REVIEWS

Polymeric particle-based therapies for acute inflammatory diseases

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Abstract | Acute inflammation is essential for initiating and coordinating the body's response to injuries and infections. However, in acute inflammatory diseases, inflammation is not resolved but propagates further, which can ultimately lead to tissue damage such as in sepsis, acute respiratory distress syndrome and deep vein thrombosis. Currently, clinical protocols are limited to systemic steroidal treatments, fluids and antibiotics that focus on eradicating inflammation rather than modulating it. Strategies based on stem cell therapeutics and selective blocking of inflammatory molecules, despite showing great promise, still lack the scalability and specificity required to treat acute inflammation. By contrast, polymeric particle systems benefit from uniform manufacturing at large scales while preserving biocompatibility and versatility, thus providing an ideal platform for immune modulation. Here, we outline design aspects of polymeric particles including material, size, shape, deformability and surface modifications, providing a strategy for optimizing the targeting of acute inflammation.

Inflammation plays an essential part in the immune response against harmful stimuli and injury through recognition and containment of invading pathogens and toxins. Overly responsive or uncontrolled inflammation can lead to tissue damage and organ dysfunction[1–3], and is associated with numerous human disorders, such as acute lung and liver injury, sepsis, asthma, inflammatory bowel disease, rheumatoid arthritis and neurodegenerative diseases[2,3]. Acute inflammation, regulated by the innate immune system, is responsible for the initial recognition of an inflammatory stimulus and focuses on the rapid containment of the offending pathogen or injury. Such a response aims at accelerating inflammatory resolution and typically lasts on a scale of hours to days (FIG. 1a). If the acute inflammation response is excessive or fails to contain the inflammatory stimulus, the response is shifted to a chronic (pathological) phase characterized by prolonged inflammatory episodes and can last on a scale of weeks to years[3–5]. Although chronic inflammation has mainly been associated with cells from the adaptive immune system, the innate arm of the immune system also has a role, because, in chronic inflammatory diseases, repeated acute inflammatory episodes propagate tissue damage[2,3,5,6]. Recognizing the persistent role of acute inflammation in chronic diseases has, in part, contributed to the growing interest in developing therapeutics aimed at suppressing this acute response. In this Review, we summarize crucial aspects of the acute inflammation response and discuss particle-based therapies developed towards modulating or resolving this process.

Acute inflammation

Acute inflammatory cascade. Acute inflammation is initiated by either pathogenic infections or exogenously by mechanical trauma, ischaemia-reperfusion or chemicals[2,3]. Pattern recognition receptors (PRRs) are proteins circulating in the blood or expressed on innate immune cells[7]. Pathogens entering the body through punctured skin, orally or inhalation, are recognized by PRRs through pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), which trigger an inflammatory response[1,8]. Within the infected tissue space, resident macrophages, dendritic cells (DCs) and neutrophils are the first cells to interact with invading pathogens. Activated macrophages and DCs function as antigen-presenting cells, phagocytose foreign bodies, migrate to lymph nodes and present the processed antigen to lymphocytes[3,9]. Concurrently, activated endothelial cells release inflammatory cytokines, including tumour necrosis factor (TNF), several interleukins (IL-1, IL-6, IL-8, IL-12 and IL-17) and interferon-γ (IFNγ), which accumulate in the bloodstream, calling white blood cells (WBCs; also known as leukocytes) into action[10].

Neutrophils are the first circulating WBCs recruited to the infected tissue space and they have an essential role in pathogen clearance and inflammation resolution. Representing about 60–70% of all circulating WBCs in humans, neutrophils locate the inflammation by following the release of cytokines and chemokines, then slowly rolling along the endothelium mediated by weak adhesive

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interactions with endothelial surface-expressed proteins, such as upregulated selectin molecules[2,9,11,12]. Once at the site of inflammation, enhanced integrin expression on

the endothelium firmly adheres the neutrophils through chemokine-activated lymphocyte function-associated antigen 1 (LFA1) on the neutrophil surface to initiate
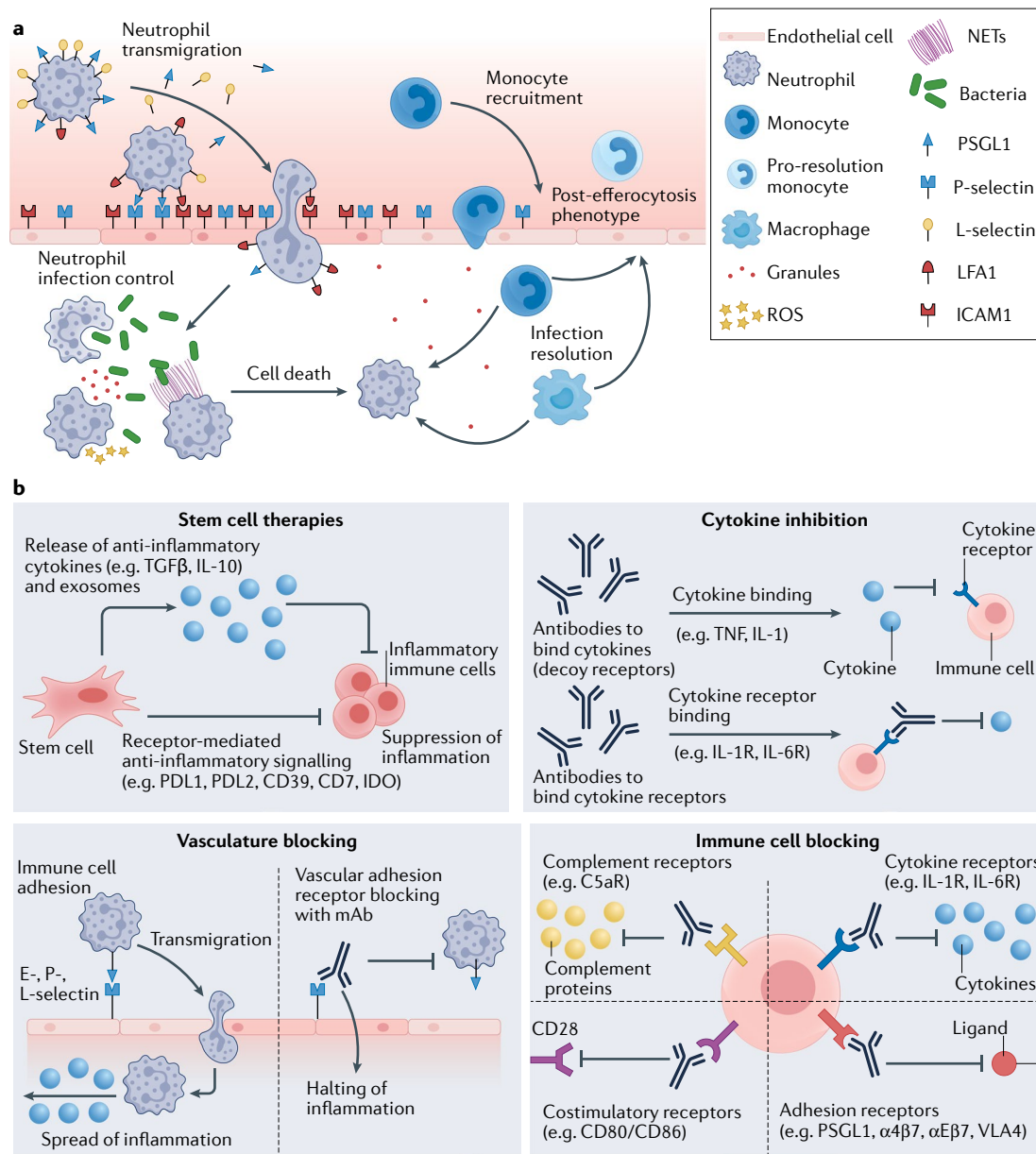

Fig. 1 | **Inflammatory cascade and strategies for modulating inflammation. a** | Neutrophil recruitment and functions in inflammation. Neutrophils slowly roll along the endothelium by expressing P-selectin glycoprotein ligand 1 (PSGL1) and L-selectin, which bind to their corresponding ligands on the endothelium. Once at the site of inflammation, lymphocyte function-associated antigen 1 (LFA1) expressed on the neutrophil locks with intercellular adhesion molecule 1 (ICAM1) on the endothelium to initiate transmigration to the infected or inflamed tissue space. At the site of infection, neutrophils phagocytose pathogens or release reactive oxygen species (ROS), granules or neutrophil extracellular traps (NETs) to prevent pathogenic spread. Neutrophils then commit to apoptosis, initiating migration of other immune cell types. Monocytes and macrophages clean up dead cellular materials (pathogens and neutrophils) by efferocytosis and ultimately migrate to the liver and lymph nodes to remove and process pathogenic materials. Additionally, post efferocytosis monocytes shift to a pro-resolution phenotype to promote tissue restoration. **b** | Non-particle-based therapeutics for modulating inflammation. Stem cell therapies: transplanted mesenchymal stem cells (MSCs) can secrete immunosuppressive cytokines to promote regulatory T (T_{reg}) cell production and inhibit T helper 1 (T_H1) and T helper 2 (T_H2) cell differentiation or suppress immune cell recruitment and activation. Cytokines and antibody-based therapies: blocking antibodies or decoy receptors bind to inflammatory cytokines to inhibit their activity and dampen systemic inflammation. Vasculature blocking: biological agents prevent transmigration of immune cells by blocking specific leukocyte adhesion molecules on vascular endothelial cells, halting the inflammatory response. Targeted immune cell blocking: therapeutics can directly inhibit immune cells from pathological activation by blocking specific receptors on their surface. mAb, monoclonal antibody.

transmigration[12]. At this stage, activated neutrophils shed P-selectin glycoprotein ligand 1 (PSGL1) and L-selectin (also known as CD62L) from their membrane surface[13,14]. Once inside, neutrophils deploy several mechanisms to contain pathogenic infections, including phagocytosis, the release of reactive oxygen species (ROS), degranulation and the production of neutrophil extracellular traps (NETs)[2]. Once the infection has been contained, released granules, NETs and apoptotic neutrophils recruit monocytes and adaptive immune cells to initiate inflammation resolution[2,15] (FIG. 1a).

Although it is typically associated with an invading pathogen, inflammation can also arise from sterile, non-pathogenic events. Sterile inflammations such as mechanical injury, blood clots or chemical irritants can cause damage at the cellular or tissue scale, initiating the release of DAMPs[1]. The released DAMPs are sensed by resident immune and endothelial cells, leading to inflammatory cytokine production (TNF and IL-1)[1,2]. Similar to pathogenic infections, these immunostimulatory molecules initiate neutrophil recruitment to the injured site[2]. Despite the absence of pathogens in sterile injuries, neutrophils still employ similar tactics to contain the inflammation, followed by monocytes clearing out any remaining necrotic cells and apoptotic neutrophils in a process called efferocytosis[1,16].

Excess release of granules, ROS and NETs by an overabundance of neutrophils could still cause damage in surrounding host cells[1,2], leading to acute pathological conditions such as acute lung and liver injuries or chronic inflammation.

Inflammatory disease propagation. A failure to contain the acute inflammatory response might stem from prolonged infection, foreign body presence or an underlying genetic condition[4,10]. Prolonged neutrophil mobilization alongside host tissue damage leads to an increased release of inflammatory cytokines, also known as a cytokine storm[17]. A cytokine storm can cause a positive feedback loop, bringing other immune cells to the site of inflammation, thereby further increasing inflammation and organ damage[18]. Some of the detrimental effects of a cytokine storm include changes in immune cell proliferation, such as excess granulocyte and reduced lymphocyte production, preventing inflammation resolution[19]. Cytokine storms, in particular, have been related to tissue damage in patients with COVID-19 (REF.[18]), as indicated by the many therapeutic approaches against COVID-19 that are focused on minimizing the occurrence of these storms[20]. Finally, greater neutrophil infiltration further increases vascular permeability, allowing pathogens to enter the bloodstream, which ultimately causes systemic inflammation[21].

The innate immune response is not limited to cellular components, but is also facilitated by protein mediators[10,22]. In the blood and interstitial fluid, the complement system becomes activated in the presence of pathogens through the classical, lectin or alternative pathway[22]. The complement system, consisting of distinct plasma proteins, plays a part in targeting or marking foreign materials by coating their surface (also known as opsonization), which in turn can elicit severe immune responses termed complement activation-related pseudo allergy (CARPA)[23,24].

The complement system opsonizes foreign bodies and enzymatically cleaves C3 to the anaphylatoxins C3a and C5a, causing downstream inflammation[22]. Complement activation combined with pathogen or injury-generated systemic inflammatory cytokines can induce tissue factor expression on endothelial cells, initiating the coagulation pathway[10]. Once triggered, the coagulation pathway is difficult to contain by standard feedback mechanisms, such as antithrombin, activated protein C or tissue factor pathway inhibitor, and can thus result in distant intravascular coagulation and eventually multi-organ failure[10].

Acute inflammatory disease treatments

Most clinical treatments for acute inflammatory diseases centre on infection control through antibiotics, pain management and supportive care, involving steroidal and nonsteroidal anti-inflammatory therapies[21,25–28]. However, these approaches have limitations, including increased risk of secondary infections with prolonged use owing to their lack of specificity, coupled with their systemic (oral or intravenous) mode of delivery[27,29–34]. Alternatively, intravenous cellular and monoclonal antibody therapies have emerged as promising agents to target and treat the damaging effects of inflammation[35–39] (FIG. 1b).

Stem cell therapy. Stem cell therapies against inflammation typically involve transplantation of autologous mesenchymal stem cells (MSCs), which are multipotent cells derived from bone marrow, adipose tissue, dental pulp or umbilical cord tissue. Following implantation, MSCs secrete immune-suppressive cytokines (IL-10 and transforming growth factor-β (TGFβ)) to promote regulatory T (T_{reg}) cell production and inhibit differentiation of T helper 1 (T_H1) and T helper 2 (T_H2) cells, aiding in containing the pathological inflammation[40–43]. Finally, MSCs can suppress neutrophil recruitment and activation through secretion of superoxide dismutase 3 (REFS.[41,43,44]). Several clinical trials using MSCs have shown promising results in improving the symptoms of inflammatory disorders, including rheumatoid arthritis, multiple sclerosis and acute respiratory distress syndrome (ARDS)[45]. For example, intravenously injected human umbilical cord MSCs considerably reduced the concentration of inflammatory cytokines in a COVID-19 patient with ARDS, leading to the patient's recovery[46], with similar results shown in COVID-19 patients with pneumonia (ChiCTR2000029990)[47,48].

Despite showing promise, stem cell therapies have intrinsic limitations; isolating and expanding MSCs for each donor is time-consuming, making them unfit for large-scale manufacturing as would be needed for widespread, acute inflammatory illnesses such as COVID-19. MSCs as inflammatory therapeutics also require many viable cells (10 million per dose, with multiple doses required), which can prove challenging to access for autologous transplantation[49]. To address these limitations, allogeneic MSCs can be sourced in high numbers from donors[50]. Alternatively, exosomes secreted from MSCs can be leveraged as alternatives to live-cell

therapeutics as they carry several immunotherapeutic components of the parent MSCs, including cytokines, signalling lipids and mRNA[51].

Cytokine- and antibody-based therapy. Proteins can be designed to target cytokines, such as TNF, IL-1 and IL-6, or to dampen systemic inflammation in patients with immune disorders, by blocking antibodies or by inhibiting cytokines through receptor binding[52]. Cytokine inhibitors have shown excellent efficacy in treating inflammation in clinical trials[53]; for example, the anti-TNF antibody Humira in the treatment of rheumatoid arthritis (NCT00049751)[54].

Antibodies can be deployed for targeted vasculature blocking to prevent the transmigration of immune cells and thus stop inflammatory activation[55,56]. Bimosiamose, for example, is a small-molecule inhibitor of adhesion proteins L-selectin, E-selectin and P-selectin, which showed a promising reduction of inflammation in chronic obstructive pulmonary disease, psoriasis and asthma patients during phase II clinical trials[55,56]. However, cytokine-targeting therapeutics lack specificity[52], with reduced haematopoiesis as one of the most common side effects, ultimately leading to increased infections owing to reduced WBC populations[52].

Targeted immune cell blocking. Immune cells can further be prevented from interacting with inflammation by specific immune cell blocking. Obstructing complement receptors (C5aR)[57], cytokine receptors (such as IL-1R and IL-6R)[52], B cell activation receptors (CD20)[58,59] and adhesion receptors (PSGL1, α4β7 integrin, αΕβ7 integrin and very late antigen 4 (VLA4))[55,56,60] on the surface of immune cells can selectively inhibit inflammatory activation. For example, the small molecule CCX168 is a C5aR inhibitor that blocks binding to the activating complement protein C5a on neutrophils and has demonstrated efficacy in reducing inflammation in a phase III clinical trial (NCT02994927) for vasculitis (inflammation of blood vessels)[57,61]. Similar to cytokine targeting, targeted immune cell blocking can have systemic consequences owing to redundancies within the immunity cascade[62]. Furthermore, complexities associated to ligand-receptor-mediated responses can cause unintended downstream signalling effects[62].

Cellular and antibody-based approaches, however, remain limited owing to the complexity of the inflammatory cascade, and they do not target the root cause of acute inflammation[63]. Alternatively, polymeric antibody-based approaches can mitigate overzealous inflammatory responses in acute lung injury (ALI), ARDS, sepsis, asthma, rheumatoid arthritis, type I diabetes, coagulopathic diseases and neurodegenerative diseases.

Promising particle-based therapeutics

Drug delivery systems can be applied to avoid adverse effects related to systemic treatments of inflammation. For example, lipid nanoparticles and lipid-based drug delivery systems, such as liposomes, show high biocompatibility and cargo stability, as demonstrated by the recent success of lipid-nanoparticle-based mRNA vaccines[64]. These carriers have mainly been deployed for priming immune cells in developing cancer vaccines and, recently, for vaccine against SARS-CoV-2 viral infections[64–66]. However, lipid systems are limited by poor structural stability, a limited range of potential cargos, low drug loading and poor circulation time[67–69]. Alternatively, synthetic polymer-based drug carriers provide spatiotemporal control over release and reproducibility compared to other drug delivery formulations[70,71]. The choice of LNPs versus polymeric carriers depends on the use and type of drug cargo, the cellular target and the in vivo delivery route[72].

Liposomal particles were first used as drug delivery vehicles in cancer therapy to improve drug delivery efficiency to solid tumours; however, immunotoxicity remains a serious side effect for intravenous formulations[73]. Surface modifications of particle-based drug carriers, such as the grafting of polyethylene glycol (PEG) chains on particles, often referred to as PEGylation, were intended to help particles evade the immune system, while also increasing efficiency and reducing side effects of cancer therapeutics[74]. However, immunotoxicity issues persist in intravenous (as opposed to intramuscular) injections, leading researchers to re-evaluate the therapeutic potential of immune cell–particle interactions[75–77].

The tendency of particulate therapies to interact with immune cells can be independently exploited as a therapeutic strategy. For example, in an in vivo model of melanoma, mice treated with poly(lactic-*co*-glycolic acid) (PLGA) particles loaded with a chemotherapeutic drug (paclitaxel) in combination with the CXCL1 chemokine, had significant reduction in tumour size compared to all control groups[78]. Interestingly, neutrophil uptake of the particles followed by chemotaxis to the CXCL1-treated tumour was responsible for the decrease in tumour burden, pointing to the potential applicability of particle-based therapeutics in immune-cell-related diseases[78]. Therefore, particle-based therapeutics have been explored for tissue-localized and systemic treatment of inflammation (FIG. 2 and TABLE 1).

Tissue-specific targeting. Local tissue immunomodulation can be achieved by stimulating or activating tissue-resident immune cells, for example, by vaccination[79–84]. However, particle-based vaccine therapeutics can also be designed to target and passively reprogram inflammatory DCs within a draining lymph node, acting as regulatory vaccines for immune suppression in autoimmune diseases[81,85,86] (FIG. 2a).

DC-based immunomodulatory therapeutics mostly rely on autologous transplantation of exogenously tolerized DCs, which can be costly and plagued by variability of the transplanted DC populations[85]. Injecting specialized polymeric particle-based therapeutics circumvents the limitations of autologous transplantation by directly conditioning and reprogramming DC populations within the host's lymphoid organs[87]. One approach by which polymeric particles modulate tissue relies on tissue draining; for example, a steroid hormone can be co-delivered with immunosuppressive cytokines loaded into a PLGA nanoparticle for the treatment of rheumatoid arthritis[85]. This immunosuppressive approach
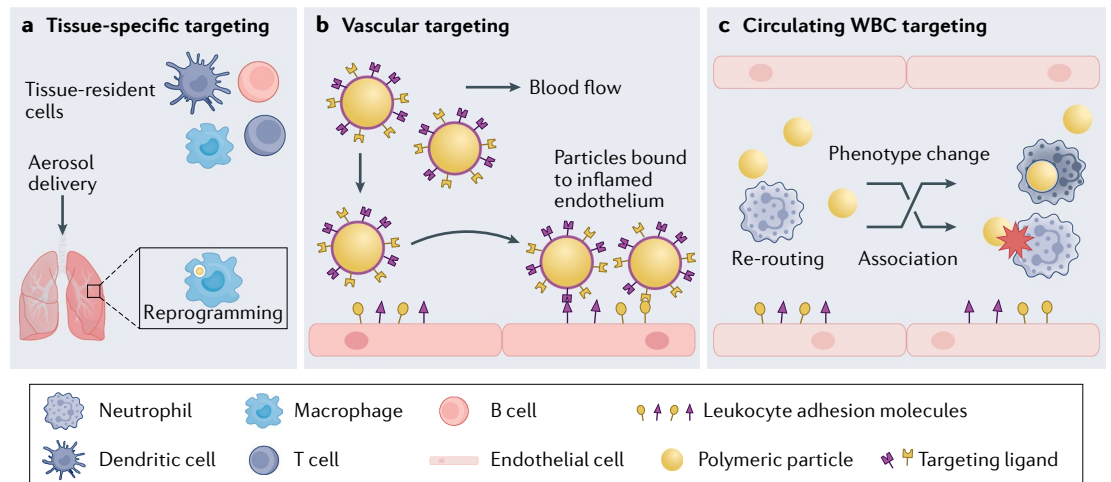
Fig. 2 | **Targeting immune cells by particle-based therapeutics. a** | Tissue-resident immune cells, such as macrophages, dendritic cells, memory T cells and B cells, are directly targeted through local tissue immunomodulation. Particle administration can passively reprogram inflammatory cells for immunosuppressive purposes. **b** | Polymeric particles are designed with ligands or antibodies that target leukocyte adhesion molecules overexpressed in inflamed vasculature. The ligand-mediated anchoring of particles to the endothelium permits accumulation of drug carriers to pathological areas, halting inflammation. Targeted particles can also competitively block binding sites used in immune cell migration, preventing immune cell accumulation at sites of inflammation. **c** | Polymeric particles can divert or reroute circulating blood-resident cells, such as neutrophils and monocytes, from inflammation sites through particle–cell association and cell phenotypic changes after particle uptake. WBC, white blood cell.

reprogrammed DCs within the draining lymph node, effectively regressing rheumatoid arthritis symptoms in mice[85].

Similar particle-based treatments containing immunosuppressive cytokines and autoantigens within PLGA particles were shown to retrain DCs in mouse models of type 1 diabetes and multiple sclerosis, reducing disease presentation and progression[86,88–90]. More specifically, co-delivery of autoantigens and cytokines through a PLGA-based particle therapeutic provided the antigen-specific immune tolerance necessary to reduce disease presentation and progression in a mouse model of multiple sclerosis[88]. The three main routes for therapeutic particle delivery are intravenous, mucosal and direct tissue injection (subcutaneous or lymphoid) (FIG. 3). Subcutaneously injected particles traffic to lymph nodes through tissue-resident antigen-presenting cells and ultimately induce tolerance by DCs, following natural peripheral tolerance pathways[88]. Conversely, intravenously injected particles affect tolerance through liver-resident antigen-presenting cells (Kupffer cells) and macrophage scavengers in the spleen[88]. Similar to subcutaneous injection, particle-based therapeutics directly injected into the lymph node stimulate an increase in the expansion of antigen-specific effector T cells[89] (BOX 1).

Polymeric particles can not only be designed to reprogram immune cells, but can also be exclusively immunosuppressive and directly target sites of inflammation, for example, by being loaded with immunosuppressive drugs[81,91–93]. This approach is beneficial given that most immunosuppressants used to treat inflammatory diseases can oversuppress the immune system, causing several side effects. For example, rapamycin acts as an immunosuppressant, anti-inflammatory and anti-proliferative agent that can lead to diarrhoea, headaches, myelosuppression and hyperlipidaemia[93]. Encapsulating rapamycin and similar drugs in polymeric particles could prevent undesirable side effects, allowing efficient drug delivery at sites of inflammation in rheumatoid arthritis, multiple sclerosis and graft-versus-host disease[93,94].

Particle-based therapeutics with surface decoration of targeting ligands can improve targeting of tissue-specific inflammation sites following intravenous administration. For example, localized infection-related inflammation in the lungs of mice can be treated with intravenously injected PLGA particles that bind specifically to inflamed cells (tumour necrosis factor receptor 1 (TNFR1) on macrophages and intercellular adhesion molecule 1 (ICAM1) on endothelium) at the diseased site[95–97]. To target antigen-presenting cells such as lung-resident macrophages, mesoporous silica nanoparticles can be coated with ligands, including TNFR1, to induce endocytosis[96]. As the particles degrade, they slowly release immunosuppressant agents to reduce inflammatory signals[96]. This approach can be used for a range of diseases, including autoimmune and acute inflammatory diseases[95,96,98,99].

Vasculature targeting. Vascular endothelial cells are major participants and regulators of inflammatory reactions. During acute inflammation, the endothelium rapidly changes its phenotype to support various stages of the inflammatory response. Primarily, activated endothelial cells facilitate the capture and extravasation of leukocytes to infected or damaged tissue[100]. During the inflammatory response, leukocyte adhesion molecules are overexpressed at the injured or inflamed endothelium[100,101]. Thus, particles can be designed to

Table 1 | **Targeting cell populations in different locations**

Targeting strategy	Targeted cells	Route of administration	Platform	Size and shape	Modifications	Notes	Refs.
Tissue-specific	DCs	Subcutaneous	PLGA	~1 μm and ~30 μm spheres	Loading of TGFβ1, GM-CSF, vitamin D₃, type II collagen and insulin	Larger particles recruit and condition DCs through release of GM-CSF and TGFβ1. Simultaneously, smaller loaded particles are phagocytosed by local DCs at the injection site for reprogramming and migrate to lymph node	85,86
				~800 nm spheres	TGFβ surface modifications and loading of OVA$_{323-339}$ peptide	Co-stimulatory particles are phagocytosed by local DCs for immune reprogramming	88
		In vitro study	Polystyrene	150 nm and 2 μm spheres, 3× stretched rods from 150 nm and 2 μm spheres	Physical absorption of poly I:C or CL264	Spherical particles show stronger DC activation than rod-shaped particles. Nanospheres promote the strongest activation	200
	Lymph-node-resident immune cells (such as DCs or T cells)	Intranodal	PLGA	~5 μm and ~ 300 nm spheres	Loading of poly I:C	PLGA particles reach the lymph node through direct injection. Microparticles release poly I:C at the site of injection for sustained DCs activation. By contrast, nanoparticles are rapidly phagocytosed by lymph-node-resident DCs and macrophages	201
				~3–4 μm spheres	Loading of MOG peptide and rapamycin	Intranodal injection of microparticles to promote polarization of T cells	89
	Local phagocytic immune cells (such as macrophages)	In vitro study	PU	~35 nm and ~63 nm spheres	Negative and positive surface charge	Inhibition of M1 macrophage polarization after uptake of negatively charged nanoparticles	92
			Ac-DEX	~829 nm spheres	Loading of rapamycin	Particles are phagocytosed by activated macrophages, reducing production of pro-inflammatory molecules through pH-dependent release of rapamycin from particle matrix	93
			Polystyrene	0.5–3 μm spheres; major axis 0.35–2.5 μm, minor axis 0.2–2 μm rods; major axis 0.35–2.5 μm, minor axis 0.2–2 μm disks	–	Disk-shaped and spherical particles show enhanced macrophage uptake compared to elongated particles	152
Vasculature	Activated endothelial cells	Intravenous	Polystyrene	500 nm and 2 μm spheres; 500 nm ESD (AR = 6) and 2 μm ESD (AR = 4) rods	sLeᵃ and anti-VCAM1 surface modification	Targeted rod-shaped microparticles adhere at a higher rate than targeted microspheres to inflamed aortic segments and plaque	154
			PLGA	~200 nm spheres	γ3 peptide surface modification and loading of sparfloxacin and tacrolimus	Targeted nanoparticles concentrate antibacterial and anti-inflammatory drugs at site of inflammation (lungs)	95
			PAE	100 nm spheres	Anti-ICAM1 surface modification and loading of TPCA-1	Targeted nanoparticles concentrate in the inflamed lungs and release anti-inflammatory drug from pH-responsive polymer matrix	97
		In vitro study	Polystyrene, silica and titania	500 nm spheres	sLeᵃ surface modification	Dense nanoparticles adhere to inflamed HUVEC at a higher rate than neutrally buoyant nanoparticles	113

Table 1 (cont.) | **Targeting cell populations in different locations**

Targeting strategy	Targeted cells	Route of administration	Platform	Size and shape	Modifications	Notes	Refs.
Circulating white blood cells	Circulating phagocytes	Intravenous	Polystyrene, PLG, HPPS	2 μm, 500 nm and 15 nm spheres	Unloaded or drug-loaded particles	Particles passively target phagocytes in the bloodstream to divert them from sites of inflammation	[109,115,116]
		Intraperitoneal or intravenous	PLGA and PLA	~400 nm spheres	Varied surfactants and molecular weight of polymer for fabrication	Physiochemical properties of the particles influenced immunomodulatory effects	[114]
		In vitro study	Polystyrene	0.5–2 μm spheres	Carboxylated, PEGylated or sLeᵃ-coated particles	Collisions in blood flow, particle binding to endothelium, and particle phagocytosis were found to reduce leukocyte adhesion to inflamed endothelium in blood flow	[175]
	Neutrophils	Intravenous	PolyA	1 μm spheres	Polymerized salicylic acid	PolyA particle treatment in ALI and ARDS reduces inflammatory damage in lungs and enhance survival compared to PLGA and polystyrene particles	[117]
		In vitro study	PLGA	1–3 μm spheres or 1.5 μm (long axis) rods	–	Physical properties of particles preferentially target neutrophils through larger size or rod shape	[119,120]

Ac-DEX, acetalated dextran; ALI, acute lung injury; AR, aspect ratio; ARDS, acute respiratory distress syndrome; CL264, adenine analogue; DC, dendritic cell; ESD, equivalent spherical diameter; GM-CSF, granulocyte–macrophage colony-stimulating factor; HPPS, high-density lipoprotein-mimicking peptide-phospholipid scaffold; HUVEC, human umbilical vein endothelial cell; ICAM1, intracellular cell adhesion molecule 1; MOG, myelin oligodendrocyte glycoprotein; OVA, ovalbumin; PAE, poly(β-amino ester); PLG, poly(lactide-*co*-glycolide); PLGA, poly(lactic-*co*-glycolic acid); PolyA, PolyAspirin; poly I:C, poly(inosinic:cytidylic acid); PU, polyurethane; sLeᵃ, sialyl Lewis A; TGFβ1, transforming growth factor β1; TPCA-1, 2-[(aminocarbonyl)-amino]-5-(4-fluorophenyl)-3-thiophenecarboxamide; VCAM1, vascular cell adhesion molecule 1.

target the remodelled endothelium and underlying signalling pathways, for example, by surface modification with antibodies or cell surface proteins against leukocyte adhesion molecules, including selectins, ICAM1 and vascular cell adhesion molecule (VCAM1), which are known to be involved in leukocyte recognition, adhesion and extravasation[100,101].

Vascular-targeted carriers are advantageous for their ability to localize and accumulate at specific disease sites throughout the vasculature, providing controlled release of therapeutics and preventing systemic side effects[102,103] (FIG. 2b). For example, PLGA and poly(lactic acid)-poly(ethylene glycol) (PLA-PEG) spheres coated with biotinylated antibodies against the selectins VCAM1 and ICAM1 (REFS.[104,105]) (FIG. 3a) can target inflammation markers and exhibit selective adhesion towards inflamed endothelium both in vitro and in vivo[104,105]. Likewise, vascular-targeted carriers are often designed with dual adhesion receptors, simulating the multistep adhesion process of WBCs and improving particle adhesion properties[106,107]. The ability of vascular-targeted carriers to bind to leukocyte adhesion molecules can also be leveraged to competitively block excessive and unregulated immune cell trafficking, as occurs in conditions such as ARDS[108]. Although such an approach seems counterintuitive, preventing immune cell migration to pathological areas has already shown promising results at preventing tissue damage and accumulation of inflammatory cytokines in preclinical studies in ALI mice[109].

Limitations of vascular-targeted particles remain in terms of performance and functionality. In particular, diseased blood conditions and the physical characteristics of particles, such as size and ligand density, can affect their ability to target the inflamed endothelium, ultimately hindering full therapeutic potential[110–113].

Circulating white blood cell targeting. Given that most immune cells or cell precursors involved in pathologic inflammation circulate through the bloodstream, intravenously injected immunotherapeutics are among the most prevalent therapeutic options[27,29,39]. Polymeric particles can be used to block circulating WBCs from excessive tissue migration during severe inflammation, diverting these inflammatory cells away from the injured tissue[109,114–116]. The primary mechanism by which polymeric particles achieve immunomodulation in the bloodstream is by interaction with WBCs. Phagocytosis of particles by WBCs affects cell physiology, including cytokine release, surface protein expression and gene expression[108,114,115,117], which leads to the alteration of cell trafficking and signalling (FIG. 2c). Degradable particles alleviate the possibility of long-term particle accumulation, and their byproducts may further provide anti-inflammatory or therapeutic effects. PLG-based particles for example, degrade into lactate, which reduces the inflammatory signals of DCs and macrophages[118], as shown by drug-free PLG- or PLA-based particles in mice models of spinal cord injury and sepsis[114,115].
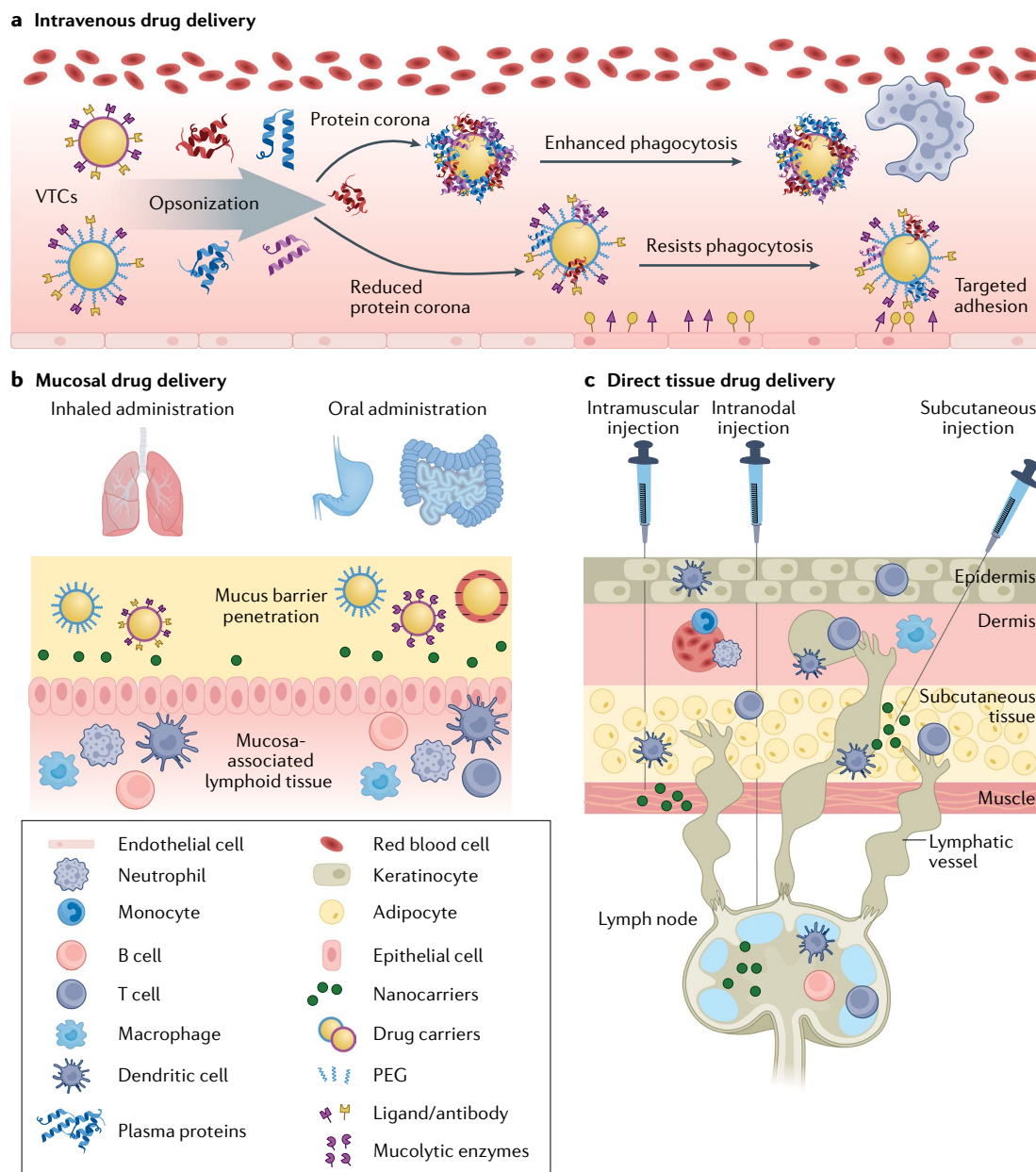
a | Intravenous drug delivery

VTCs
Opsonization
Protein corona
Enhanced phagocytosis
Reduced protein corona
Resists phagocytosis
Targeted adhesion

b | Mucosal drug delivery

Inhaled administration
Oral administration

Mucus barrier penetration

Mucosa-associated lymphoid tissue

c | Direct tissue drug delivery

Intramuscular injection
Intranodal injection
Subcutaneous injection

Epidermis
Dermis
Subcutaneous tissue
Muscle
Lymphatic vessel
Lymph node

Endothelial cell
Neutrophil
Monocyte
B cell
T cell
Macrophage
Dendritic cell
Plasma proteins
Red blood cell
Keratinocyte
Adipocyte
Epithelial cell
Nanocarriers
Drug carriers
PEG
Ligand/antibody
Mucolytic enzymes

Fig. 3 | **Route of administration for immunomodulation.** The effectiveness of particle-based therapeutics strongly depends on the route of administration. **a** | Intravenous routes allow systemic delivery, but pose challenges including quick clearance and complement activation. Grafting of polyethylene glycol (PEGylation) reduces protein corona formation allowing for improved targeting and reduced clearance. **b** | Mucosal drug delivery allows direct targeting of inflamed tissue. Here, particles are designed to target or travel through mucous membranes of diseased tissue. **c** | Direct tissue drug delivery can be applied to target lymphoid tissue by intramuscular, subcutaneous or intranodal injections. VTC, vascular-targeted carrier.

Particles fabricated from high-density lipoprotein-mimicking peptide-phospholipid scaffolds (HPPS) can also be loaded with the anti-inflammatory drug curcumin and designed to specifically target and redirect monocytes[116]. The latter are targeted by scavenger receptor class B type 1, a receptor that strongly interacts with high-density lipoproteins. In a mouse model of multiple sclerosis, treatment with curcumin-loaded HPPS led to a reduction in monocyte accumulation and morbidity at the injury site, further highlighting the potential of targeting innate immune cells, such as monocytes, to

treat inflammatory diseases[116]. Further optimization of the physicochemical properties of particles, known to affect phagocytosis of WBCs, will be required to ensure recognition of different subsets of immune cells within the blood[119,120].

Particle design optimization
For the treatment of inflammatory conditions, the material, size, shape, surface chemistry and deformability of polymeric particles can be modified to ensure efficient interaction with immune cells (FIG. 4).

Material. Material selection affects the release of byproducts and particle accumulation, thereby influencing immune cell modulation and inflammatory signals (FIG. 4a). For example, phagocytosis of non-degradable polystyrene by neutrophils can induce inflammatory neutrophil phenotypes[108]. By contrast, degradable PLG particles confer anti-inflammatory traits to DCs and monocytes[121]. Degradable polymeric materials are ideal for particle-based therapeutics of inflammatory diseases, because they are easily modified, optimized, produced in large quantities, and most importantly, do not accumulate in the body.

PLGA has been widely explored for polymeric nanoparticle design in the context of inflammation owing to its ease of synthesis, manipulation and biocompatible

degradation products (lactic and glycolic acids) which can be metabolized in vivo[122]. PLGA has been incorporated into several US Food and Drug Administration (FDA)-approved particle-based therapeutics and is thus considered a safe material[123]. In small quantities, the primary degradation byproduct of PLGA, lactic acid, has anti-inflammatory properties on both macrophages and DCs[114,121]. Depending on the molecular weight and thus degradation rate of the specific PLGA polymer, these anti-inflammatory properties may vary[121]. For example, low-molecular-weight PLGA (10 kDa) that degrades quickly will have inherently anti-inflammatory properties, whereas a high-molecular-weight PLGA polymeric particle will take longer to degrade and may have initial inflammatory properties prior to degradation[121,124,125]. However, PLGA particles can be used to deliver anti-inflammatory therapeutics such as nonsteroidal anti-inflammatory drugs (NSAIDs) to further reduce inflammation and to overcome any immediate side effects of PLGA degradation[126].

In treating neurological inflammation, particles comprised of polymerized phosphatidylserine, a marker for apoptotic cells, reduced inflammation of activated microglial cells and macrophages in vitro[127]. Although in vitro studies of these biomimetic particles have proved promising, in vivo experiments have only been completed in a myocardial infarction mouse model using phosphatidylserine loaded liposomes, resulting in improved angiogenesis and scar formation[128].

Polymeric particles can also be fabricated from polymerized anti-inflammatory compounds. Degradable polymers can be functionalized with a range of anti-inflammatory agents, including aspirin, naproxen and ibuprofen[129,130]. The resulting compound can then be synthesized into a particle by single oil–water emulsion[117,131]. Intravenous injection of the resulting polymerized salicylic acid (PolyAspirin) particles have shown to alleviate lung inflammation in an endotoxin and a bacterial mouse model of ALI and ARDS, respectively[117]. PolyAspirin particles more efficiently diverted neutrophils from the inflamed lungs and further reduced inflammatory cytokines compared to non-treated polystyrene and PLGA particles[117]. One suggested mechanism is that interactions between neutrophils and PolyAspirin particles prevent the initial accumulation of neutrophils in the lungs, and the degradation of PolyAspirin may ameliorate inflammation[117].

Degradable polymeric particles can also be designed to degrade at the site of inflammation, typically within the inflamed tissue space, by incorporating stimuli-responsive properties. Site-dependent degradation at low pH or through cleavage by matrix metalloproteinases (MMPs) can be implemented in particles, allowing the stimulus-triggered release of incorporated anti-inflammatory drugs[132]. Furthermore, vanillyl alcohol, an antioxidant and anti-inflammatory agent, can be incorporated into copolyoxalate through hydrogen-peroxide-sensitive peroxalate ester bonds, resulting in a polymer that can easily be formulated into a particle-based therapeutic[125]. The particle then degrades through hydrogen peroxide scavenging when exposed to nitric oxide, a molecule heavily expressed

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Box 1 | Routes of administration for immunomodulation

The therapeutic efficacy of particle-based immunomodulation therapies is strongly dependent on the route of administration. Intravenous, local, oral and inhaled delivery each require distinct particle designs[210,211].

Intravenous drug delivery. Intravenously delivered particles can access the entire body and provide immediate drug effects. Systemic administration of therapeutics is typically hindered by rapid capture and clearance of particulates by circulating immune cells, ultimately preventing prolonged accumulation at sites of inflammation[212,213]. The circulation time of intravenously injected therapies can be improved by modifying the physiochemical properties of particles (for example, hydrophobicity) through functionalization with stealth polymers, such as polyethylene glycol (PEG). PEGylation of particles has become standard in the design of long-circulating particle formulations to improve systemic administration[170,212]. The size and charge of particles can be optimized further to improve blood residence time and promote specific interactions with circulating white blood cells (WBCs)[213,214]. However, challenges remain for intravenously injected particle-based formulations, including particle-induced complement activation and development of anti-PEG antibodies[23,165,212,215,216].

Mucosal drug delivery. Oral and inhaled administration allows the accumulation of particles in pathological tissue of the lungs and gastrointestinal tract through mucosal tissue targeting. The therapeutic efficacy of oral and inhaled administration is strongly dependent on tissue-resident cells and organ-specific barriers, such as the mucus layer. The airway and the gastrointestinal tract are common target sites for asthma, cystic fibrosis and inflammatory bowel disease therapies[217,218]. The mucus layers coating these organs pose a barrier, preventing particles from reaching the underlying epithelial surfaces. Mucosal networks vary in different diseases, making customization of drug delivery systems challenging[217–219]. For example, in airway diseases, mucus overproduction and a decrease in mesh pore size hinder the diffusion of pulmonary drug therapeutics[220]. Unlike the dense mucus network in lung diseases, the mucus layer in active ulcerative colitis shows abnormal penetrability, which is advantageous for the design of colon-targeted oral particle formulations, preventing inflammatory episodes and allowing particle uptake and retention within the colon region[221].

The surface and charge of particles can be modulated to increase muco-penetration and mucoadhesive properties of particles, for example, by coating carriers with PEG and mucolytic enzymes[222–225]. Accumulation and retention time of particles in the mucus can be improved by reducing the size of particles to the nanoscale, particularly in the inflamed colon[221,226,227]. Epithelia below mucosal surfaces can also be targeted by pH-dependent and functionalized nanoscale delivery carriers[221,228–230]. Once trapped in the mucosal lining, particles can interact with epithelium and ultimately reach the mucosa-associated lymphoid tissues[231,232], where they can interact with a variety of immune cells.

Direct tissue drug delivery. Particle-based therapeutics designed for tissue drug delivery are typically delivered directly into tissue by subcutaneous, intramuscular or intranodal injection. Tissue-specific injection routes are often used for vaccines to tolerize dendritic cell populations in lymph nodes. Intranodal injections can be the most effective owing to the ensured delivery to lymphoid tissue; however, getting a needle and syringe directly into a lymph node requires specific training and ultrasound technology[89,201,210]. These hurdles can be avoided by injecting therapeutics subcutaneously or intramuscularly, where they will drain to the lymph node[87,233–235]. However, efficacy may be affected owing to inefficiencies of particle transport to the lymph node.
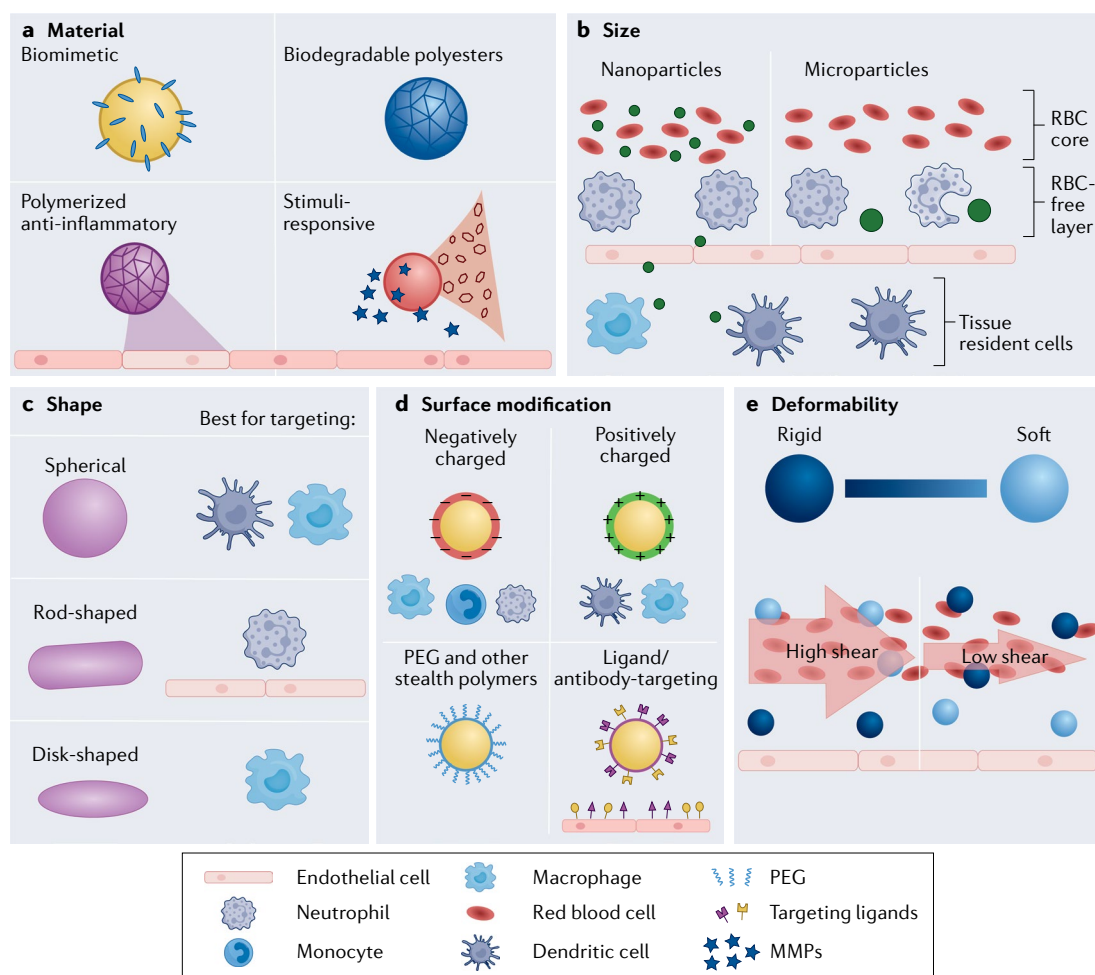
Fig. 4 | **Particle optimization. a** | Materials can be designed to be biodegradable, anti-inflammatory, biomimetic or stimuli-responsive. **b** | Microparticles are phagocytosed and target the vascular wall, whereas nanoparticles permeate the vasculature. **c** | Polymeric materials can be formulated into a variety of shapes to target specific cell populations. **d** | Functional groups on polymeric materials can be conjugated with targeting ligands or stealth polymeric chains. In addition, the polymer can be positively or negatively charged. **e** | Particle rigidity can be modified to selectively target specific cell populations and endothelium in the blood. Soft particles are ideal for marginating along the endothelium in blood flow compared to rigid particles. RBC, red blood cell; PEG, polyethylene glycol; MMP, matrix metalloproteinase.

by the endothelium during inflammation[125]. Similarly, naproxen, an anti-inflammatory drug, can be modified with the ROS scavenging linker, phenylboronic acid (PBA), and then conjugated onto dextran[133]. The modified PBA–dextran can then be formulated into nanoparticles together with a pH-sensitive acetylated dextran, resulting in significantly reduced cytokine release from stimulated macrophages in vitro[133]. Crosslinked poly-amino acid-conjugated polyethylene glycol (PAAP) is another example of a degradable polymer that breaks down at low pH and can be loaded with anti-inflammatory proteins, such as DNAse1, to degrade NETs[134]. ROS-responsive poly(propylene sulfide) (PPS) microparticles loaded with curcumin have shown in vivo efficacy after being intramuscularly injected at the site of ischaemia in a diabetic mouse model[135]. When exposed to ROS, the PPS particles degraded, leading to ROS scavenging and curcumin release. Here, the curcumin functioned synergistically with PPS particles; however, non-loaded PPS particles

also had therapeutic properties, suggesting that ROS scavenging may be enough to reduce inflammation[135]. Overall, versatile stimuli-responsive materials have great potential for treating inflammatory diseases as well as for immunotherapeutic applications[136].

Size. The size customizability of particulates makes them particularly interesting for immunotherapeutics, as they can be designed to mimic pathogens and airborne particles while driving specific immune responses[124,137] (FIG. 4b). Upon particle administration, microparticles (≥1 μm) are rapidly cleared through phagocytosis by macrophages, including rat alveolar macrophages, murine peritoneal macrophages and human spleen macrophages[138–140]. By contrast, nanoparticle uptake can occur through multiple mechanisms, including phagocytosis, pinocytosis, caveolae-, clathrin- and scavenger receptor-mediated endocytosis[139,140]. Nanoparticles have a low risk of capillary occlusion, and they travel passively across permeable vasculature, which is a common

feature of inflammation[141]. The passive transport of nanoparticles makes them ideal candidates for accumulation within the inflamed tissue. For example, PEGylated polyalkylcyanoacrylate nanoparticles injected into an experimental autoimmune encephalomyelitis rat model, can accumulate in the central nervous system[142]. The passive passage of nanoparticles through the blood–brain barrier is attributed to an increase in cerebrovascular permeability, characteristic of such animal model of brain inflammation. Another example is the spleen, where nanoparticle accumulation is greater for 500 nm and 100 nm than for 20 nm polystyrene particles, as shown in an endotoxin-induced systemic inflammation mouse model[143]. Optimum particle size is also crucial for particle retention to inflammation sites that do not intend to reach the vasculature or lymphatic system. For example, intra-articular injection of poly(D,L)-lactic (PLA) particles in a mouse model of arthritis showed that 300 nm and 3 μm particles could rapidly diffuse out of the inflamed joint, hindering long-term accumulation and thus, therapeutic benefit[144].

Particle accumulation and retention at inflammation sites through vascular immunotargeting is also dependent on the carrier size. For example, vascular-targeted nanoparticles often lack high targeting efficiency owing to poor vascular wall localization[110–113,145]. Although micrometre-sized particles can exhibit higher vascular targeting, they are more susceptible to immune cell uptake and dangerous capillary occlusion compared to nanoparticles[110,145,146].

Particle association with inflammatory cells could also provide therapeutic benefits for unresolved inflammatory conditions through immune cell rerouting[109]. For intravenously injected therapies, particle–cell association can be improved by exploring microspheres as therapeutic carriers. Micrometre-sized carriers display enhanced migration out of the red blood cell core in blood flow, consequently co-localizing these particles with leukocytes that are also enriched near the blood vessel wall[110,112]. Polymeric microparticles successfully modulated inflammation through cell–particle interaction in multiple inflammatory mouse models[109,147]; daily intravenous injection of drug-free polymeric microparticles target inflammatory monocytes in the circulation and redirect their migration out of the injured site[147]. Microparticles can further prevent neutrophil adhesion to inflamed tissue in vitro, where selectin-targeted polystyrene (≥2 μm) particles reduced neutrophil adhesion to activated human umbilical vein endothelial cells (HUVECs) more efficiently compared to nanoparticles at equal concentration[108]. Therefore, therapeutic use of particles requires an optimum size range design, depending on the type of inflammatory condition, desired immune response and route of particle administration.

Shape. Phagocytic cells internalize pathogens and airborne particles of various size and shape (FIG. 4c). Despite considerable progress in understanding the mechanisms of cellular recognition of conventional spherical carriers, our knowledge about the effect of the carrier's shape on phagocytosis and the subsequent immune response

remains limited. Early reports describe that the particle axis of elongated polystyrene particles modulates the mechanism of macrophage uptake[148]. Macrophages proceed with phagocytosis only if the first point of contact is at the minor axis (that is, the smaller side) of elongated particles. Such axis-dependent uptake was attributed to actin remodelling, which is necessary for engulfing particles, indicating that the minor axis of elongated particles favoured actin cup formation rather than cell spreading on the particles[148]. Thus, owing to the high energy requirement for actin remodelling, high-aspect-ratio carriers such as elongated particles show reduced phagocytosis by macrophages compared to spherical carriers, ultimately increasing carrier residence time at sites of particle delivery[149–151].

When macrophages are exploited as therapeutic targets, other particle shapes can be explored; for example, low-aspect-ratio spherical and disk-shaped polystyrene particles are phagocytosed by macrophages at a faster rate than are elongated particles[152].

Unlike macrophages, both primary human and mouse neutrophils preferentially internalize rod-shaped particles over spherically shaped ones. Here, the selective particle-neutrophil uptake is independent of material type, and increasing aspect ratios of the particles increase phagocytosis[120]. The observed higher internalization of rod-shaped particles by neutrophils was associated with possible neutrophil-specific phagocytic mechanisms[120], probably linked to the role of neutrophils as the primary human defence against bacterial infection, many of whom have elongated shapes. Such a shape-dependent internalization is an excellent opportunity to engineer particle-based therapies for neutrophilic inflammatory disorders.

The advantages of non-spherical polymeric carriers for anti-inflammatory therapies go beyond their morphology-dependent and cell-type-specific uptake. In particular, rod-shaped and disk-shaped particles demonstrate greater particle margination within the blood compared to spherical carriers[153–155]. These geometries partially counteract hydrodynamic forces in the bloodstream, enabling a large contact area between carriers and cells, thus being attractive for vascular-targeted drug delivery. For example, rod-shaped and spherical polystyrene particles coated with anti-VCAM1 were designed to evaluate the effect of particle shape on binding affinity. Targeted elongated particles showed greater targeting efficiency than targeted spheres in inflamed brain endothelial cells in vitro[156]. ICAM1-targeted rod-shaped polystyrene nanoparticles also showed preferential accumulation in the endothelium of the brain and lungs of healthy mice compared to targeted spherical particles, providing opportunities to enhance selective organ targeting using shape effects[157].

Benefits of non-spherical particles for inflammatory therapies also include overcoming cardiopulmonary reactions caused by both complement activation and responsive macrophages. Unlike with spherical particles, rod-shaped and disk-shaped polystyrene particles did not induce cardiopulmonary distress post-intravenous injection in pigs[158]. Hence, shape modification of polymeric particles is an appealing strategy to leverage

particle-based therapies for desired immune responses, and to circumvent adverse effects of such treatments.

Surface modifications. Surface chemistry and coatings of particulate systems substantially affect the carrier's interaction with immune cells, including particle clearance and therapeutic effect. Intravenously injected particles are inevitably tagged by plasma proteins that form a protein corona. Particle parameters such as surface charge and hydrophobicity have an essential role in protein corona formation and composition, which dictates subsequent cellular interactions (FIG. 4d). In general, hydrophobic particles showcase higher protein absorption than hydrophilic ones. Likewise, surface charge affects the level of absorption of plasma proteins. For example, increasing the negative surface charge of polystyrene nanoparticles boosts protein absorption, but not protein corona species[159]. The composition of protein corona can vary among particles with different levels of surface hydrophobicity and cationic or anionic surface charges, ultimately governing uptake by phagocytes[160,161]. Typically, proteins adsorbed onto particles behave as opsonins, enhancing particle internalization[161].

Rapid particle clearance is a major challenge for designing particle-based immunotherapies that aim to reach the vascular wall or inflamed or damaged tissue. The cellular uptake of carriers can be mitigated by modifying their surface with a hydrophilic polymer, such as PEG[161–163]. PEGylated particle formulations can evade uptake by immune cells, extending their blood circulation time[161–163] (FIG. 3a). Besides intravenous delivery, PEGylated particles also showcase longer residence time through other routes of administration, such as the pulmonary route. Pulmonary delivery of non-spherical polymeric hydrogels functionalized with PEG coatings reduced mouse alveolar macrophage uptake in vitro and in vivo. Accordingly, PEGylated particles showed increased retention in the lungs and minimal inflammatory response for at least a month[164].

Although PEG is often recognized as immunologically safe and allergies caused by this compound are rare, some PEGylated drug formulations can trigger complement activation and, in a small portion of patients, lead to severe anaphylaxis[165–169]. Additionally, the widespread use of PEGylation in pharmaceutical research has led to the discovery of PEG-specific antibodies that compromise its potential efficacy[67,170]. For example, increased clearance of PEGylated particles from blood circulation in mouse and rats have been reported after repeated doses, particularly for liposome carriers[67,170–172]. Thus, PEG alternatives are being explored, including biodegradable polymers such as poly(glutamic acid) (PGA) and ionic liquid coatings[173,174].

The immune evasive effects of particle PEGylation have mainly been explored for macrophage and monocyte uptake and less for neutrophils, despite their important role in immune response modulation and pathogen removal[163,175]. Surprisingly, PEGylation of carriers had the opposite effect on particle uptake in human blood; PEGylated polystyrene or PLGA particles showed increased uptake by human neutrophils compared to their non-PEGylated counterparts[175]. It was determined that factors present in the human plasma contribute to the lost immune evasive properties of PEGylated particles[175].

Surface modification further includes decorating particles with vascular-targeted ligands to localize and accumulate carriers at sites of inflammation or injury. Defining the optimal ligand surface density is essential to prevent suboptimal targeting of the endothelium or nonspecific targeting effects. In general, high ligand density on the particle surface increases the probability of encountering the specific binding partners and reduces particle-detaching forces owing to increased multivalent interactions[107,176,177]. However, excessive ligand density may inhibit optimal carrier binding to target cells owing to antibody steric hindrances or overcrowding.
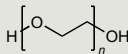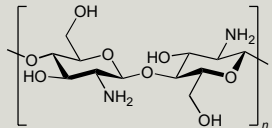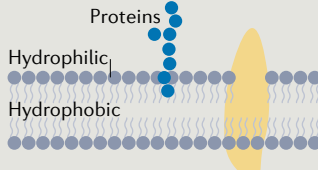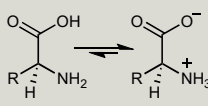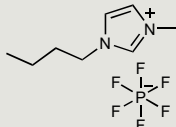
Optimal ligand surface density is also crucial in controlling selective binding of vascular-targeted carriers to pathological vasculature while minimizing binding to healthy tissue sites[107]. For example, carriers targeted with excessively high anti-ICAM1 surface density face a high off-target risk owing to the ubiquitous basal expression of ICAM1 on the vascular wall in healthy tissues[102]. In a mouse model of ALI, low density of ICAM1 on poly(4-vinylphenol) (PVPh) nanoparticles increased selective binding of these nanoparticles to inflamed pulmonary tissue relative to healthy vasculature[177]. By contrast, high ICAM1 density resulted in nanoparticle binding to both healthy and injured endothelium[177]. In vitro, in vivo and in silico binding assays showed that a low ligand density minimizes binding to areas with low receptor expression but maximizes binding to surfaces with highly expressed receptors[107]. In the case of inflammation, receptor expression increases at the vascular wall, improving the likelihood that particles decorated with a low density of ligands finding the receptors to enable adhesive and multivalent interaction[107].

In summary, the examples above illustrate the heterogeneous nature of particle surface chemistry on broad aspects of blood circulation and particle uptake. Specifically, the differences observed in immune cell populations affect the design of particle-based immunotherapies. Likewise, it showcases the importance of designing safe formulations to minimize exacerbation of inflammatory and allergic responses (TABLE 2).

Deformability. Particle deformability provides a tuneable factor in particle-based therapeutic design. By adjusting the polymer content in the polymer precursor solution or the functionality of the polymer building block, the degree of crosslinking can be modulated[178]. Therefore, the particle's elasticity and flexibility can be tuned to improve leukocyte avoidance, vascular localization, vascular navigation and biodegradation[178–180]. Thus, recent work has sought to understand the role of particle deformability in designing particle-based drug carriers.

Studies investigating the effect of particle elasticity with regards to drug carrier design work across a range of moduli, typically from around 10 kPa up to approximately 1,000 kPa (REF.[178]). Within this range, a softer particle benefits from a longer circulation time, thereby avoiding clearance by leukocytes. Conversely, comparatively stiffer particles exhibit a shorter circulation time

Table 2 | **Particle coatings to promote stealth characteristics**

Stealth coating	Mechanism of action	Clinical applications	Advantages	Disadvantages
Polyethylene glycol (PEG)	Hydrophilic polymer generates steric repulsion, reducing protein adsorption[202]	Chronic inflammatory diseases (multiple sclerosis, arthritis, Crohn's disease), gout, haemophilia, chronic kidney disease, prostate cancer, leukaemia, acromegaly, and hepatitis B and C[203]	Biocompatible[202] FDA approval for human use[123] Tuneability: effective PEGylation depends on chain length, PEG chain architecture, grafting density[202]	Does not completely eliminate protein adsorption[202] Does not protect polymer particle from phagocytosis by neutrophils in human blood[175]
Chitosan	Polysaccharide primary amino groups yield cationic properties[204]	No FDA-approved particle-based formats, but has been evaluated in a clinical study in a nasal spray formulation of fentanyl chitosan[205]: chitosan nanoparticles enhanced bioavailability and systemic exposure[205]	Biocompatible, biodegradable, non-toxic, stable[206] Fine tuning of properties by tuning molecular weight[206] Mucoadhesive[204,206] Antimicrobial[206] Controlled drug release[204,206]	Weak non-fouling properties[204]
Cell membrane	Natural cell membranes are collected and coated onto synthetic particles[207]	Polymeric nanoparticles coated with prostate-specific membrane antigens enhanced particle accumulation within prostate tumours[207]	Prolonged circulation[207] Enhanced targeting capabilities[207] Ability to directly modulate immunity[207] Biomimetic	Batch-to-batch variation[207]
Zwitterion	Contains both positive and negative moieties, creating overall neutral charge[202]; both moieties interact with water molecules so that the hydration layer prevents opsonization[202]; the anti-fouling properties increase as the distance between oppositely charged moieties decreases[202]	No FDA-approved product	Non-haemolytic[202] Reduced nonspecific protien adhesion[202]	Cannot be used for active targeting[202] Difficult to tune surface properties[202] Cellular uptake is not inhibited[202]
Ionic liquids	Particles can be suspended in ionic liquid emulsions or covalently bonded with ionic liquids[208]; intramolecular and intermolecular interactions between the ionic liquid and particle/loaded drug determine the particle properties[208]	No FDA-approved product	Tuneable[208] Stealth[208] Antimicrobial[208] Stable[208]	Mechanism of degradation is unknown[208,209]

and increased phagocytosis[181–183]. For example, stiff (3,000 kPa) PEG-based nanoparticles are engulfed at a faster rate by J774 macrophages compared to softer (10 kPa) ones in vitro. Soft particles also have a higher persistence in the blood for up to four hours, after which this difference is substantially reduced[181]. Similarly, micrometre-sized, rigid polyacrylamide beads having a threefold-higher modulus have a greater propensity of being phagocytosed by bone-marrow-derived macrophages in vitro compared to softer beads[182]. Bone-marrow-derived monocytes exhibit similar behaviour, with up to threefold-reduced uptake of soft (1.3 kPa) disk-shaped particles compared to their rigid counterparts (15 kPa)[183]. These studies suggest that deformability is an important parameter to consider, especially in avoiding leukocyte clearance for vascular-targeted approaches to immunomodulation.

In addition to leukocyte–particle interactions, the role of elasticity in modulating particle accumulation at specific sites has been explored[179,180]. Soft PEG-based particles (20–100 kPa) outperform stiffer particles (300–500 kPa) in an in vitro blood flow system under various shear rates; at low rates (500 s^{-1} or less), softer particles adhere to the endothelium at the same or greater rate compared to their rigid counterparts[179,180]. This trend is reversed at high-shear (1,000 s^{-1} or greater) conditions[179]. Additionally, soft hydrogel microparticles can shuttle nanoparticles to the vascular wall[184]; for example, intravenous delivery of nanoparticles to the endothelium of mice can be enhanced by loading them into deformable microparticles[184]. Deformable particles in particular are better suited for immunomodulatory approaches that do not rely on cellular uptake for activity, especially in the case of loading and delivering

smaller particles to a site of inflammation such as in vascular-targeted approaches.

Deformable particles can also be used to mimic cells, such as platelets, for therapeutic applications. For example, despite showing great potential for treating coagulopathic diseases (in which clotting does not occur fast enough)[185,186], platelet transfusions can still result in immunogenic side effects[187]. Poly(N-isopropylacrylamide-co-acrylic-acid) microgel particles (1 μm) conjugated to a fibrin antibody can mimic the size, morphology and fibrin binding of platelets[187]. These platelet-like particles increase clot formation and stability in traumatic brain injuries, preventing post-traumatic neuroinflammation. Additionally, they have a longer shelf life compared to natural platelets, with potential applicability for treating other haemorrhagic bleeding disorders that lead to downstream inflammation[187].

Deformability mainly influences particle circulation and uptake; however, it could also be tuned to achieve stimuli-responsive properties. For example, deformable materials designed to degrade at specific sites with low pH or high MMP concentrations enable selective protein or drug release[188].

Outlook

Polymeric particle-based therapeutics are extremely versatile and are therefore an excellent tool for designing treatment strategies against inflammatory diseases. By designing the material, size and shape of particles, sites and cell subtypes can be specifically targeted to distinct inflammatory diseases. Particle-based therapeutics have substantially improved the clinical efficacy of a variety of therapies, including therapies for endometriosis, cancer, growth failure, gum disease and mood disorders[123]. Despite a range of clinically available polymeric-particle-based therapeutics and the plethora of literature on the topic, only 12 PLGA particle-based formulations have been approved by the FDA over the past 30 years[123,189]. This stark contrast between research and clinical approval stems mainly from translational inconsistencies between animal models and humans.

Although our understanding of inflammatory pathways is constantly evolving, the exact relation between particle design and subsequent inflammatory responses remains to be investigated. For example, the immune cells work in concert with complement pathways to respond to all invading foreign materials, including particles designed as immunotherapeutics[24]. Despite this known involvement, in vitro assays are limited owing to the difficulties of recapitulating inflammatory signalling pathways in a test tube[24]. Additionally, complement reactions vary across species, making it challenging to develop reliable in vivo assays for clinical translation[24]. Pigs have high CARPA reactions to particle-based therapeutics and have become an expensive but reliable model for a variety of applications[24,190]. Slower infusion rates, coupled with optimized surface properties, can help to prevent CARPA reactions[190]. However, screening assays need to be developed to investigated how to prevent CARPA reactions.

The design of new particle-based therapeutics further poses challenges in terms of regulatory approval. Unlike systemic, carrier-free therapeutics, particle-based medicines are typically composed of polymeric vehicles, therapeutic agents and surface modifications[191–193]. A slight change in any of these components can considerably alter particle function, biodistribution and toxicity, which makes regulatory evaluation challenging. For this reason, the National Cancer Institute instigated the establishment of the Nanotechnology Characterization Laboratory (NCL) to develop standardized assays to characterize particle-based therapeutics and related toxicities[191]. The NCL was established to streamline the clinical trial and FDA approval process; however, these procedures are designed for cancer therapeutics and not for generalized therapies[191–193]. Importantly, NCL guidelines, such as prolonged evasion of the mononuclear phagocyte system, inherently exclude particle-based therapeutics that are designed to target circulating phagocytes[193]. Despite these translational hurdles, the consistent progress made by the scientific community and a streamlined approval process could revolutionize particle-based therapeutics.

Particle technologies are practical solutions for several severe inflammatory diseases. The customizable nature and the physical and chemical attributes of particles fit the demand for innovative clinical applications, including the treatment of system-wide inflammation and vaccine development[64,117,194–196]. The synthesis of polymers can now be fine-tuned; however, the clinical translation of polymeric-based particles remains limited owing to a lack of scaling-up technologies for the fabrication of non-spherical particles in large quantities. The physicochemical parameters governing laboratory-batch particle fabrication are often very complex, and so large-scale production workflows need to be developed. Fortunately, promising large-scale processes are currently being explored for complex-shaped particle fabrication, including lithography-based and microfluidics technologies[197,198]. Although more work is needed to overcome these obstacles, the rapid expansion of particle-based medicine can offer state-of-the-art solutions to global problems[199].

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Author contributions

E.R.B. and M.V.G. wrote the abstract, introduction and main sections of the manuscript, Box 1 and Fig. 3. E.R.B. created Table 2, Fig. 1a and Fig. 4, and edited Table 1. M.V.G. created Fig. 2 and edited Table 1. N.J.P. wrote Table 1, created Fig. 1b and edited the manuscript. J.K.L. wrote the deformability section. J.S.L. and O.E.-A. laid the framework for, wrote, edited and reviewed the manuscript.

Competing interests

O.E.-A. serves as a consultant for Asalyxa Bio, working to develop 'Polymer Particle for Neutrophil Injury'. O.E.-A. is listed as inventor on a recently filed patent application (US Provisional Application No. 62/870,879). The other authors declare no competing interests.

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