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 dysfunction1–3, and is associated with numerous human disorders, such as acute lung and liver injury, sepsis, asthma, inflammatory bowel disease, rheumatoid arthritis and neurodegenerative diseases2,3. 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 years3–5. 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 damage2,3,5,6. 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 chemicals2,3. 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 response1,8. 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 action10.

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
interactions with endothelial surface-expressed proteins, such as upregulated selectin molecules. 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 monocyte recruitment.

**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 P-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 (Treg) cell production and inhibit T helper 1 (Th1) and T helper 2 (Th2) 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. At this stage, activated neutrophils shed P-selectin glycoprotein ligand 1 (PSGL1) and L-selectin (also known as CD62L) from their membrane surface. 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). Once the infection has been contained, released granules, NETs and apoptotic neutrophils recruit monocytes and adaptive immune cells to initiate inflammation resolution (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. The released DAMPs are sensed by resident immune and endothelial cells, leading to inflammatory cytokine production (TNF and IL-1) and other pro-inflammatory mediators such as cytokines, leukotrienes and reactive oxygen species (ROS). Similar to pathogenic infections, these immunostimulatory molecules initiate neutrophil recruitment to the injured site. 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.

Excess release of granules, ROS and NETs by an overabundance of neutrophils could still cause damage in surrounding host cells, 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. Prolonged neutrophil mobilization alongside host tissue damage leads to an increased release of inflammatory cytokines, also known as a cytokine storm. 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. 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. Cytokine storms, in particular, have been related to tissue damage in patients with COVID-19, as indicated by the many therapeutic approaches against COVID-19 that are focused on minimizing the occurrence of these storms. Finally, greater neutrophil infiltration further increases vascular permeability, allowing pathogens to enter the bloodstream, which ultimately causes systemic inflammation.

The innate immune response is not limited to cellular components, but is also facilitated by protein mediators. In the blood and interstitial fluid, the complement system becomes activated in the presence of pathogens through the classical, lectin or alternative pathway. 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).

The complement system opsonizes foreign bodies and enzymatically cleaves C3 to the anaphylatoxins C3a and C5a, causing downstream inflammation. Complement activation combined with pathogen or injury–generated systemic inflammatory cytokines can induce tissue factor expression on endothelial cells, initiating the coagulation pathway. 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.

Acute inflammatory disease treatments
Most current treatments for acute inflammatory diseases centre on infection control through antibiotics, pain management and supportive care, involving steroidal and nonsteroidal anti-inflammatory therapies. 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. Alternatively, intravenous cellular and monoclonal antibody therapies have emerged as promising agents to target and treat the damaging effects of inflammation.

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 (Treg) cell production and inhibit differentiation of T helper 1 (Th1) and T helper 2 (Th2) cells, aiding in containing the pathological inflammation. Finally, MSCs can suppress neutrophil recruitment and activation through secretion of superoxide dismutase 3 (SOD3) and tissue factor pathway inhibitor. 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). 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, with similar results shown in COVID-19 patients with pneumonia.

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. To address these limitations, allogeneic MSCs can be sourced in high numbers from donors. 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.

**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. Cytokine inhibitors have shown excellent efficacy in treating inflammation in clinical trials; for example, the anti-TNF antibody Humira in the treatment of rheumatoid arthritis (NCT00049751)

Antibodies can be deployed for targeted vasculature blocking to prevent the transmigration of immune cells and thus stop inflammatory activation. 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. However, cytokine-targeting therapeutics lack specificity, with reduced haematopoiesis as one of the most common side effects, ultimately leading to increased infections owing to reduced WBC populations.

**Targeted immune cell blocking.** Immune cells can further be prevented from interacting with specific immune cell blocking. Obstructing complement receptors (C5aR), cytokine receptors (such as IL-1R and IL-6R), B cell activation receptors (CD20) and adhesion receptors (PSGL1, α4β7 integrin, αEβ7 integrin and very late antigen 4 (VLA4)) 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).

Similarly to cytokine targeting, targeted immune cell blocking can have systemic consequences owing to redundancies within the immunity cascade. Furthermore, complexities associated to ligand-receptor-mediated responses can cause unintended downstream signalling effects.

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. 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. These carriers have mainly been deployed for priming immune cells in developing cancer vaccines and, recently, for vaccine against SARS-CoV-2 viral infections. However, lipid systems are limited by poor structural stability, a limited range of potential cargos, low drug loading and poor circulation time. Alternatively, synthetic polymer-based drug carriers provide spatiotemporal control over release and reproducibility compared to other drug delivery formulations. 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.

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. 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. However, immunotoxicity issues persist in intravenous (as opposed to intramuscular) injections, leading researchers to re-evaluate the therapeutic potential of immune cell–particle interactions.

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. 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. 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. 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.

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. 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. 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. This immunosuppressive approach
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. 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 diarrhea, headaches, myelosuppression and hyperlipidaemia. 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.

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. To target antigen-presenting cells such as lung-resident macrophages, mesoporous silica nanoparticles can be coated with ligands, including TNFR1, to induce endocytosis. As the particles degrade, they slowly release immunosuppressant agents to reduce inflammatory signals. This approach can be used for a range of diseases, including autoimmune and acute inflammatory diseases.

**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. During the inflammatory response, leukocyte adhesion molecules are overexpressed at the injured or inflamed endothelium. Thus, particles can be designed to...
| 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<sub>223-239</sub> Peptide | Co-stimulatory particles are phagocytosed by local DCs for immune reprogramming | | | | |
| 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 | | | | |
| 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 | sLe<sup>+</sup> 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 | γ<sub>3</sub> peptide surface modification and loading of sparfloxacin and tacrolimus | Targeted nanoparticles concentrate antibacterial and anti-inflammatory drugs at site of inflammation (lungs) | | 99 |
| 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 | sLe<sup>+</sup> surface modification | Dense nanoparticles adhere to inflamed HUVEC at a higher rate than neutrally buoyant nanoparticles | 113 |
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. 106,107

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 For example, PLGA and poly(lactic acid)-poly(ethylene glycol) (PLA–PEG) spheres coated with biotinylated antibodies against the selectin 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. 106,107

### 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 Polymorphic particles can be used to block circulating WBCs from excessive tissue migration during severe inflammation, diverting these inflammatory cells away from the injured tissue. 110–113 The primary mechanism by which polymorphic 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. 108,114,115,116,117 This leads to the alteration of cell trafficking and signalling. 27,29,39

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, as shown by drug-free PLG- or PLA-based particles in mice models of spinal cord injury and sepsis. 118,119

### 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 | 106,115,116 |
| Intraperitoneal or intravenous | PLGA and PLA | ~400 nm spheres | Varied surfactants and molecular weight of polymer for fabrication | | | Physicochemical properties of the particles influenced immunomodulatory effects | 114 |
| In vitro study | Polystyrene | 0.5–2 µm spheres | Carboxylated, PEGylated or sLe*-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 | 118,119 |

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

**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.

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**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.
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\(^\text{188}\). By contrast, degradable PLG particles confer anti-inflammatory traits to DCs and monocytes\(^\text{211}\). 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\(^\text{125}\). PLGA has been incorporated into several US Food and Drug Administration (FDA)-approved particle-based therapeutics and is thus considered a safe material\(^\text{221}\). In small quantities, the primary degradation byproduct of PLGA, lactic acid, has anti-inflammatory properties on both macrophages and DCs\(^\text{114,121}\). Depending on the molecular weight and thus degradation rate of the specific PLGA polymer, these anti-inflammatory properties may vary\(^\text{217}\). 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\(^\text{121,124,125}\). 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\(^\text{216}\).

In treating neurological inflammation, particles comprised of polymerized phosphatidylserine, a marker for apoptotic cells, reduced inflammation of activated microglial cells and macrophages in vitro\(^\text{221}\). 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\(^\text{111}\).

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\(^\text{110,111}\). The resulting compound can then be synthesized into a particle by single oil–water emulsion\(^\text{129,130}\). 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\(^\text{117}\). PolyAspirin particles more efficiently diverted neutrophils from the inflamed lungs and further reduced inflammatory cytokines compared to non-treated polystyrene and PLGA particles\(^\text{117}\). 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\(^\text{117}\).

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\(^\text{122}\). 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\(^\text{221}\). The particle then degrades through hydrogen peroxide scavenging when exposed to nitric oxide, a molecule heavily expressed...
by the endothelium during inflammation. Similarly, naproxen, an anti-inflammatory drug, can be modified with the ROS scavenging linker, phenylboronic acid (PBA), and then conjugated onto dextran. 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. 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. 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. 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. Overall, versatile stimuli-responsive materials have great potential for treating inflammatory diseases as well as for immunotherapeutic applications.

**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 (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. By contrast, nanoparticle uptake can occur through multiple mechanisms, including phagocytosis, pinocytosis, caveolae-, clathrin- and scavenger receptor-mediated endocytosis. Nanoparticles have a low risk of capillary occlusion, and they travel passively across permeable vasculature, which is a common

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**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.
feature of inflammation. 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. 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. 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.

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. Although micrometre-sized particles can exhibit higher vascular targeting, they are more susceptible to immune cell uptake and dangerous capillary occlusion compared to nanoparticles.

Particle association with inflammatory cells could also provide therapeutic benefits for unresolved inflammatory conditions through immune cell rerouting. 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. Polymeric microparticles successfully modulated inflammation through cell–particle interaction in multiple inflammatory mouse models; daily intravenous injection of drug-free polymeric microparticles target inflammatory monocytes in the circulation and redirect their migration out of the injured site. 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. 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. 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. 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. 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.

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. 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. The observed higher internalization of rod-shaped particles by neutrophils was associated with possible neutrophil-specific phagocytic mechanisms, 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. 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. 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.
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 polymeric nanoparticles boosts protein absorption, but not protein corona species. 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.

Typically, proteins adsorbed onto particles behave as opsonins, enhancing particle internalization.

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. PEGylated particle formulations can evade uptake by immune cells, extending their blood circulation time. Besides intravenous delivery, PEGylated particles also show 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.

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. Additionally, the widespread use of PEGylation in pharmaceutical research has led to the discovery of PEG-specific antibodies that compromise its potential efficacy. For example, increased clearance of PEGylated particles from blood circulation in mice and rats have been reported after repeated doses, particularly for liposome carriers. Thus, PEG alternatives are being explored, including biodegradable polymers such as poly(glutamic acid) (PGA) and ionic liquid coatings.

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. 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. It was determined that factors present in the human plasma contribute to the lost immune evasive properties of PEGylated particles.

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. 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. 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. 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. By contrast, high ICAM1 density resulted in nanoparticle binding to both healthy and injured endothelium.

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. 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.

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 tunable 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. Therefore, the particle’s elasticity and flexibility can be tuned to improve leukocyte avoidance, vascular localization, vascular navigation and biodegradation.

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. 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.
and increased phagocytosis. 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. 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. 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). 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. 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. This trend is reversed at high-shear (1,000 s⁻¹ or greater) conditions. Additionally, soft hydrogel microparticles can shuttle nanoparticles to the vascular wall, for example, intravenous delivery of nanoparticles to the endothelium of mice can be enhanced by loading them into deformable microparticles. 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

| Stealth coating | Mechanism of action | Clinical applications | Advantages | Disadvantages |
|----------------|---------------------|----------------------|------------|---------------|
| Polyethylene glycol (PEG) | Hydrophilic polymer generates steric repulsion, reducing protein adsorption | Chronic inflammatory diseases (multiple sclerosis, arthritis, Crohn’s disease), gout, haemophilia, chronic kidney disease, prostate cancer, leukaemia, acromegaly, and hepatitis B and C | Biocompatible, FDA approval for human use, Tuneability: effective PEGylation depends on chain length, PEG chain architecture, grafting density | Does not completely eliminate protein adsorption, Does not protect particle from phagocytosis by neutrophils in human blood |
| Chitosan | Polysaccharide primary amino groups yield cationic properties | No FDA-approved particle-based formats, but has been evaluated in a clinical study in a nasal spray formulation of fentanyl chitosan; chitosan nanoparticles enhanced bioavailability and systemic exposure | Biocompatible, biodegradable, non-toxic, stable,Fine tuning of properties by tuning molecular weight, Mucoadhesive, Antimicrobial, Controlled drug release | Weak non-fouling properties |
| Cell membrane | Natural cell membranes are collected and coated onto synthetic particles | Polymeric nanoparticles coated with prostate-specific membrane antigens enhanced particle accumulation within prostate tumours | Prolonged circulation, Enhanced targeting capabilities, Ability to directly modulate immunity | Batch-to-batch variation |
| Zwitterion | Contains both positive and negative moieties, creating overall neutral charge; both moieties interact with water molecules so that the hydration layer prevents opsonization; the anti-fouling properties increase as the distance between oppositely charged moieties decreases | No FDA-approved product | Non-haemolytic, Reduced nonspecific protein adhesion | Cannot be used for active targeting, Difficult to tune surface properties, Cellular uptake is not inhibited |
| Ionic liquids | Particles can be suspended in ionic liquid emulsions or covalently bonded with ionic liquids, intramolecular and intermolecular interactions between the ionic liquid and particle/loaded drug determine the particle properties | No FDA-approved product | Tuneable, Stealth, Antimicrobial, Stable | Mechanism of degradation is unknown |
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)\(^5\),\(^6\),\(^7\), platelet transfusions can still result in immunogenic side effects\(^7\). 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\(^7\). 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\(^7\).

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\(^8\).

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\(^9\). 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\(^10\),\(^11\). 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\(^4\). Despite this known involvement, in vitro assays are limited owing to the difficulties of recapitulating inflammatory signaling pathways in a test tube\(^4\). Additionally, complement reactions vary across species, making it challenging to develop reliable in vivo assays for clinical translation\(^4\).

Pigs have high CARPA reactions to particle-based therapeutics and have become an expensive but reliable model for a variety of applications\(^12\),\(^13\). Slower infusion rates, coupled with optimized surface properties, can help to prevent CARPA reactions\(^14\). However, screening assays need to be developed to investigate 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\(^15\),\(^16\). 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\(^17\),\(^18\). 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\(^19\),\(^20\). Importantly, NCL guidelines, such as prolonged evasion of the mononuclear phagocyte system, inherently exclude particle-based therapeutics that are designed to target circulating phagocytes\(^21\). 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\(^4\),\(^10\),\(^17\),\(^19\),\(^42\). 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\(^15\),\(^20\). 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\(^19\).

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1. Chen, G. Y. & Núñez, G. Sterile inflammation: sensing and reacting to damage. Nat. Rev. Immunol. 10, 826–837 (2010).
2. Kolaczkowska, E. & Kubes, P. Neutrophil recruitment and function in health and inflammation. Nat. Rev. Immunol. 13, 159–175 (2013).
3. Navegantes, K. C. et al. Immune modulation of some autoimmune diseases: the critical role of macrophages and neutrophils in the innate and adaptive immunity. J. Transl. Med. 15, 56 (2017).
4. Gabay, C. Interleukin-6 and chronic inflammation. Arthritis Res. Ther. 8, 53 (2006).
5. Lawrence, T. & Gilroy, D. W. Chronic inflammation: a failure of resolution? Int. J. Exp. Pathol. 88, 85–94 (2007).
6. Su, Y., Gao, J., Kaur, P. & Wang, Z. Neutrophils and macrophages as targets for development of nanotherapeutics in inflammatory diseases. Pharmaceutics 12, 1222 (2020).
7. Amarante-Mendes, G. P. et al. Pattern recognition receptors and the host cell death molecular machinery. Front. Immunol. 9, 2579 (2018).
8. Mogensen, T. H. Pathogen recognition and inflammatory signaling in innate immune defenses. Clin. Microbiol. Rev. 22, 240–275 (2009).
9. Koltsova, E. K. et al. Dynamic T cell–APC interactions sustain chronic inflammation in atherosclerosis. J. Clin. Invest. 122, 5114–5126 (2012).
10. Castelhano, A., Brekke, O. L., Espevik, T., Harboe, M. & Molines, T. E. Innate immune responses to danger signals in systemic inflammatory response syndrome and sepsis. Scand. J. Immunol. 69, 479–491 (2009).
11. George-Gay, B. & Parker, K. Understanding the complete blood count with differential. J. Perianesth. Nurs. 18, 56–117 (2003).
Bongartz, T. et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 291, L200–L207 (2006).

Bos, A., Zhang, X., Yang, Y. & Nani, H. Humanized monoclonal antibody against the chemokine CXCL8 (IL-8) effectively prevents acute lung injury. *Int. Immunopharmac.* 10, 259–263 (2010).

Bosch, L., Kumpf, M. E., Hudson, S. A., Mayer, R. J. & Bochner, B. S. Activation of human leukocytes reduces surface P-selectin glycoprotein ligand-1 (PSGL-1) and adhesion to P-selectin in vitro. *J. Immunol.* 165, 2764 (2000).

Bu, Y. et al. Accelerated blood clearance of PEGylated liposomes following preceding liposome injection: effects of lipid dose and PEG surface-density and chain length of the first-dose liposomes. *J. Control. Release* 105, 301–315 (2005).

Cannata, N., Vai, L., Mazzini, N. & Zanini, M. Polymeric nanoparticles and nanostructured lipid carriers: structure, preparation and application. *Adv. Pharm. Buil.* 50, 305–313 (2015).

Capek, M., Zeilinger, S. & Windhager, R. Macrophages in atherothrombosis. *Nat. Rev. Cardiol.* 14, 75–86 (2017).

Carrington, R. B., Papapetropoulos, A., Coughlan, J. M., Greenhalgh, R. & Wing, R. J. Neutrophil activation by lipopolysaccharide in vivo: a potential mechanism for the induction of fever. *Biol. Chem.* 392, 477–485 (2011).

Cathcart, T. et al. Neutrophil-derived DNA and RNA contribute to severe acute respiratory syndrome coronavirus-cytokine-storm.html (2020).
viral-targeted spherical drug carriers. Biomaterials 31, 1392–1402 (2010).
111. Gutierrez, M., Ojeda, L. S. & Eniola-Adefeso, O. Vascular-targeted particle binding efficacy in the presence of micro- and nanospheres for applications in improved targeting of diseased blood. Biomaterials 12, 1037–1043 (2011).
112. Thompson, A. J. & Eniola-Adefeso, O. Dense nanoparticles exhibit enhanced vascular wall targeting over neutrally buoyant nanoparticles in human blood flow. Acta Biomater. 21, 99–108 (2015).
113. Case, L. M. et al. Exposure of nanoparticles program innate immune cell responses to Toll-like receptor activation. Biomaterials 218, 119353 (2019).
114. Park, J. et al. Intravascular innate immune cells reprogrammed via intravenous nanoparticles to promote functional recovery after spinal cord injury. Proc. Natl Acad. Sci. USA 116, 14547 (2019).
115. Lu, L. et al. Targeted immunomodulation of inflammatory monocytes across the blood-brain barrier by curcumin-loaded nanoparticles delays the progression of experimental autoimmune encephalomyelitis. Biomaterials 245, 119887 (2020).
116. Brannon, E. R. et al. Poly-salicyl acid polymer nanoparticles demonstrate therapeutic efficacy in treating acute respiratory distress syndrome. Adv. Healthc. Mater. 11, 2101554 (2022).
117. Sanguinetti, M. G. et al. Lactate exposure promotes immunosuppressive phenotypes in innate immune cells. Cell Mol. Bioeng. 13, 541–550 (2020).
118. Bisso, P. W., Gaggin, H. G., P. C. & Mitchell, J. M. & Langer, R. Nanomaterial interactions with human neutrophils. ACS Biomater. Sci. Eng. 4, 2425–2432 (2018).
119. Safar, H. et al. Neutrophils preferentially phagocyte elongated particles — an opportunity for selectingtargeting in acute inflammatory diseases. Sci. Adv. 6, eaba1472 (2020).
120. Allen, R. P., Bolandparvar, A., Ma, J. A., Manickam, V. A. & Lewis, J. S. Latent immunosuppressive activity of poly(salicyl-c-glycolic acid) microparticles. ACS Biomater. Sci. Eng. 4, 900–918 (2018).
121. Danhier, F. et al. PLGA-based nanoparticles: an overview of biomedical applications. J. Control. Release 161, 505–522 (2012).
122. Park, K. et al. Injectable, long-acting PLGA formulations: analyzing PLGA and understanding microsphere formation. J. Control. Release 304, 125–134 (2019).
123. Nicollet, R. et al. Nanos, D. F. & Faccioli, L. H. The uptake of PLGA micro- and nanoparticles by macrophages provokes distinct in vitro inflammatory response. Int. Immunopharmacol. 11, 1557–1561 (2011).
124. Jeong, D. J. et al. Polymeric microspheres as therapeutic systems for the airflow inflammatory diseases. J. Control. Release 235, 72–80 (2016).
125. Baek, J.-S., Yeo, E. W., Lee, Y. H., Tan, N. S. & Loo, S. C. J. Controlled-release nanocapsulating microparticles entrapment for long-term encephalomyelitis in the rat. Drug Des. Dev. Ther. 11, 1707–1717 (2017).
126. Nakagawa, Y. et al. Apoptotic cell-injured polymeric particles for controlling microglial inflammatory signaling toward neurodegenerative disease treatment. ACS Biomater. Sci. Eng. 5, 5705–5713 (2019).
127. Harelet-Adar, T. et al. Modulation of cardiac macrophages by phagolysosome-presenting liposomes improves infarct repair. Proc. Natl Acad. Sci. USA 108, 1827 (2011).
128. Erdmann, L. & Urich, K. E. Synthesis and degradation characteristics of silycic acid-derived poly(anhydride esters). Biomaterials 21, 1941–1946 (2000).
129. Rosario-Meléndez, R., Yu, W. & Urich, K. Biodegradable polyesters containing ibuprofen and naproxen as nanoscale drug carriers. Biomacromolecules 14, 5542–5548 (2013).
130. Rosario-Meléndez, R., Quimet, M. A. & Urich, K. E. Formulation of silycic acid-based poly(anhydride ester) microspheres for silycic acid delivery. Polym. Bull. 70, 345–351 (2013).
131. He, L. et al. Dual-stimuli responsive polymer micelles for drug delivery in pH-responsive microspheres for silycic acid delivery. Biomacromolecules 13, 3426–3435 (2012).
132. Lee, S. et al. Dual-stimuli responsive polymer micelles for drug delivery in pH-responsive microspheres for silycic acid delivery. Biomacromolecules 13, 3426–3435 (2012).
133. Park, J. et al. Interactions of nanoparticles with endothelial cells in inflammation/injury. Biomaterials 26, 661–670 (2005).
134. Sharma, G. et al. Polymer particle shape independently influences binding and internalization by macrophages. J. Control. Release 147, 408–412 (2010).
135. Costello, M. J. et al. Influence of drug particle size and shape on their margination and wall-adhesion: implications in drug delivery vehicle design across nano-to-micro scale. Biomaterials 130, 15930–15946 (2016).
136. Namdee, K. et al. Using shape effects to target vessel-endothelium. Beilstein J. Nanotechnol. 5, 776 (2014).
137. Dangupta, S., Aust, T. & Gompert, G. Shape and orientation matter for the cellular uptake of nanoparticles across non-phagocytic cell types. Adv. Funct. Mater. 25, 1–13 (2015).
138. Nikep, L. et al. Dynamically deformable protein delivery strategy disassembles neutrophil extracellular traps to prevent liver metastasis. Adv. Funct. Mater. 31, 2105089 (2021).
139. Poole, K. M. et al. ROS-responsive microspheres for on demand antioxidant therapy in a model of diabetic peripheral arterial disease. Biomaterials 41, 166–175 (2015).
140. Pacifici, N. & Bolandparvar, A. & Lewis, J. S. Stimuli-responsive biomaterials for vaccines and immunotherapeutic applications. Adv. Ther. 3, 1–12 (2001).
141. Malachowski, T. & Hassell, A. Engineering nanoparticles to overcome immunological barriers for enhanced drug delivery. Adv. Drug Deliv. Rev. 157, 161–178 (2020).
142. Caho, D. et al. Quantification and characterization of PECDglycopolycyanacrylate nanoparticles in brain and spinal cord during experimental allergic encephalomyelitis in the rat. Eur. J. Neurosci. 15, 1317–1326 (2002).
143. Chen, K. H. et al. Nanoparticle distribution during systemic inflammation and organ-specific. Nano Lett. 7, 15865–15872 (2017).
144. Pralad, J. et al. Effect of particle size on the biodistribution of nano- and microparticles following intra-arterial injection in mice. Int. J. Pharm. 498, 119–129 (2020).
145. Namdee, K., Thompson, A. J., Charoenphol, P. & Eniola-Adefeso, O. Molecular tuning of vascular-targeted spherical nanoparticles for improved target delivery (review). Mol. Membr. Biol. 27, 190–205 (2010).
146. Gerts, D. et al. Therapeutic inflammatory monocyte modulation using immune-modifying microparticles. Sci. Transl. Med. 6, 219ra217 (2014).
147. Champion, J. A. & Mitragotri, S. Role of target geometry in phagocytosis. Nat. Rev. Drug Discov. 10, 49350 (2010).
148. Champion, J. A. & Mitragotri, S. Shape induced inhibition of phagocytosis by particulate drug carriers. Pharm. Res. 26, 244–249 (2009).
149. Yoo, J. W., Chambers, E. & Mitragotri, S. Factors that control the circulation time of nanoparticles: challenges, solutions and future prospects. Curr. Pharm. Des. 16, 2298–2307 (2010).
150. Dangupta, S., Aust, T. & Gompert, G. Shape and orientation matter for the cellular uptake of nanoparticles. Nano Lett. 14, 687–693 (2014).
151. Sharma, G. et al. Polymer particle shape independently influences binding and internalization by macrophages. J. Control. Release 147, 408–412 (2010).
152. Costello, M. J. et al. Influence of drug particle size and shape on their margination and wall-adhesion: implications in drug delivery vehicle design across nano-to-micro scale. Biomaterials 130, 15930–15946 (2016).
153. Namdee, K. et al. In vivo evaluation of vascular-targeted spherical microparticles for imaging and drug delivery application. Atherosclerosis 237, 279–286 (2016).
154. Thompson, A. J., Mastrina, E. M. & Eniola-Adefeso, O. The marginization propensity of ellipsoidal micro- and nanoparticles to the endothelium of human blood flow. Biomaterials 34, 5865–5871 (2013).
155. Da Silva-Candia, A. et al. Shape effect in active targeting of nanoparticles across the endothelium under static and flow conditions. J. Control. Release 309, 94–105 (2019).
156. Kolhar, P. et al. Using shape effects to target antibody-coated nanoparticles to lungs and brain endothelial cells. Proc. Natl Acad. Sci. USA 110, 10753 (2013).
158. Wilnrow, P. et al. Bypassing adverse injection reactions to nanoparticles through shape modification and attachment to erythrocytes. *Nat. Nanotechnol.* 12, 589–594 (2017).

159. Grasser, A., Radel, A., Pauke, B. & Müller, R. Influence of surface charge density on protein adsorption on polymeric nanoparticles: analysis by two-dimensional electrophoresis. *J. Am. Chem. Biol.* 54, 165–170 (2020).

160. Pustulka, S. M., Ling, K., Pish, S. L. & Champion, J. A. Protein nanoparticle charge analysis and hydrophobicity govern protein corona and macrophage uptake. *ACS Appl. Mater. Interf.* 12, 68284–68295 (2020).

161. Walkley, C. D., Olsen, J. B., Gao, H., Emil, A. & Chen, W. Complement activation in brain injury: diversification of complement chemistry determine serum protein adsorption and macrophage uptake. *J. Am. Chem. Soc.* 134, 21394–21407 (2012).

162. Perry, J. et al. PEGylated PRINT nanoparticles: the impact of PEG density on protein binding, macrophage association, biodistribution, and immunomodulation. *Nano Lett.* 12, 5530–5540 (2012).

163. Yang, Q. et al. Evading immune cell uptake and clearance requires PEG grafting at densities substantially exceeding the minimum for brush formation. *Mol. Pharm.* 12, 1250–1258 (2014).

164. Shen, T. et al. Distribution and cellular uptake of PEGylated nanoparticles in the lung towards cell-specific targeted delivery. *Pharm. Res.* 32, 3248–3260 (2015).

165. Kooi, G. J. et al. Pseudo-anaphylaxis to polyethylene glycol (PEG)-coated liposomes: roles of anti-PEG IgM and complement activation in a porcine model of human anaphylaxis reactions. *ACS Nano* 13, 9531–9534 (2019).

166. Moghimi, S. M. et al. Complement activation cascade triggered by PEG-coated nanoparticles: the role of PEG and carbon nanotubes: the challenges ahead. *J. Control. Release* 146, 175–181 (2010).

167. van Raaij, P. J. et al. Pre-existing anti-polyethylene glycol antibodies: possible evidence for first-exposure allergic reactions to pegyvacig, a PEGylated RNA aptamer. *J. Allergy Clin. Immunol.* 137, 1610–1615.e7 (2016).

168. Salehi-Isfahani, E., Pavan, E. PEGylated glycol-coated systemic allergic reactions (anaphylaxis). *J. Allergy Clin. Immunol. Pract.* 9, 670–675 (2021).

169. Kooi, G. J. et al. PEGylation of siRNA: in vitro and in vivo studies. *Acta Biomater.* 112, 861–865 (2021).

170. Suk, J. S., Xu, Q., Kim, N., Hanes, J. & Ensign, L. M. Protein nanoparticle charge and hydrophobicity association, biodistribution, and pharmacokinetics. *J. Am. Chem. Soc.* 135, 559–568 (2013).

171. Kelley, W. J., Fromen, C. A., Lopez-Cazares, G. & Su, J. S. et al. Polyethylene glycol (PEG) is a cause of human infusion reactions. *J. Control. Release* 353, 123–130 (2018).

172. Ilinskaya, A. N. et al. Nanoparticle physicochemical properties determine the activation of intracellular complement. *Nat. Biotechnol.* 27, 266–275 (2019).

173. Sakurai, T. & Lai, S. K. Anti-PEG immunity: emergence, characteristics, and unanswered questions. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* 7, 655–677 (2016).

174. Fahy, J. V. & Doney, B. F. Airway mucus function and dysfunction. *N. Engl. J. Med.* 363, 2295–2297 (2010).

175. Bobo, D., Robinson, K. J., Islam, J., Thurecht, K. J., Mathaes, R., Winter, G., Siahaan, T. J., Besheer, A., Wang, J. et al. US NCI launches nanotechnology plan. *Nat. Biotechnol.* 5, 66–73 (2010).

176. Fahy, J. V. & Doney, B. F. Airway mucus function and dysfunction. *N. Engl. J. Med.* 363, 2295–2297 (2010).

177. Bobo, D., Robinson, K. J., Islam, J., Thurecht, K. J., Mathaes, R., Winter, G., Siahaan, T. J., Besheer, A., Wang, J. et al. US NCI launches nanotechnology plan. *Nat. Biotechnol.* 5, 66–73 (2010).

178. Fahy, J. V. & Doney, B. F. Airway mucus function and dysfunction. *N. Engl. J. Med.* 363, 2295–2297 (2010).

179. Hua, S., Marks, E., Schneider, J. J. & Keely, S. Advances in oral nano-devices for colon targeted drug delivery. *Int. J. Clin. Pharmacol. Ther.* 41, 83–94 (2013).

180. Masel, K. et al. Nanoparticles coated with high molecular weight PEG penetrate mucus and provide uniform vaginal and colonic distribution in vivo. *Nano. Med.* 11, 1357–1345 (2015).

181. Huckaby, J. T. & Lai, S. K. PEGylation for enhancing nanoparticle diffusion in mucus. *Adv. Drug Deliv. Rev.* 124, 125–139 (2015).

182. Pereira de Sousa, I. et al. Nanoparticles decorated with proteolytic enzymes, a promising strategy to overcome the mucus barrier. *Eur. J. Pharm. Biopharm.* 97, 257–264 (2015).

183. Korn, P. R., Vasik, Z., Pepić, I. & Skalko-Basnet, N. Mucocidal liposomal delivery systems: the choice of coating material. *Drug Dev. Ind. Pharm.* 37, 482–491 (2011).

184. Mahlkönig, A., Tschöp, Y., Kneifel, S. & Senn, H. Mucocidal liposomal delivery systems: choices of coating material. *Eur. J. Pharm. Biopharm.* 72, 1–8 (2009).

185. Mane, V. & Muro, S. Biodistribution and endocytosis of ICAM-1-targeting antibodies versus nanoparticles in...
the gastrointestinal tract in mice. *Int. J. Nanomed.* **7**, 4233–4237 (2012).

231. Huff, R. D., Carlsten, C. & Hirota, J. A. An update on immunologic mechanisms in the respiratory mucosa in response to air pollutants. *J. Allergy Clin. Immunol.* **143**, 1989–2001 (2019).

232. Turner, J. R. Intestinal mucosal barrier function in health and disease. *Nat. Rev. Immunol.* **9**, 799–809 (2009).

233. McLennan, D. N., Porter, C. J. H. & Charman, S. A. Subcutaneous drug delivery and the role of the lymphatics. *Drug Discov. Today Technol.* **2**, 89–96 (2005).

234. Nestle, F. O., Di Meglio, P., Qin, J.-Z. & Nickoloff, B. J. Skin immune sentinels in health and disease. *Nat. Rev. Immunol.* **9**, 679–691 (2009).

235. Randolph, G. J., Angel, V. & Swartz, M. A. Dendritic-cell trafficking to lymph nodes through lymphatic vessels. *Nat. Rev. Immunol.* **5**, 617–628 (2005).

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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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