti-tumour immunity[81]. These examples highlight the potential beneficial effects of systemic immunization on the immune response. Following these principles, a clinical trial in the Netherlands is currently evaluating i.v.-administered PLGA-based nanoparticles delivering a tumour antigen together with a small molecule as innate immune activator designed to promote DC activation through invariant NK T cells (NCT04751786, Table 1)[82].

APC populations in the liver and spleen are known to play important roles in systemic tolerance, and are therefore being targeted for tolerance and autoimmunity. For example, i.v.-administered biodegradable PLGA NPs carrying rapamycin were efficiently captured by DCs in the spleen, and elicit a Treg-generating, tolerizing phenotype in these cells that blocked generation of cellular and humoral responses against co-administered antigens[83]. Following this approach, a clinical trial aimed at blocking anti-drug antibody responses against recombinant uricase in gout patients demonstrated promising efficacy and safety data in humans (NCT02648269)[84]. Similarly, i.v. administration of biodegradable polymer NPs coupled to autoantigens for tolerance induction led to efficient uptake in tolerance-promoting $MARCO^+$ APCs in the spleen and liver, fostering protection in mouse models of diabetes and other autoimmune conditions[85 86]. Subcutaneously-injected diabetes autoantigens coupled to hyaluronic acid polymers were delivered to both disseminated LNs and spleen, promoting systemic expansion of $CD4^+$ T cells with an immunosuppressive phenotype[87]. I.v. injection of biodegradable PLGA NPs loaded with a model antigen and functionalized with stabilin to target scavenger receptors expressed by liver sinusoidal endothelial cells resulted in an almost exclusive accumulation in the liver, providing

protection from airway-induced allergic inflammation (Fig. 4)[88]. As a final example, liposomes were administered intraperitoneally to deliver alpha-galactosyl ceramide to marginal zone B cells in the spleen. Presentation of the ligand to invariant NK T cells promoted the development of regulatory T cells and tolerogenic DCs in the spleen of mice[89]. This treatment suppressed graft versus host disease (GVHD) following bone marrow transplant[90], and is now moving into early stage clinical trials (NCT04014790 and NCT01379209; Table 1)[91]. In these examples, different materials were used to target antigens and stimuli to relevant immune cells. An important but understudied parameter is how the duration of cargo release in recipient target cells affects their tolerizing effect. For example, loaded PLGA particles could be engineered to release antigens over weeks, whereas fast-degrading surface-conjugated particles or liposomes could provide rapid release following endocytosis. Whether these kinetics have a substantial impact remain unknown.

Targeting immune cells in bone marrow

The bone marrow is a primary lymphoid organ for hematopoiesis and myelopoiesis, and also a site housing a large pool of memory T cells (Fig. 1a)[92]. Myeloid precursors, in particular, have received recent attention because they drive a process known as “trained immunity”. This phenomenon occurs when innate immune cells or their progenitors receive certain microbial stimuli (including Bacillus Calmette-Guérin bacteria, Candida albicans yeast, β-glucan, or peptidoglycan[93]) that drive epigenetic changes rewiring their metabolic and functional state[94,95]. When induced in progenitor cells, these epigenetic modifications are passed on to their progeny and confer a prolonged and elevated state of responsiveness to microbial stimuli in monocytes, macrophages and natural killer cells. Therapeutic induction (or suppression) of trained immunity is now being considered as a promising approach to treat diverse diseases[93]. For example, i.v. injection of apolipoprotein-A1-based lipid nanodiscs carrying the minimal peptidoglycan muramyl dipeptide preferentially accumulated in myeloid cells and their precursors in the blood, spleen and tumours in a mouse model of melanoma, resulting in enhanced cytokine production and increased efficacy of checkpoint blockade therapy (Fig. 4) [96]. Such innate immune modulation could be a powerful complement to therapeutic strategies focused on boosting adaptive immunity.

Targeting circulating leukocytes

Many immune cells continuously recirculate between secondary lymphoid organs, the blood and tissues, patrolling for cognate foreign antigens. The ability of immune cells to home from the blood into disease sites forms the basis of adoptive cell therapies, where engineered immune cells are infused i.v. in patients and subsequently home to targeted distal sites. These cells can be targeted while in the blood to serve as chaperones to transport drugs into disease sites.

‘Backpacking’ cells

Adoptive cell therapies based on the injection of autologous cells engineered to have disease-specific functions is a steadily expanding approach for immunotherapy[97,98]. To date, the most clinically successful example is chimeric antigen receptor (CAR) T cell therapy,

where lymphocytes isolated from cancer patients are transduced to express a CAR that enables recognition and selective killing of tumour cells. CAR T cells are then expanded ex-vivo and re-infused into the patient[99]. So far, six different CAR T cell products have been approved for hematologic malignancies, with several ongoing clinical trials to extend CAR T therapy to solid tumours and infectious diseases[100–102]. Adoptive cell therapies are also being developed using natural or transgenic T cell receptor (TCR)-expressing T cells, natural killer cells, macrophages, Tregs (for autoimmune disease and transplant tolerance) and other immune cell populations[103]. Adoptively transferred cells benefit from supporting stimulation to maintain their function or promote their expansion and survival, however, as with other immunomodulators, systemic co-administration of supporting drugs can be toxic owing to non-specific effects on endogenous immune cells.

To provide sustained and localized stimulation, therapeutic carriers have been directly attached to the surface of donor cells prior to infusion (an approach termed ‘backpacking’) (Fig. 5a). This strategy has been used to load tumour-specific T cells and Tregs with cytokines, small molecule drugs or chemotherapeutic agents[104–107]. Early studies showed that LNP backbacks carrying cytokines such as IL-15 remained on the cell surface for extended periods, inducing potent autocrine stimulation and proliferation of adopted antigen-specific T cells in vivo[107]. [107–104, 6]Backpacking protein nanogels onto T cells enabled a more controlled release of supporting cytokines in response to altered cell surface reduction activity after TCR or CAR stimulation in mice[108]. This strategy restricted donor cell stimulation to tumours and tumour-dLNs (where the antigen is encountered), improving therapeutic efficacy and safety[108]. Interim results from a phase I clinical trial of this approach in cancer patients (NCT03815682; Table 1) showed that only one tenth the amount of administered interleukin (IL)-15 was detectable in the blood despite backpacking 3 times the maximum tolerated dose of free systemic Fc-fused IL-15[109] onto T cells, leading to stable disease in 10 out of 17 patients[110]. A limitation of this approach is that the therapeutic payload is by definition finite, and will be diluted over time as T cells proliferate in vivo. However, it could still provide immediate autocrine stimulation following adoptive transfer, enabling cells to successfully engraft and initiate tumour rejection. Owing to the cytokine carrier being directly conjugated to the cell membrane, the concentration of newly-released cytokines at the cell surface is substantial, and it was estimated that the IL-15 nanogels will continue to stimulate T cells through at least 7 cell divisions before stimulatory capacity is lost[108].

Backpacking approaches have also been developed for innate immune cells; discoid polymer particles carrying interferon gamma (IFN-γ), adhered to the surface of macrophages without inducing phagocytosis, resulting in persistent polarization into an ‘M1’ phenotype that promoted tumour rejection in a murine breast cancer model[111]. Importantly, the use of a discoid morphology was crucial to avoiding phagocytosis of the backpack (Fig. 5a)[112].

Targeting immune cells in blood

Targeting circulating cells that traffic drugs into tissues—Targeting immune cells in the blood is an attractive strategy to circumvent physical barriers in tissues. For example, lymphocytes populating Peyer’s patches and mesenteric LNs express well-defined adhesion

and chemokine receptors ($\alpha_4\beta_7$ integrin and CCR9, respectively[113,114]) that direct their homing to these sites (Fig. 5b). I.v. administration of lipid-coated polymer NPs loaded with an HIV antiretroviral drug and surface-functionalized with antibodies against $\alpha_4\beta_7$ promoted uptake in gut lamina propria cells, which transported the particles to the gut of mice[115]. Functionalizing silencing-RNA (siRNA)-loaded LNPs with recombinant mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1), the ligand recognized by the high-affinity conformation of $\alpha_4\beta_7$, increased the particle's specificity to gut-homing lymphocytes resulting in silencing of IFN-γ in a murine model of colitis[116].

NPs have also been used to target circulating immune cells that home into tumours or sites of inflammation. Intraperitoneally-injected hyaluronic acid-polyethyleneimine hybrid NPs carrying miR-125b, a microRNA known to induce an anti-tumour 'M1' phenotype in macrophages[117], were taken up by these cells which then migrated to lung tumours and repolarized tumour-associated macrophages towards an M1 phenotype. Of note, choosing the right administration route is important to avoid unexpected transduction of macrophages in the liver or bone marrow. I.v. administration of liposomes or lipid nanoemulsions conjugated with arginylglycylaspartic acid (RGD) peptides, known to bind to α_V integrins which are highly expressed by monocytes and neutrophils, led to rapid uptake by these cells in the blood, and these innate cells subsequently carried the particles to tumours in mice[118] (Fig. 5b). The same approach enabled the delivery of neuroprotective drugs across the blood-brain barrier to sites of ischemia in mice[119]. Thus, targeting of immune cells in the blood is a promising strategy to hitchhike drugs into disease sites.

Antigen-specific targeting of circulating T cells.—Targeting of antigen-specific T cells in the blood has been pursued to enhance adoptive cell therapy and promote protective T cell responses. For example, in mouse models of autoimmunity, i.v. injection of iron oxide NPs coated with disease-relevant peptide-major histocompatibility complexes (pMHC) induced expansion of $CD4^+$ or $CD8^+$ T cells with a regulatory phenotype[120,121]. I.v.-injected class II pMHC-displaying NPs can further expand Tregs to control liver autoimmune diseases without systemically suppressing immunity in other organs[122]. In the setting of cancer, artificial APCs were generated by conjugating biodegradable PLGA/poly(β-amino-ester) (PBAE) microparticles with pMHC and anti-CD28 antibodies[123]. I.v. administration of these particles expanded antigen-specific cytotoxic $CD8^+$ T cells in vivo, and, in combination with checkpoint blockade therapy, increased the median survival time by 31% compared to single checkpoint blockade therapy in a mouse model of melanoma.[123] The same strategy was used to develop tolerogenic particles that promoted the expansion of forkhead box P3 ($Foxp3^+$) regulatory T cells, which, after a single i.v. injection, resulted in a 20% increase of these cells in lymph nodes compared to untreated mice.[124]

Targeting circulating T cells for gene delivery in vivo.—CAR T cell therapy is having substantial clinical impact against hematologic malignancies; however, its patient-specific nature and complex manufacturing process of transducing T cells ex vivo, limits its widespread application[125]. A potential alternative is to genetically modify T cells in vivo. Engineered viral vectors are being developed for this purpose[126,127]; however, viral vectors raise concerns of strong immune reactions and toxicity[128–130]. Another

option is to use synthetic NP gene delivery vectors. I.v.-injected poly(β-amino ester) NPs carrying transposon DNA encoding a CAR, which targets T cells through anti-CD3 antibody fragments, proved safe and effective in mouse models of leukaemia (Fig. 5c)[131]. Recently, in vivo mRNA delivery to T cells generated transient CAR T cells capable of eliminating fibrosis-promoting fibroblasts in models of heart failure[132]. Of note, immune cells (including T cells) are notoriously resistant to conventional transfection methods, therefore, it is important to identify more effective lipid/polymer compositions for nucleic acid delivery[133–135]. CAR T cells have also been produced in vivo using an implantable macroporous alginate scaffold, which provides a contact interface for T cells and retroviruses and facilitates vector-mediated CAR gene transfer[136]. Subcutaneous implantation of these scaffolds seeded with human peripheral blood mononuclear cells and CD19-encoding retroviral particles reduced ex vivo cell processing times to a single day, compared to 2–4 weeks for conventional CAR T cells, while keeping similar anti-tumour efficacy [136].

Targeting tissue-resident cells

Certain innate and adaptive immune cell populations permanently reside in tissues and provide functions such as immediate immune defence at barrier tissues, local production of protective antibodies and tissue-resident immune memory. In addition, these cells infiltrate sites of tissue damage, inflammation and tumours, making them important therapeutic targets for disease treatment.

Delivery at mucosal barriers

Several immune cell populations reside at mucosal barriers, such as the skin, airways, gastrointestinal and reproductive tract. DCs serve as sentinels of pathogen entry by sampling foreign antigens; tissue-resident memory lymphocytes and plasma cells provide frontline adaptive immune protection[137,138]; while mucosa-associated lymphoid tissues, such as the Peyer's patches and nasal-associated lymphoid tissue (NALT), serve as secondary lymphoid organs that rapidly respond to antigens entering through the mucosae[139]. These cells are important targets for vaccination, because antigens taken up across mucosal barriers prime lymphocytes in the draining lymphoid tissues that home back to these sites[137]. Moreover, mucosa-resident immune cells can be preferential targets of infection (for example, gut-resident memory $CD4^+$ T cells in HIV infection), posing them as interesting therapeutic targets for viral latency-reverting drugs against HIV[31,140]. A key challenge in targeting immune cells at these sites is that mucosal barriers have evolved to efficiently block incoming pathogens and foreign materials[141–142].

One promising strategy for effective drug delivery across mucosal surfaces is to exploit a natural bidirectional transport pathway for crossing the epithelial barrier. Following endocytosis in epithelial cells, immunoglobulin G (IgG) and albumin bind to the neonatal fragment crystallisable (Fc) receptor (FcRn) in endosomes, triggering transcytosis and release at the apical surface[143]. Fusing therapeutic proteins with Fc domains or albumin promotes uptake at the mucosal surface[144] (Fig. 5d). Similar to the backpacking approach, protein or peptide antigens linked to PEG-lipids (amph-vaccines) associate with albumin

in the airway fluid and ‘hitchhike’ through the mucus across the epithelial barrier in an FcRn-dependent manner[28,145]. Peptide amph-vaccines which were administered into the lungs primed robust lung tissue-resident memory T cells that enhanced vaccine protection against respiratory viral or tumour challenge[28]. By contrast, intranasal administration of protein amph-vaccines amplified germinal centre responses in the NALT, promoting higher mucosal antibody titers in both mice (100- to 1000-fold increase) and non-human primates (10-fold increase), compared to unmodified proteins[145].

Biomaterials are also being developed to target immune cells at sites of mucosal inflammation. For example, conjugation of the hydrophilic ECM polymer hyaluronic acid with the natural gut anti-oxidant bilirubin led to the formation of NPs 80–400 nm in size. After oral administration in mouse models of colitis, these NPs were efficiently taken up at the inflamed epithelium by macrophages expressing the hyaluronic acid receptor CD44, leading to polarization of these cells toward an anti-inflammatory phenotype[146] (Fig. 5d). Interestingly, this treatment caused an increase in microbial diversity in the microbiome, which promoted epithelial healing and inflammation reduction.

Targeting immune cells in tumours

Systemic targeting of immune cells in tumours—Instead of targeting circulating immune cells destined to migrate into tumours, there is also interest in delivering drugs directly to tumour-resident immune cells. For many years, biomaterials scientists have sought to target tumours by exploiting the enhanced permeation and retention (EPR) effect, a phenomenon first described in animal models in the late 1980s; here, large proteins or NPs accumulate in tumours owing to their hyperpermeable vasculature and reduced lymphatic clearance[77] (Fig. 5e). However, the efficiency of EPR-based tumour targeting remain low and penetration of NPs deep into tumours is often poor[147,148]. Therefore, new approaches are being pursued to facilitate targeting of immune cells in tumours. For example, the STimulator of Interferon Genes (STING) pathway, a cytosolic danger sensor in host immune cells[149], have gained particular interest. However, its natural ligands cyclic dinucleotides are labile and poorly taken up by cells in vivo. Conjugating PEGylated lipid nanodiscs with cyclic dinucleotide prodrugs enabled penetration into solid tumours, activating DCs to drive T cell-mediated tumour rejection[150]. Passive NP uptake in tumours can be further exploited to localize immune cell activation to tumors. For example, i.v.-injected PEGylated gold nanorods accumulated in tumours and then were irradiated by a near-infrared laser to induce photothermal heating of the tumour-resident nanorods[151]. This heating activated thermally-responsive gene cassettes in co-administered engineered T cells and induced localized CAR or cytokine expression in mice[151]. Nonetheless, the clearing mechanism of gold nanoparticles remains unclear, because these materials are not resorbable in vivo[152]. (Fig. 5e). NPs have also been targeted to T cells in tumours via conjugation with antibody fragments binding to T cell receptors. In one example, PD-1-targeted PLGA/PEG-based NPs were detected on intratumoural T cells within 1 hr of i.v. injection and enabled pronounced therapeutic modulation of tumours through delivery of a small molecule TLR-7/8 agonist[153].

One factor limiting NP dissemination deep into the tumour parenchyma is their propensity to be captured by tumour-associated macrophages residing near blood vessels[154–156]. This

affinity is now being exploited to reprogram tumour myeloid cells into a pro-immune phenotype using polymeric or lipid carriers loaded with immunomodulators such as TLR-7/8 agonists and colony stimulating factor 1 receptor inhibitors[157,158]. As another example, polymer NPs carrying mRNA targeted to myeloid cells through di-mannose moieties reprogramed tumour-associated macrophages toward an M1 phenotype[159]. Although promising, these approaches will need to assess potential side effects of non-specific uptake by macrophages in the liver, spleen and bone marrow, given the tendency of nanoparticles to be captured by macrophages in these organs[160,161].

In addition to capture by macrophages, abnormal tumour vasculature limits dissemination of NPs and immune cells in the TME. Inhibiting proangiogenic factors, such as vascular endothelial growth factor (VEGF) and angiopoietin 2 (ANG2) –at low to intermediate doses– normalizes tumour vasculature and perfusion, thereby improving the efficacy of anticancer treatments, including immunotherapy[162–167]. For example, tumour biopsies from breast cancer patients treated with an anti-VEGF antibody in a phase 3 clinical trial (NCT00546156) showed increased infiltration of $CD4^+$ T, $CD8^+$ T and mature dendritic cells[168]. Moreover, combining antiangiogenic agents with immunotherapies, including cancer vaccines and immune-checkpoint inhibitors, enhanced tumour infiltration of effector immune cells and improved therapeutic efficacy in murine cancer models[169–176].

Intratumoural delivery of biomaterials for immune cell targeting—Biomaterials can also be directly injected into the tumour. Importantly, to ensure efficacy, the delivered payload needs to remain in the tumour (or tumour- dLNs) after injection. Conjugation of immunomodulatory payloads to antibodies or engineered proteins that bind to tumour cell surface antigens[177] or ECM components such as collagen[178–180] improves safety and efficacy compared to intratumoral or peritumoral administration of free immunotherapy drugs. However, these approaches suffer from short-lived tumour stimulation (typically only a few days or less) because these agents are internalized by tumour cells or released out of the tumour microenvironment (TME)[178]. Biomaterial-based treatments can extend the window of drug exposure and enable efficacy from single injections, which is important for treating deep visceral lesions that require surgical access. For example, IL-12 bearing a phosphoserine peptide tag enables stable high-avidity binding to aluminium hydroxide (alum), a common clinical vaccine adjuvant[181]. Intratumoural injection of cytokine-loaded alum particles allowed drug retention in tumours for more than 2 weeks, resulting in pronounced regressions and complete responses in several tumour models in mice (Fig. 5e). Similarly, spherical nucleic acids, nanoparticles with surface-conjugated oligonucleotides as ligands for TLR-9, led to strong immunomodulatory activity[182]. In a phase I b/2 clinical trial, as of the data cut-off date of July 1st 2021, two and one out of 14 patients had a complete and partial response, respectively, and side effects were mostly limited to injection site reactions and flu-like symptoms[183,184] (NCT03684785; Table 1). Another promising approach consists of in situ vaccination using viral NPs derived from the virus cowpea mosaic virus, which shifts the immune composition of the TME towards a pro-inflammatory profile[185,186].

Biomaterials are also being considered as depots for the local release of immunotherapy payloads to the TME (Fig. 5e). For example, chitosan microparticles were developed that

following intratumoural injection released IL-12 over 1–2 weeks and elicited complete tumour regression in 80–100% of animals in murine cancer models[187,188]. Highlighting its synergistic potential, in pancreatic cancer models in mice, intratumoral injection of IL-12-loaded polymer microspheres at 24 hr following local stereotactic body radiation therapy resulted in increased TME reprogramming, systemic T cell responses and antitumor efficacy compared with IL-12-loaded microspheres or radiation only treatments. [189]. Hydrogels releasing innate immune stimulating small molecule drugs, such as TLR7/8 or STING agonists, decreased tumour recurrence when implanted at surgical resection sites in mouse models of breast and lung cancer[190]. Sprayable fibrin hydrogels releasing an anti-CD47 antibody at tumour resection sites stimulated macrophage phagocytic activity while neutralizing the acidic pH at the tumour site, triggering myeloid cells to eliminate residual tumour cells[191].

Biomaterials have also been used to deliver and locally stimulate adoptively transferred T cells in tumours. For example, intratumoural implantation of alginate hydrogels loaded with polyclonal tumour-specific T cells or CAR T cells, cytokines and immunostimulatory antibodies, led to enhanced tumour elimination in mouse models of breast and ovarian cancer[192]. In the adjuvant setting, hyaluronic acid hydrogels encapsulating CAR T cells together with stimulatory factors for localized immunostimulation implanted into the tumour bed following surgical resection protected against tumour recurrence and inhibited distant tumour growth[193]. In another report, nitinol metal scaffolds, a material routinely used as cardiovascular stents, were functionalized with T cell-stimulatory antibodies and loaded with CAR T cells for implantation peritumorally. In a mouse model of non-resectable ovarian cancer, these scaffolds eradicated tumours in 70% of animals and extended the average tumour survival time 2.7-fold compared with untreated controls[194]. All of the described materials have different in vivo lifetimes and might require surgical retrieval. Clinical implications are still unclear as none of these approaches have entered clinical testing yet.

Engineered materials can also be used to increase uptake and promote cytosolic delivery of therapeutics in immune cells following localized delivery to tumour sites. For example, intratumoural administration of endosome-disrupting polymersomes delivering cyclic dinucleotides into phagocytes improved STING activation, indicated by an 11-fold decrease in melanoma growth rate and complete tumour rejection in one-third of the mice [195]. Similarly, intratumoural injection of CDN-loaded lipid-calcium phosphate NPs surface-treated with phosphatidyl serine, promoted CDN uptake by myeloid cells and DCs in the pleural space in a mouse model of malignant pleural effusion [196]. mRNA also requires cytosolic delivery to immune cells (Fig. 5e). Intratumoural injection of mixtures of LNPs delivering mRNA encoding cytokines and membrane-bound T cell costimulatory receptor OX40L, led to pronounced immune activation and complete tumour regression in 50% of animals bearing s.c. hepatoma tumours[197]. Similarly, intratumoural injection of saline formulations or polymer NPs delivering mRNAs encoding selected potent cytokine combinations (e.g. IL-12, granulocyte-macrophage colony-stimulating factor, IL-15, and IFN-α) led to robust tumour regressions and induction of systemic T cell responses that regressed even distal untreated lesions[198,199]. Interim data from a follow-up phase I clinical trial showed that LNPs encapsulating mRNAs encoding OX40L, IL-23 and IL-36γ, in

combination with a PD-1 immune checkpoint inhibitor, resulted in increased levels of proinflammatory cytokines in both plasma and tumour biopsies (NCT03739931; Table 1)[200]. These LNP formulations were shown to primarily transduce cancer cells and myeloid cells. Another approach is to deliver mRNA directly into tumour-infiltrating T-cells; LNPs incorporating ionizable lipids transfected up to over 5 and 10% of tumour infiltrating $CD4^+$ and $CD8^+$ primary T cells respectively following intratumoral injection in a murine melanoma model, and when used to deliver mRNA encoding OX40 in combination with systemic administration of anti-OX40 agonist antibodies, resulted in 60% tumour rejection in a murine lymphoma model.[133].

Targeting sites of inflammation

Immune cells are central to the pathology of inflammatory diseases, therefore, targeting them at sites of inflammation is a potentially effective strategy for disease treatment. Phagocytes are involved in generating persistent inflammation, thereby providing a first-line target choice for drug development. [201]For example, polymersomes, vesicles formed by the self-assembly of amphiphilic block copolymers, were efficiently taken up by neutrophils through scavenger receptors[202]. Using pH-responsive polymersomes that disrupt endosomes in response to acidification of these compartments, cytosolic delivery of cyclin-dependent kinase inhibitor (R)-roscovitine induced neutrophil apoptosis and suppressed inflammation in a sterile injury zebrafish model. Immune cells can also serve as chaperones to concentrate nanocarriers at sites of inflammation and angiogenesis; for example, i.v. administration of nanoemulsions functionalized with cyclic RGD peptides that bind to $\alpha_V\beta_3$ integrins expressed on inflamed blood vessels rapidly adhered to circulating neutrophils and monoyctes in a mouse model of acute wound-derived inflammation within minutes. These NPs also directly bound to the endothelium of inflamed vessels at later times, suggesting transfer from leukocytes to endothelial cells[203]. Neutrophils are known to effectively capture opsonized particles in the blood, a process exploited to target these cells at sites of lung inflammation using NPs of different size, charge and composition, provided they are rapidly opsonized with complement upon injection[201] (Fig. 5f). I.v.-injected synthetic high density lipoprotein NPs carrying the mammalian target of rapamycin (mTOR) inhibitor efficiently targeted myeloid cells and blocked the expression of inflammatory cytokines by macrophages infiltrating heart allografts, resulting in long-term allograft survival[204]. Interestingly, i.v.-injected empty PLGA NPs were reported to be taken up by monocytes and neutrophils in the blood, leading to their reprogramming into an anti-inflammatory phenotype and localization to sites of spinal cord injury, promoting a pro-regenerative milieu that enabled axon recovery[205].

Biomaterials are also being explored to modulate adaptive immune responses at tissue transplant sites. For example, biodegradable polymer microspheres releasing TGF-β and naïve $CD4^+$ T cells promoted Treg development in vitro, and promoted Treg infiltration of allogeneic pancreatic β cell transplants for treatment of an in vivo diabetes model[206]. In a rat model of vascularized hindlimb allogeneic tissue grafting, local administration of microspheres releasing TGF-β, rapamycin and IL-2 promoted induction and expansion of Tregs at the implant site, leading to long-term tissue engraftment[207].

LNs draining sites of disease are also modulated by upstream inflammation. For example, high endothelial venules (HEVs) are specialized blood vessels of the LNs that express the lymphocyte homing protein peripheral node addressin (PNAd), which supports naïve lymphocyte entry into LNs. Notably, PNAd expression is upregulated in LNs draining sites of chronic inflammation[208]. Exploiting this process, i.v.-injected PLGA microparticles carrying the immunosuppressive drug tacrolimus and functionalized with a PNAd-targeting antibody enabled accumulation of the drug at LNs draining the transplanted tissues[209]. Because microparticles are too large to passively transport across the endothelium, this finding suggests particle accumulation on the luminal surfaces of the HEVs, followed by drug diffusion into the tissue across the endothelial barrier. Building on these findings, PNAd-targeted PLGA NPs were found not only bind to the HEVs of inflamed dLNs, but were also further transported into the LN parenchyma, leading to substantially prolonged allograft survival in a model of MHC-mismatched heart tissue transplantation[210] (Fig. 5f).

Outlook

Biomaterials-mediated targeting of immune cells and tissues is starting to have clinical impact, holding great promise for the future of vaccines and immunotherapy. However, there remain important fundamental aspects of immunology to be understood, and a number of technological and translational drawbacks remain to be solved for these technologies to reach their full potential.

For example, there is still much to learn about the dynamics of immune cells during disease and treatment. The reciprocal trafficking of lymphocytes from LNs to blood and tumours, as well as between tumours, has received limited attention[211,212]. However, this information is essential for the design of targeted immune-oncology therapeutics that will ‘hit’ cells at a desired location or timepoint in their life cycle. The role of stem-like $CD8^+$ T cells in diseases, such as autoimmunity[213], infections[214] and cancer[215,216], is gaining particular attention, because these cells appear to play an important role as responders to immunotherapies such as checkpoint blockade[214,217], by producing progeny that are important effector cells (either in LNs or directly at peripheral tissue sites). These cells are promising targets for immunotherapy, but how they can be generated and expanded in vivo remains poorly understood.

Biomaterial interactions with the immune system also need further assessment. The SARS-CoV-2 pandemic revealed that LNPs used for mRNA delivery have direct adjuvant activity in vaccines[218–220] by triggering inflammatory cytokine production in LNs; however, the exact mechanisms remain to be elucidated. Other biomaterials, for example, biodegradable polymers, such as PLGA, are generally considered passive scaffolds or drug-release matrices; however, lactic acid produced by PLGA hydrolysis is known to be immunomodulatory,[221–223] and PLGA particles promote a pro-regenerative phenotypic state when phagocytosed by innate immune cells[205]. These effects can promote tolerance in conditions such as autoimmune disease[224], but would be undesirable in other settings (e.g., cancer immunotherapy).

One reality that the field of biomaterials-based immune therapies must face is that complex multicomponent formulations requiring the production of multiple recombinant proteins and exotic multi-step chemistries using different clinical-grade materials, are unlikely to be clinically translated owing to the prohibitive cost and complexities involved in the good manufacturing practice (GMP) of such systems. To ensure clinical translation, “less is more” should be a motivating mantra. This reality is evident by looking at the technologies undergoing clinical trials (Table 1). Furthermore, different technologies are often confined to the expertise of individual laboratories. Sharing methods in the field will enable broader experimental validation and testing in different disease models.

The success of LNP-delivered SARS-CoV-2 mRNA vaccines provides an important proof-of-concept in humans, but there is much room for improvement to realize their full potential. Despite important advances over the past 20 years, LNPs remain substantially inferior to biological vectors, such as viruses, at transfecting cells. Systemic or intratumoural injection of LNPs to deliver mRNA to T cells transfects only 2% or less of T cells[131,198]. In addition, what makes LNPs suitable for packaging nucleic acids (for example, their charge) also makes them prone to opsonization and non-specific binding to cells and matrices. Moreover, allergic reactions elicited in a small proportion of individuals with current PEG-stabilized LNP formulations represent a potential safety issue [225,226]. Despite the clinical success of LNPs as delivery materials for mRNA and siRNA, other materials, such as endosome-responsive polymers,[227–229] can outperform LNPs for nucleic acid delivery in some cell types. Furthermore, combinatorial library studies of LNP compositions revealed that LNP formulations can be tuned to target specific tissues and immune cell types without even the need for specific antibody or other binder-based targeting[201,230,231]. Materials with improved delivery efficiency will increase the utility of mRNA, as well as DNA and CRISPR-based gene editing systems.

Despite existing knowledge gaps and challenges, the use of biomaterials to enable cell- and organ-specific targeted immune modulation is an important and exciting area of research and clinical development, which can unlock the full potential of immunotherapies for different diseases.

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Box 1 |

Defining optimal immune cell targets for disease modulation.

Modulation of the immune system can only be effective if the targeted cells and their responses are well understood. For example, different phenotypic and functional states exist for antigen-specific T cells; Inactivated precursors, early activated cells (including short-lived and memory precursor effector cells), activated effector cells, memory cells and memory stem cells and 'exhausted' effector cells[233] have been defined, all with different functionality and ability to respond to immunostimulation. 'Stem-like' CD8+ T cells, in particular, share characteristics between memory cells and more activated cells [215–217,234,235], and express specific transcriptional and protein signatures (for example, T cell factor-1 (TCF-1^{+}), programmed cell death protein 1 (PD-1^{+}) and self-ligand receptor of the signalling lymphocytic activation molecule 6 (SLAM6^{+})), which are important modulators of anti-tumour immune response. Fundamental studies identifying these important but possibly rare cell types will be required to develop targeted immunotherapies and vaccines.

Key points

- In immunotherapy, choosing the right target cell, tissue and treatment duration is essential to ensure effective immunomodulation while avoiding toxicity
- Biomaterials-mediated targeting of immune cells in lymph nodes improves the potency and efficacy of vaccines by promoting immunity or tolerance
- Circulating migratory immune cells can be targeted to perform as living chaperones to carry therapeutics into tissues
- Systemic administration or intratumoural injection of nanomaterials and therapeutic depots can selectively accumulate and target immune cells in tumours
- Reducing biomaterial complexity is essential to facilitate clinical translation

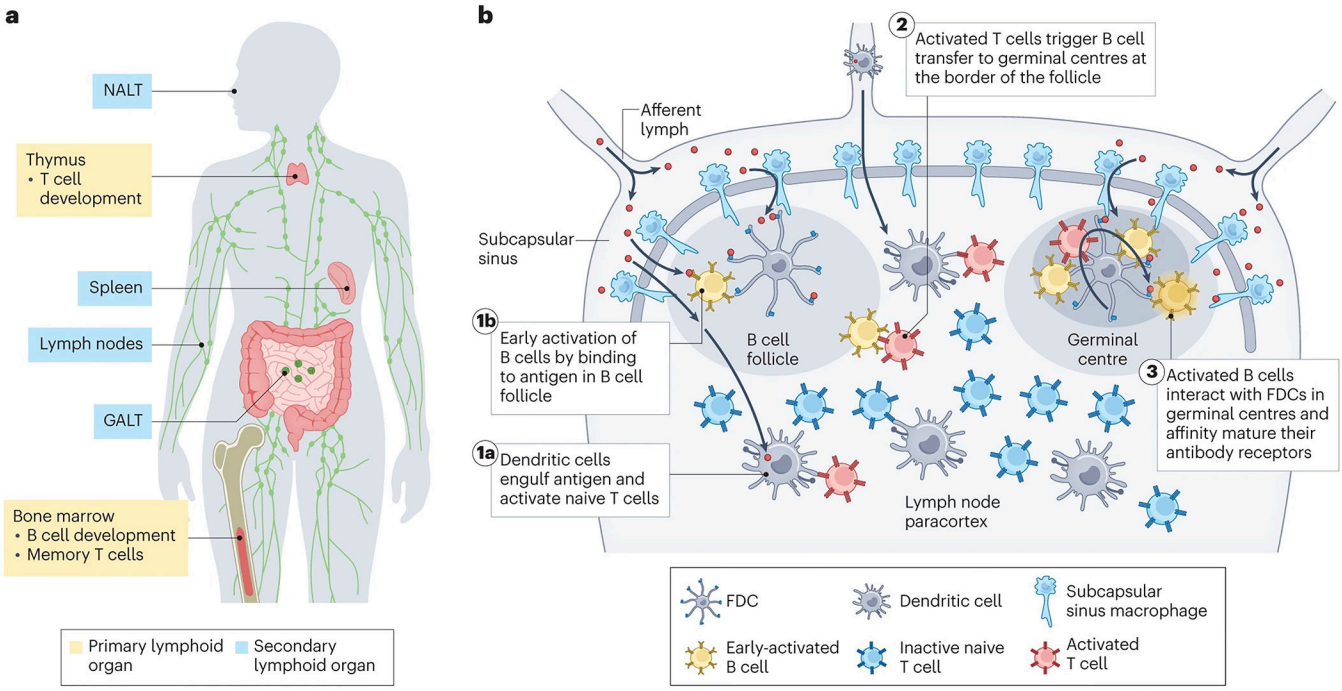

Figure 1 |. Primary and secondary lymphoid organs.

a | Anatomic distribution of primary and secondary lymphoid organs. NALT, nasal-associated lymphoid tissue; GALT, gut-associated lymphoid tissue. **b |** General organization of secondary lymphoid organs and sites of key interactions leading to adaptive immunity, using the lymph node (LN) as an example. Shown are orchestrated steps in the early activation of adaptive immune response in response to an antigen (orange): (1a) dendritic cells (DCs, light purple) acquire antigens trafficked into the LN or migrate to the LN from peripheral tissues carrying antigens, which they then present to naïve T cells (blue) to drive T cell activation and proliferation. (1b) B cells (orange) bind to antigens arriving in follicles, triggering initial B cell activation and proliferation. (2) Early-activated B cells receive help signals from $CD4^+$ T cells at the T zone-follicle border, providing signals to drive entry into germinal centres. (3) Activated B cells enter germinal centres where they undergo proliferation and somatic hypermutation to affinity mature their antibody receptor through interactions with follicular helper T cells and the antigens captured on the dendrites of follicular dendritic cells (FDCs).

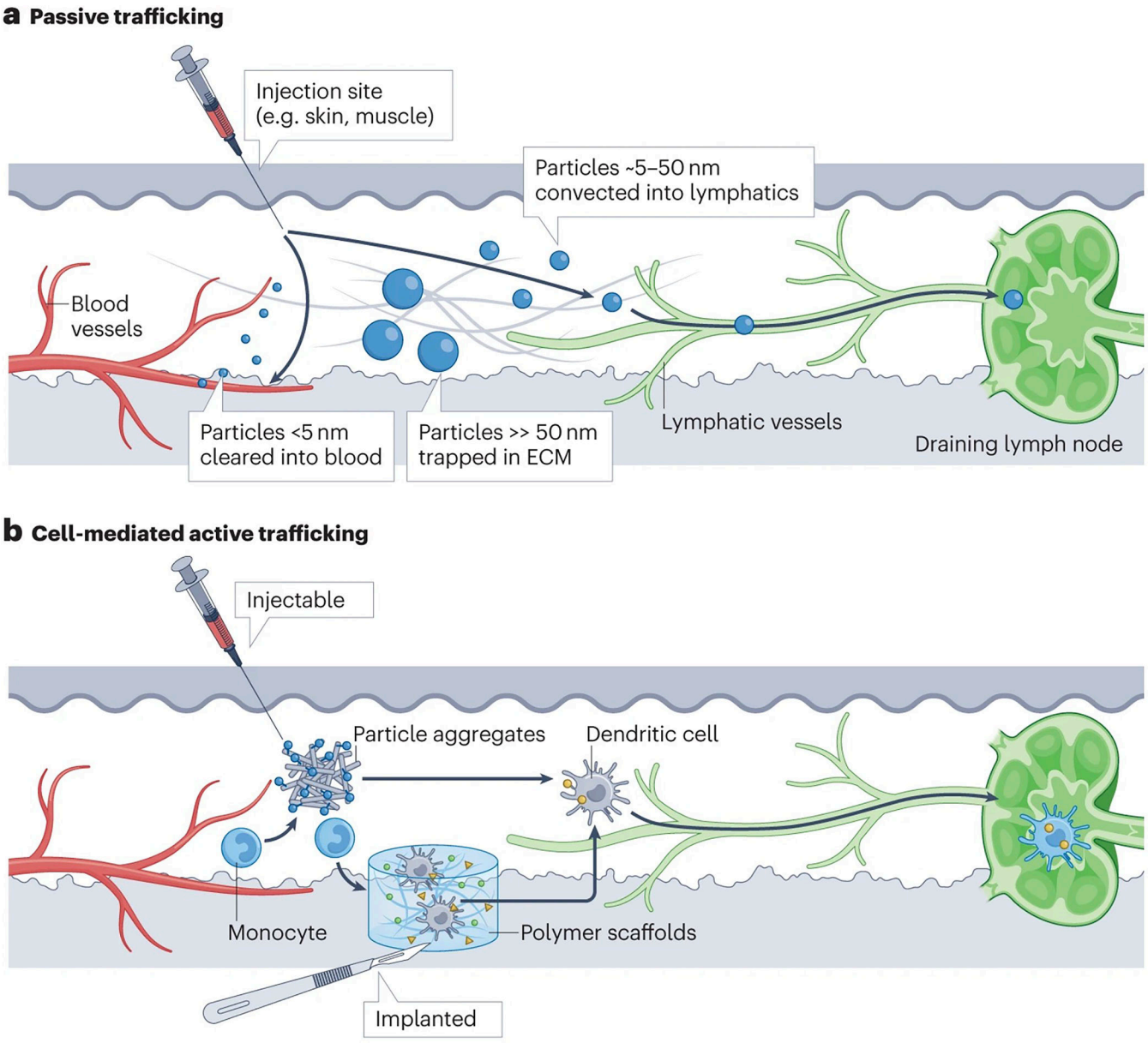

Figure 2 |. Targeting therapeutics to tissue-draining lymph nodes.

a | Passive targeting of lymphatics through particle size. Particles < 5 nm in diam. are preferentially cleared into the blood vasculature, while particles > 50 nm in diam. tend to become trapped in the tissue. Intermediate sized particles (5–50 nm diam.) exhibit preferential trafficking into lymphatic vessels. ECM, extracellular matrix. **b |** Targeting migratory leukocytes to traffic vaccines and therapeutics to draining lymph nodes. Shown are examples of injectable or implantable biomaterials that attract monocytes or dendritic cells from the local tissue and peripheral blood. The cells are then stimulated by the implanted material, triggering activation and differentiation into migratory antigen presenting cells that carry antigens or other compounds to the draining lymph nodes.

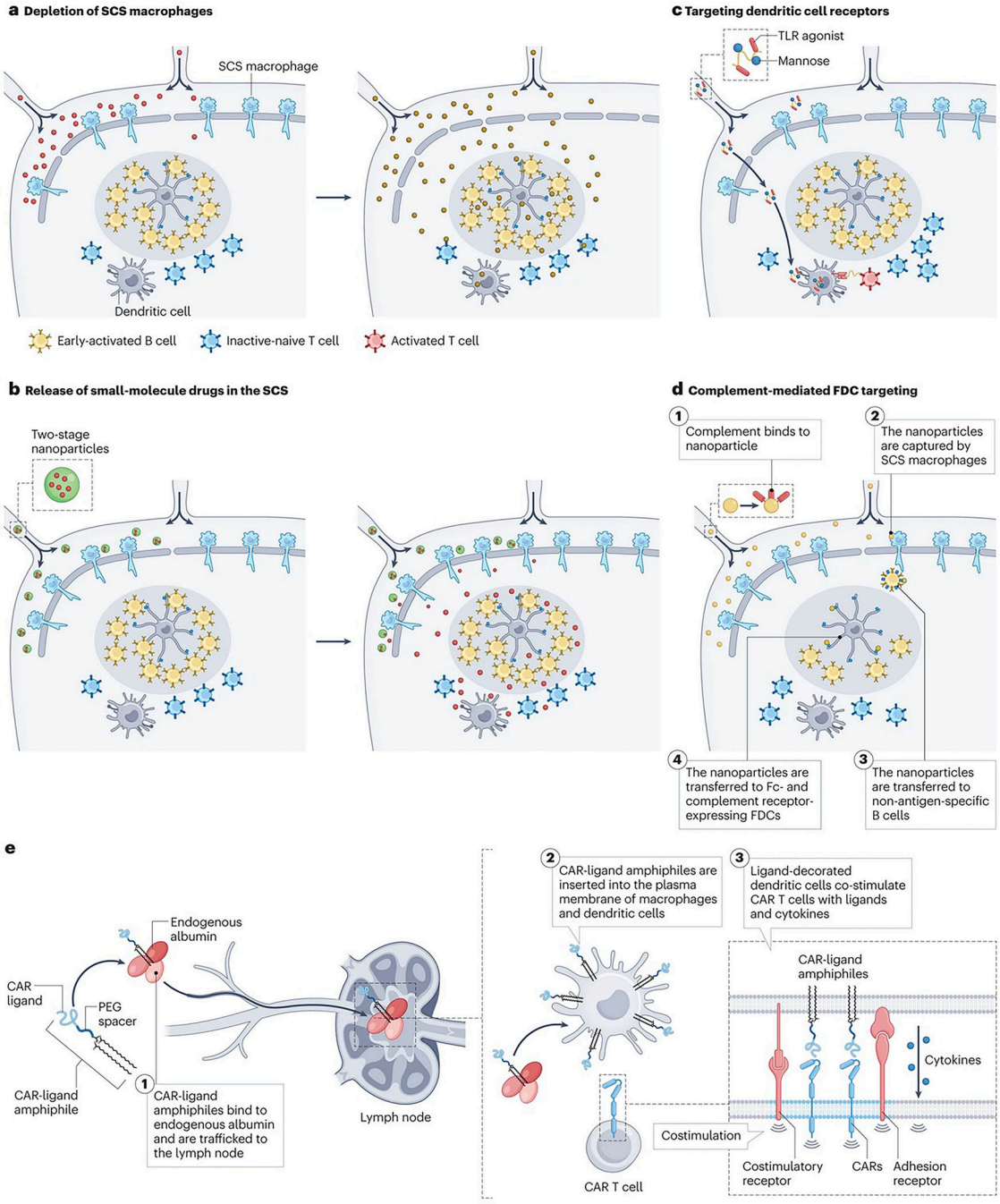

Figure 3 |. Targeting lymph node-resident cells and lymph node subregions.

a | Promoting therapeutic entry into lymph nodes (LNs) through depletion of subcapsular sinus (SCS) macrophages. Vaccine adjuvants (red) induce rapid death of SCS macrophages, leading to enhanced entry of antigens and other compounds (orange) into LNs. **b |** Polymer nanoparticles (blue) efficiently traffic into lymphatic vessels (20–30 nm) but are too large to penetrate the LN paracortex. They chemically release small molecule payloads (red) that rapidly permeate throughout the node. **c |** Soluble polymers and polymer nanoparticles (NPs) conjugated with ligands for receptors expressed by specific target cell types (such

as dendritic cells (DCs)), are taken up by antigen presenting cells (APCs) in LNs and co-deliver vaccine antigens or DC activating compounds. **d |** (1) NPs activate complement, (2) are captured by SCS macrophages (3) and transferred to non-antigen-specific B cells through complement receptors. (4) These NPs are then transferred to follicular dendritic cells (FDCs), which express high levels of complement and (fragment crystallisable) Fc receptors. **e |** (1) Ligands for chimeric antigen receptor (CAR) T cells linked to albumin-binding poly(ethylene glycol) (PEG)-lipid moieties traffic from an injection site and bind to endogenous albumin. These compounds are then transferred to LNs (2) where they are inserted into the plasma membrane of macrophages and DCs. Subsequent encounter of CAR T cells with the ligand displayed on the surface of DCs will lead to CAR T cell tandem stimulation by natural costimulatory receptors and cytokine signals provided by the ligand-decorated DCs.

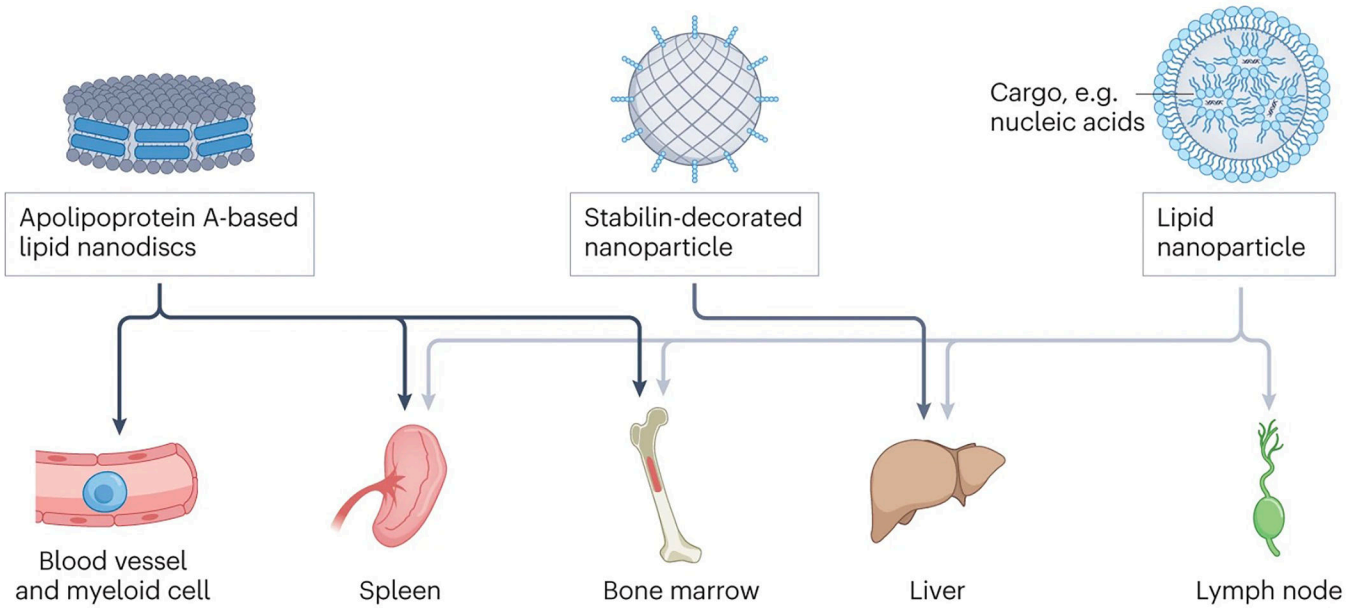

Figure 4 |. Targeting systemic lymphoid organs.

Nanoparticle (NP) carriers can target lymphoid organs systemically, including lymph nodes, spleen, bone marrow and tolerogenic antigen presenting cells in the liver. For example, Apolipoprotein-based lipid nanodiscs a preferentially taken up by myeloid cells in the liver, spleen, and bone marrow. Stabilin-funcitonalized nanoparticles are efficiently scavenged by endothelial cells in the liver. Anionic LNPs target antigen presenting cells in the liver, spleen, lymph nodes, and bone marrow.

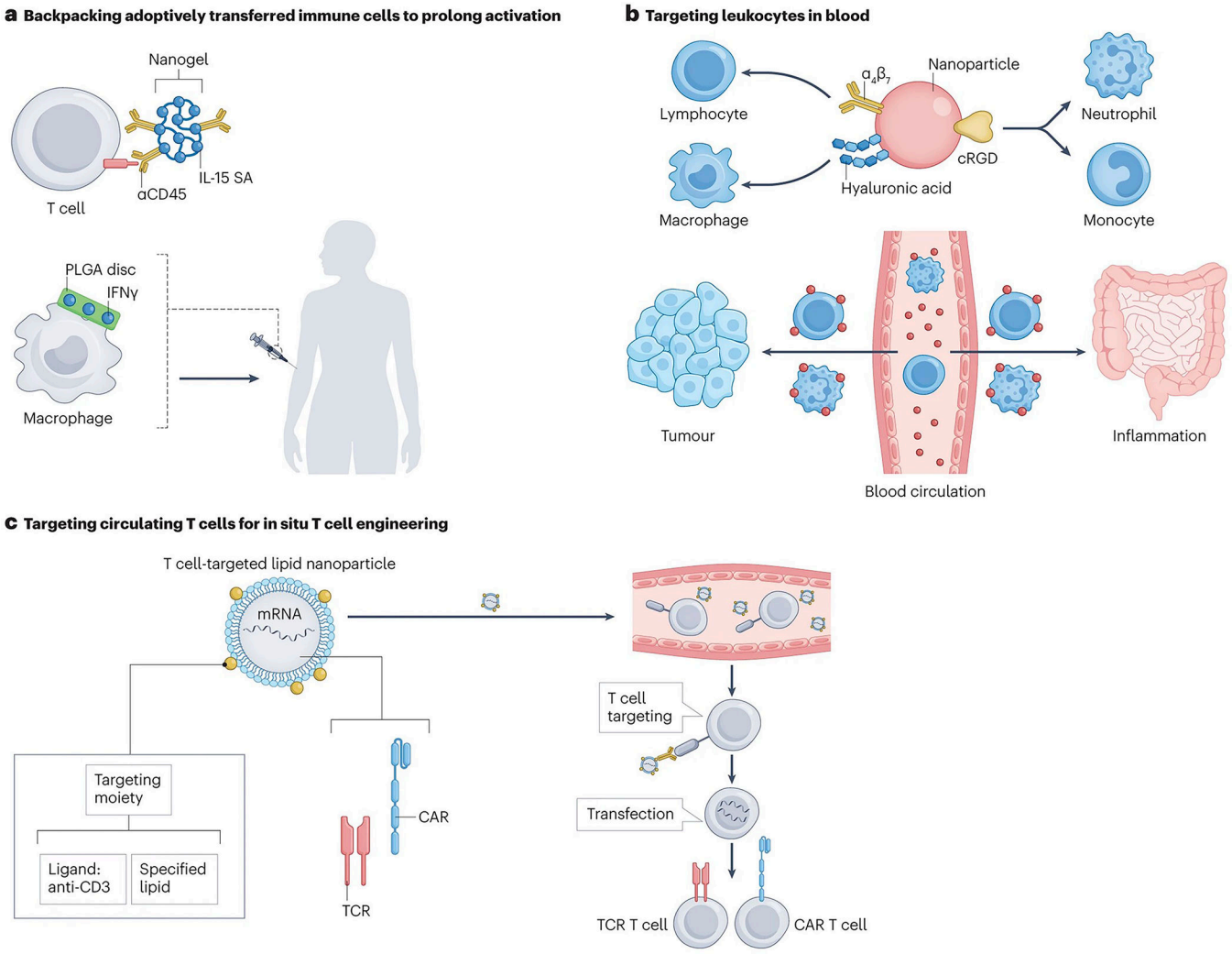

Figure 5 |. Targeting circulating and tissue-resident immune cells.

a | "Backpacking" cells by attaching drug-releasing materials to cells ex vivo prior to adoptive transfer. IL-15 SA, interleukin-15 super agonist; PLGA, poly(lactide-co-glycolide); IFN, interferon. **b |** Nanoparticles (NPs) functionalized with targeting moieties can bind to circulating immune cells in the blood, which then traffic into different tissues sites with the drug carrier. cRGD, cyclic arginine-glycine-aspartic acid. **c |** T cell-targeted NPs deliver nucleic acid payloads (DNA or RNA) to circulating lymphocytes, resulting in the expression of chimeric antigen receptors (CARs) and other immunomodulatory gene payloads in situ. **d |** Albumin is used as a chaperone to transport vaccines across the epithelial barrier in the nasal and respiratory pathways through the neonatal fragment crystallisable (FcRn) receptor. NPs functionalized with hyaluronic acid are phagocytosed by macrophages and other myeloid cells at sites of intestinal inflammation in the gut. **e |** Systemically-injected NPs passively accumulate in tumours through the enhanced permeation and retention (EPR) effect, or functionalized NPs actively target cells such as programmed death-1 (PD-1+) lymphocytes. Alternatively, biomaterials can be directly injected into tumours to locally present or release immunostimulatory agents in the tumour microenvironment, or promote

gene delivery to tumour cells for localized expression of immunomodulatory factors. **f |** NPs can be modified with targeting moieties or opsonization-triggering components to bind to the endothelial cells of HEVs of the inflamed draining lymph nodes or target different innate immune cells that home to sites of inflammation. cRGD, cyclic arginine-glycine-aspartic acid; HDL, high-density lipoprotein; HEV, high endothelial venules; PNAd, Peripheral lymph node addressin.

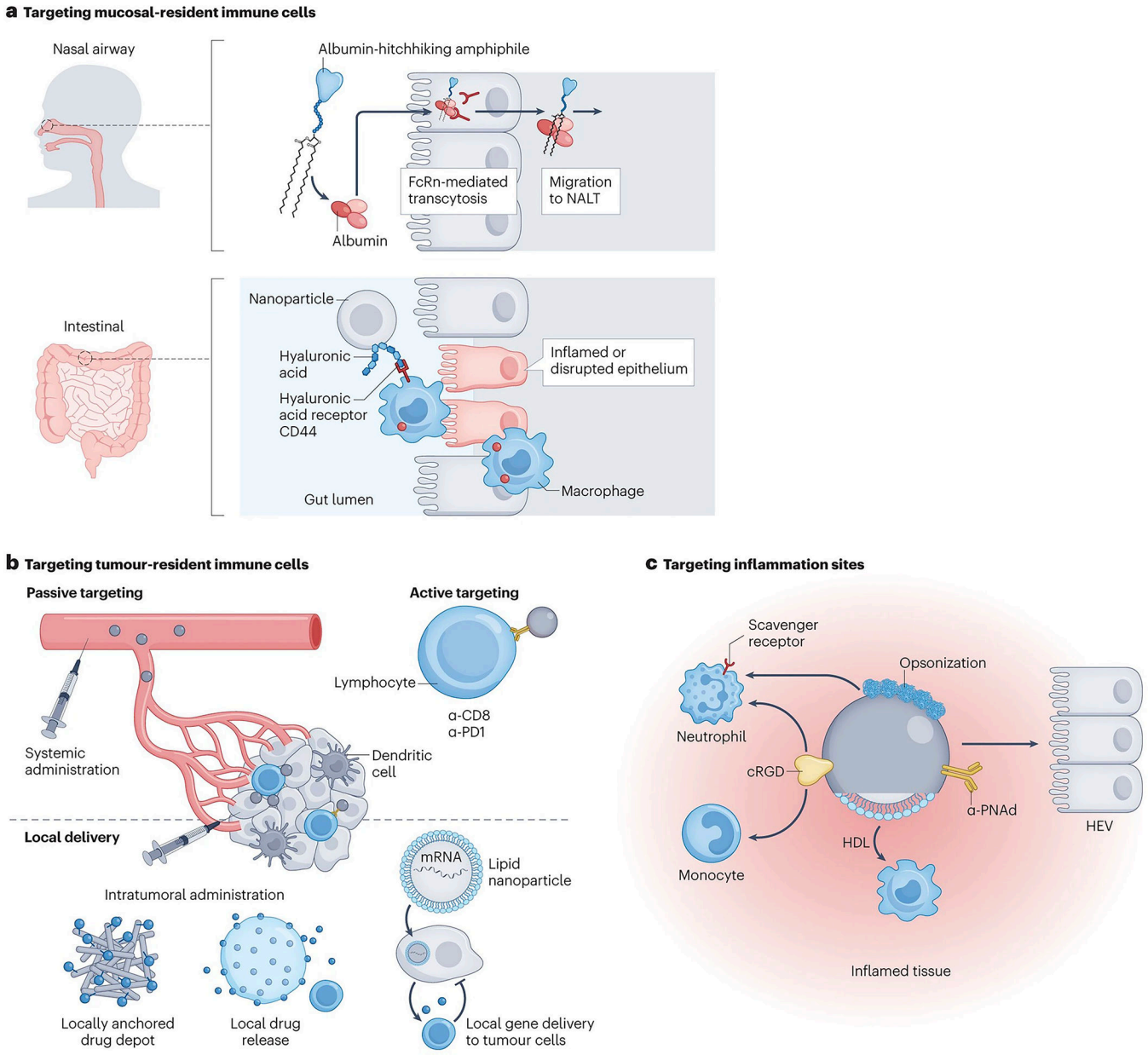

Figure 6.
Targeting tissue-resident immune cells.

Table 1 |

Ongoing clinical trials of immune cell- and tissue-targeted biomaterials therapeutics

Immune cell and target site	Technology	Phase	Condition or disease	Clinical trial identifier	Refs.
Migratory APCs	Polymer scaffolds carrying tumor antigen, GM-CSF and CpG as a cancer vaccine	1	Stage IV melanoma	NCT01753089	36,37
B cell follicles in LNs	eOD-GT8 60mer protein NP vaccine	1	HIV and AIDS	NCT03547245	17,68,70
B cell follicles in LNs	Influenza HA ferritin NP vaccine	1	Influenza	NCT03186781	21
LNs	GBP510 SARS-CoV-2 designed protein NP vaccine	1/2, 3	COVID-19	NCT04750343, NCT05007951	22
LNs	Amph-CpG7909 combined with amph-KRAS peptide antigen cancer vaccine	1	KRAS mutated PDAC and other solid tumor cancers	NCT04853017	26–28,30
LNs	Matrix M adjuvant in Novavax COVID-19 vaccine	approved	COVID-19	NCT05463068, NCT05468736, NCT05112848	25
Systemic APCs	LNP vaccine encapsulating mRNA encoding the viral oncogenes E6 and E7	2	Head and neck cancer	NCT04534205	79
Systemic APCs	LNP vaccine encapsulating mRNA encoding the viral oncogenes E6 and E7	1, 2	Advanced HPV16+ cancer (head and neck, anogenital, penile or cervical)	NCT03418480	79
Systemic APCs	Liposomal RNA vaccine	1	Melanoma	NCT02410733	78,80
Systemic APCs	PLGA NPs vaccine carrying NY-ESO-1 antigen and IMM60 invariant NK T cell activator	1	NY-ESO-1+ tumours	NCT04751786	82
Spleen and liver APCs	Rapamycin-encapsulating NPs	3	Chronic Gout	NCT04596540	84
Splenic B cells	Liposomes carrying iNK T cell ligand	1	Treatment for graft versus host disease post allogeneic stem cell transplant	NCT04014790, NCT01379209	89–91
Adoptively transferred T cells	IL-15 nanogels backpacked on T cells	1	Selected solid tumours, lymphoma	NCT03815682	108
TLR9+ myeloid cells	TLR-9 agonist-presenting spherical nucleic acids	1b/2	Advanced solid tumours	NCT03684785	183,184
Intratumoral lymphocytes	LNPs encapsulating mRNAs encoding IL-12	1	Solid tumours	NCT03946800	232
Intratumoural lymphocytes	Saline-formulated mRNA cocktail encoding single-chain IL-12, interferon-α2b, GM-CSF and IL-15 superagonist	1	Metastatic neoplasm	NCT03871348	198
Intratumoural lymphocytes	LNPs encapsulating mRNAs encoding OX40L, IL-23 and IL-36γ	1	Selected solid tumours, lymphoma	NCT03739931	197,200
Intratumoural lymphocytes	LNPs encapsulating mRNA encoding OX40L	1/2	Relapsed and refractory solid tumours, lymphoma and ovarian cancer	NCT03323398	197

Ref., reference; APC, antigen presenting cells; GM-CSF, granulocyte-macrophage colony-stimulating factor; CpG, unmethylated cytosine–guanine dinucleotide; LN, lymph node; NP, nanoparticle; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; HA, hemagglutinin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease-19; Amph, amphiphilic; KRAS, Kirsten rat sarcoma; PDAC, pancreatic ductal adenocarcinoma; mRNA, messenger ribonucleic acid; HPV, human papillomavirus virus; PLGA, poly(lactide-*co*-glycolide); NY-ESO-1, New York esophageal squamous cell carcinoma 1; NK T, natural killer T; IL, interleukin; TLR, toll-like receptor