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Engineering the drug carrier biointerface to overcome biological barriers to drug delivery

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Abstract

Micro and nanoscale drug carriers must navigate through a plethora of dynamic biological systems prior to reaching their tissue or disease targets. The biological obstacles to drug delivery come in many forms and include tissue barriers, mucus and bacterial biofilm hydrogels, the immune system, and cellular uptake and intracellular trafficking. The biointerface of drug carriers influences how these carriers navigate and overcome biological barriers for successful drug delivery. In this review, we examine how key material design parameters lead to dynamic biointerfaces and improved drug delivery across biological barriers. We provide a brief overview of approaches used to engineer key physicochemical properties of drug carriers, such as morphology, surface chemistry, and topography, as well as the development of dynamic responsive materials for barrier navigation. We then discuss essential biological barriers and how biointerface engineering can enable drug carriers to better navigate and overcome these barriers to drug delivery.

Keywords

Drug delivery; Biointerface; Nanomaterials; Physicochemical; Barriers; Mucus; Tight junctions; Biofilm; Immune system; Cell uptake

1. Introduction

Micro and nanoscale drug delivery strategies have been used to increase drug biodistribution and half-lives, control the release rates of drugs, and enable the precise targeting of drugs to biological sites of interest [1]. Drug carriers can range in size from nanoparticles to wearable or implantable macroscale drug reservoirs. However, drug carriers with micro or nanoscale features are particularly attractive, as these carriers can interact with biological systems on the same length scale as cells and cellular processes [2,3]. While such drug carriers

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show promise in improving pharmacokinetics and therapeutic outcomes, achieving effective delivery to target sites remains a challenge. In the field of tumor targeting, recent studies have estimated that less than 1% of intravenously injected nanoparticles reach their tumor target [4]. Significant effort has been made to improve targeting efficiencies of drug carriers via the attachment of cell receptor-targeting ligands on the particle surface [5]. While this is an important step in achieving targeted drug delivery, there are a series of biological barriers present throughout the body that the drug carrier must first overcome in order to reach its target of interest. These biological barriers are numerous and include the bloodstream, epithelial cell barriers, biological hydrogels such as mucus, and the immune system [6,7]. And even upon reaching its cellular target, the drug carrier must effectively navigate intracellular trafficking networks to reach its subcellular target prior to drug degradation and clearance [8].

An important method to overcome these barriers to delivery is through engineering the drug carrier biointerface. The biointerface of the carrier determines how the material interacts with its biological surroundings and how the biological environment reacts to the material [9,10]. The biointerface of a material is primarily determined through its physicochemical properties. These properties include morphological characteristics such as size, shape, and rigidity, as well as surface chemistry and structural topography. Each of these properties plays a unique role in determining how living biological systems will respond to a material, as well as how a drug carrier will navigate through biological barriers [11].

Most approaches to material biointerface engineering have focused on designing the physicochemical properties of a drug carrier to enhance biodistribution and carrier half-life following intravenous administration [12,13]. In addition to carrier biodistribution, there are numerous other biological barriers that require effective navigation, and will be the focus of this review. These barriers include: (1) tissue barriers to drug penetration and access to the bloodstream (depending on administration route), (2) biological hydrogel barriers including mucus and bacterial biofilms, (3) immunological barriers such as immune activation responses and immunogenicity, and (4) cellular barriers that determine uptake and intracellular trafficking of drug carriers. While these barriers are present in all patients, certain diseases can alter the physiological makeup of these barriers [7,14]. Notable examples include the permeation of the blood-brain barrier (BBB) in glioblastoma multiforme patients, increased lung mucus stiffness in cystic fibrosis patients, and changes in the immune system in immunocompromised patients. Thus, it is important to finetune the biointerface of a drug carrier not only for standard biological barriers, but also for the altered physiological barriers of the disease target.

Importantly, all these biological barriers are dynamic systems that change not only in response to disease states, but also to small perturbations in their local microenvironments [15,16]. This can pose challenges to effective navigation of these barriers, as dynamic barrier properties can be difficult to predict. However, it also presents immense opportunities in materials-based manipulation and navigation of biological barriers, as appropriately designing materials and drug carriers to dynamically engage with biological barriers could facilitate improved drug delivery. While designing drug carriers, it is important to note that the irreversible manipulation or permeabilization of biological systems can cause severe side

effects [16]. Materials-based approaches are therefore particularly attractive, as the barrier only engages with the material with which it is in direct physical or chemical contact, and thus can return to its resting state after engaging with the drug carrier biointerface. In this review, we will provide a brief overview of the engineering approaches used to modify key physicochemical properties of drug carriers. We will then discuss critical biological barriers to targeted therapies and how biointerface engineering can enable drug carriers to better navigate and overcome these barriers to drug delivery (Fig. 1).

2. Design parameters to influence the drug carrier biointerface

Drug carriers have been developed from a wide variety of material components using numerous fabrication techniques. For each of these carrier classes, the biointerface with the biological barrier of interest can be modified through physicochemical engineering of the material. The three most important engineering parameters to consider are the drug carrier morphology, surface chemistry, and surface topography. Additionally, dynamic materials that undergo changes in physicochemical properties in response to biological stimuli could hold promise in navigating multiple biological barriers. In this section, we will briefly describe each of the key material design parameters, how they influence carrier biointerfaces, and some of the fabrication and chemical methods used to engineer these features.

2.1. Morphology

The morphology of drug carriers consists of the size, shape, and rigidity of the material. These parameters are especially important for particle-based approaches to drug delivery but are also important in the fabrication of micro or nanostructured elements onto macroscale drug reservoirs or delivery devices. The morphology of the drug carrier particle influences every aspect of its biointerface regardless of the material that the drug carrier is composed of, including inorganic particles [17,18], self-assembling peptide and protein biomaterials [19–21], and synthetic polymeric particles [22–24]. Morphology, in addition to surface chemistry, plays an important role in determining how particles traverse through the bloodstream and develop a protein corona [25], as well as how particles penetrate through size-limited biological barriers such as mucus hydrogels with finite pore sizes [26]. While the size of a particle is the most studied morphological consideration for drug delivery, both particle shape and rigidity also play key roles in determining how a material traverses barriers and interacts with biological systems. For instance, shape will determine tumbling mechanics of particles through the bloodstream and biological barriers, as well as the surface contact area between a drug carrier and a biological surface [11]. Particle rigidity is a less studied but oftentimes important parameter for drug delivery, as particle rigidity can influence overall biodistribution and ease of permeation through biological hydrogels [23,27]. Additionally, the stiffness of a material surface will have significant consequences for how that material is perceived by immune cells such as macrophages [28].

Controlling the size of particles is possible with every major fabrication technique and material component. For inorganic systems, this is in part controlled by adjusting concentrations of chemical components that make up the particle core and capping ligands

such as citrate ions in the case of gold or silver nanoparticles [29]. Polymeric particles can be fabricated using a variety of techniques, including emulsions, microfluidics, 3D printing, ion spray, and others. For each of these methods, there are stages of the fabrication process that enable finetuning the size of the particle, both by adjusting chemical components and concentrations, as well as through engineering optimization such as sonication strengths, flow rates, and temperature [30,31]. Microfluidics techniques perhaps offer the most control over particle size, with near homogeneity in particle morphologies and almost no batch-to-batch variability [31–34]. In self-assembling materials, size is typically limited to an upper regime of hundreds of nanometers for spherical particles, although size can be controlled within the nanometer length scale by adjusting the monomeric components, as well as the noncovalent forces that drive self-assembly such as hydrophobicity, electrostatics, and hydrogen bonding [35].

Particle shape is another important aspect for the carrier biointerface. While the vast majority of particle drug carriers are spherical, other asymmetric shaped particles have been reported [27]. The diversity in shape of inorganic particles is more significant, while polymeric particle shape is primarily limited to spheres, rods, ellipsoids, and disks. Nonspherical particles can be designed using self-assembling systems, as well as through microfluidics and lithographic techniques for polymeric particles [36]. Other specialized techniques can be used, such as nanotemplating of thermoplastic polymers to fabricate high aspect ratio materials [37,38], the PRINT method to generate micro and nanoparticles of controlled shape and size [39], or film-stretching techniques used to convert polymeric spherical particles into rods and ellipsoids of varying aspect ratio [40]. Some of these advanced techniques offer control over the rigidity of the particle, although this characteristic can also be tuned by adjusting polymer composition and concentration within the particle core [11].

2.2. Surface chemistry

The chemistry on the surface of drug carriers is perhaps the most important component to engineer in order to control the material biointerface, as the material surface is in direct contact with biological systems. To control interactions between the drug carrier surface and the biological barrier of interest, it is essential to consider the surface chemistry not just of the drug carrier, but also of the biological barrier. If adhesive forces are desired, then complementary electrostatic interactions can be installed onto a material surface, as is the case with positively charged chitosan-coated drug carriers designed to adhere onto negatively charged mucosal surfaces [41,42]. Alternatively, negatively charged surfaces can be fabricated to enable fast mucus penetration [43,44]. In addition to surface charge, hydrophobicity is an important parameter to consider when designing a material surface. This will influence permeation through biological hydrogels, interactions with cell membranes, and formation of protein corona on the carriers in the bloodstream [11,25]. Lastly, engineering the material surface chemistry can be extended to include the attachment of binding ligands onto particles for enhanced cellular targeting and uptake, and that topic has been covered elsewhere [5].

Surface chemistry can be altered through changing the core material component of the drug carrier, or through post-fabrication modification of the material surface. For polymeric drug carriers, the use of block copolymers offers the ability to display diverse chemical handles on material surfaces [44,45]. This is particularly beneficial with the use of hydrophobic-hydrophilic co-polymers such as those composed of poly (lactic co-glycolic acid) (PLGA) and poly(ethylene glycol) (PEG). PLGA-PEG components can be mixed with filler PLGA polymers to create PLGA particles with PEG decorated on the surface through the phase separation of hydrophilic PEG from hydrophobic PLGA [44–47]. This strategy have been used to improve systemic circulation time of carriers owing to decreased immunogenicity due to the protection offered by PEGylation. This method also works well with self-assembling systems, whereby different monomers can be mixed together in varying concentrations to decorate the surface of drug carriers with functional chemical handles, or to change the material surface properties such as charge or hydrophobicity [35,48].

Post-fabrication functionalization of particles offers a more robust method of surface functionalization, as the reaction conditions available for surface functionalization are less harsh than during particle fabrication. However, post-fabrication functionalization can be less efficient in reaction conversion and can limit control over surface ligand density, as reaction conditions and kinetics can be difficult to control on particle surfaces. Using this approach, particles are first fabricated to display a chemical handle, either with a single material system, or by using copolymers [45,47]. Conjugation chemistry is then employed to modify the surface of a particle with the chemical group of interest. As most particle systems are colloidal suspensions in water, bioconjugation chemistries such as azide-alkyne click chemistry, as well as host-guest supramolecular interactions are particularly amenable to material modification in aqueous solutions [49–51]. For inorganic particles, direct chemical modification of the surface can be achieved through silanization of silica particles or through thiol-mediated conjugation [52]. An alternative approach to post-fabrication surface functionalization is through the use of layer-by-layer (LbL) assembly. LbL takes advantage of noncovalent forces such as electrostatics or hydrogen bonding to deposit polymers of complementary interactions onto the surface of materials [53]. LbL has been used extensively to modify the surface of drug carriers, although the binding strengths and lifetimes of layer depositions remain unclear.

2.3. Surface topography

While micro and nanotopography has been researched extensively within the fields of biofouling and tissue engineering, surface topography can also play a key role in the interactions between materials surfaces and biological barriers to drug delivery, including epithelial tight junction permeabilization, cellular membrane penetration, and immune system interactions [28,54,55].

There are several fabrication techniques to install topography on material surfaces including top-down and bottom-up techniques that are reviewed elsewhere [56]. Lithographic techniques are commonly employed and include photolithography, colloidal lithography, and nanoimprint lithography [33]. Chemical vapor deposition and reactive ion etching, as well

as micromachining, deposition of electrospun nanofibers, and 3D printing have also been employed in the fabrication of topographically functionalized materials [56]. Each method offers distinct advantages and challenges, including size limitations to achieve nano versus microstructures, as well as reproducibility and throughput of the technique. All of these topographical techniques were originally designed for macroscale materials, although the nanotopographical functionalization of microparticles has also been reported [57–61].

2.4. Dynamic responsive materials

Engineering the morphology, surface charge, and/or surface topography of drug carriers can allow for the effective navigation through a chosen biological barrier. However, oftentimes drug carriers must overcome multiple barriers to enable effective tissue targeting and drug delivery. These barriers are unlikely to require the same physicochemical parameters for effective biointerfacing, and therefore the design of innovative dynamic drug carriers that can switch physicochemical properties based on physiological context would be highly desirable. Dynamic materials have been developed to respond to numerous biological stimuli including pH, redox, enzymes, and temperature [62]. Within the context of drug delivery, these responsive materials have been primarily developed to improve the drug localization to the target site. While this approach is important to the field of drug delivery, we instead focus in this review on materials that alter their physicochemical properties such as surface charge or morphology in response to a stimulus of interest in order to overcome a biological barrier to drug delivery. We also highlight stimulus-responsive nano and micromotors, which can alter particle movement dynamics depending on the presence of biological or chemical stimuli [63].

The design of dynamic materials requires advanced fabrication and chemical modification to enable responsive behavior with sufficient kinetics and physicochemical changes. Of the dynamic properties explored in drug carrier systems, charge-switching behavior may be the most studied. This can be achieved through a variety of means, including pH-induced charge changes or through the stimulus-responsive cleavage of negatively charged moieties to expose positive charges [62,64]. Hydrophobic switching has also been explored for drug delivery. The Gianneschi group used matrix metalloproteinase (MMP) -induced cleavage of a peptide sequence to expose a hydrophobic regime on a nanoparticle surface. Not only did this facilitate hydrophobic switching of the particle, but also caused nanoparticle aggregation and clustering in the region of MMP expression, which was used to target tumors and sites of myocardial infarction [65,66]. Stimulus-responsive morphological changes of materials is more challenging, but has also been reported for applications in drug delivery [62,67,68]. This can be achieved through the stimulus-responsive swelling of hydrogel nano and microparticles, or through the responsive shedding of nanolayers on top of a particle core. Size-switching behaviors can also be accomplished through the cleavage of interparticle connections. This approach was recently taken by Loynachan et al. to induce MMP-responsive particle size-changes of gold nanoclusters to facilitate renal clearance of catalytic gold for the colorimetric urine detection of colon cancer in mice [69]. Thus, there are a variety of chemical and engineering tools available to create dynamic responsive materials that change physicochemical properties in response to a unique biological barrier.

3. Biological barrier navigation with engineered drug carriers

Following administration, drug carriers must traverse a series of barriers and obstacles prior to reaching their disease targets. The body erects active barriers to drug delivery, which include tissue barriers, biological hydrogels, the immune system, and cellular trafficking pathways. These biological barriers are necessary physiological components that protect the body from invading pathogens and maintain homeostasis, however they also pose unique challenges to drug carrier entry and navigation to their tissue target. In this section, we will provide examples of innovative material designs that allow dynamic biointerfacing between drug carriers and biological barriers to improve drug delivery outcomes. For each barrier we highlight, we will briefly describe the barrier biology, the challenges it poses, and provide examples of material biointerface design parameters (morphology, surface chemistry, surface topography, and dynamic materials) to overcome these biological barriers to drug delivery.

3.1. Tissue barriers

Tissue barriers are the most widespread biological barriers for drug delivery. These barriers are composed of closely packed cells that can limit drug penetration into the bloodstream by inhibiting both transcytosis through and across the cell, and paracellular transport between cells [70]. Between closely packed epithelial cells are multiprotein complexes called tight junctions (TJs), which act as gatekeepers to paracellular transport. TJs are found just below the apical surface of cells and are composed of a series of claudin and occludin proteins, as well as the membrane protein zonular occludens 1 (ZO-1), which functions as a key player in regulating TJ activity [71]. Epithelial barriers and TJs pose challenges for numerous drug delivery targets and administration routes, including ocular, transdermal, oral, and lung delivery [70]. In addition to epithelial barriers, endothelial barriers can also inhibit drug transport, as is the case with the blood-barrier (BBB), which limits the delivery of therapeutics to the brain following intravenous administration [70,72]. Tight junctions are dynamic systems that can be remodeled in response to biological or chemical cues. Small molecules have been studied for decades to remodel TJs and induce paracellular drug transport [16]. However, intact tissue barriers are necessary to maintain proper health and homeostasis of biological systems, and it is therefore essential that TJs not be permanently damaged. This is especially true in the field gastrointestinal (GI) drug delivery, where permeabilized tissue barriers could lead to the transport of microbiota out of the GI tract, causing infectious microbial colonization elsewhere in the body. Thus, materials-based strategies that reversibly remodel TJs and deliver cargo at the cell barrier are particularly promising for drug delivery. An alternative strategy is to design drug carriers that can directly penetrate though tissue barriers as intact particles and then deliver their cargo to the drug target [73].

3.1.1. Tight junction remodeling with drug carriers—The surface chemistry of drug carriers is a key parameter in the modulation of TJ behavior. One application of TJ remodeling is in the delivery of insulin via oral administration. Epithelial TJs and gastrointestinal (GI) mucus barriers that lie atop the epithelial lining impair insulin penetration across the GI tract into the bloodstream, thereby limiting its bioavailability [74]. To develop a nanoparticle-based approach to improve oral insulin delivery, Lamson

et al. studied the effects of surface charge and particle size on TJ remodeling [75]. The researchers found that small (<200 nm) anionic particles induced the most dramatic barrier permeabilization, as observed in Caco-2 cell monolayers (Fig. 2a). TJ remodeling via silica particles was shown to be integrin-mediated and reversible. Based on these *in vitro* findings, 50 nm silica particles were chosen for in vivo therapeutic studies, as they maintained a balance between sufficient mucus permeation and TJ remodeling. The researchers were able to achieve blood glucose correction in diabetic mice following oral co-delivery of insulin and silica particles within pH-responsive capsules. They further observed an estimated dose-adjusted bioactivity of 23% that of subcutaneous insulin injection, demonstrating improved bioactivity over other reported nano and microtechnology based approaches to insulin delivery. This phenomenon of TJ-remodeling through materials biointerface engineering has also been demonstrated with other systems, including gold nanoparticles [76], carbon nanomaterials [77], polymeric nanoparticles [78], and protein-based nanofibers [79]. This diverse portfolio of TJ-remodeling materials highlights the immense potential of this drug delivery strategy to improve the bioactivity of orally administered therapeutics.

In addition to surface electrostatics, certain biofunctional chemical motifs displayed on the surface of a material can facilitate TJ remodeling and permeabilize epithelial barriers. Of the chemical handles studied, chitosan polymers have shown the most promise in the reversible modulation of TJs [81]. Chitosan is a polysaccharide that is generated from the deacylation of chitin amides into amines to create a positively charged biomaterial. Chitosan and its derivative trimethyl chitosan have been used for decades in diverse biomaterial applications including wound healing, antimicrobial applications, mucoadhesion, and oral drug delivery [81]. It is hypothesized that the positive charge of chitosan binds to glycosylated portions of key TJ proteins such as integrins and claudin-4 to facilitate remodeling and permeabilization of barriers [81,82]. Since this discovery nearly 30 years ago, chitosan has been explored as a soluble polymer for TJ remodeling. Importantly, when attached to the surface of materials either through covalent chemistry or through electrostatic adsorption, chitosan retains its TJ remodeling properties [42,80,83,84].

While chitosan has been shown to remodel TJs and facilitate paracellular transport, it is also a mucoadhesive, which could limit the penetration of TJ-remodeling materials through mucus layers to reach the epithelial barriers that need to be remodeled. To overcome this issue, Liu et al. developed a dynamic polymeric drug carrier that contained insulin in its trimethyl chitosan core to facilitate TJ remodeling, followed by an external layer of *N*-(2-hydroxypropyl) methacrylamide copolymer (pHPMA), which is a mucoinert polymer (Fig. 2b) [80]. With the pHPMA coating, nanoparticle size was approximately 160 nm and had a slightly negative surface charge to increase mucus penetration. As the nanoparticle permeated through mucus barriers, the pHPMA coating was shed off to expose trimethyl chitosan for tight junction remodeling and paracellular transport of insulin. Using this approach, the researchers were able to maintain serum insulin levels for 10 hours following oral delivery. A hypoglycemic response was observed with a blood glucose decrease of 36% after 4 hours and maintenance of blood glucose levels for an additional 6 hours. This study highlights the power of combined materials engineering to design a particle with the morphology, surface chemistry, and dynamic properties necessary to navigate and overcome multiple biological barriers to drug delivery.

Another important strategy to induce TJ remodeling is through the application of micro or nanotopographical structures onto a material surface. Many cell types are sensitive to topographical cues and change behavior in response to physical contact with materials [3]. Several studies from the Desai lab have demonstrated that physical engagements between a nanotopographical surface and cellular monolayers initiate TJ remodeling and increase penetration of biologic cargo such as antibodies across epithelial barriers [54]. This TJ remodeling was characterized by a morphological ruffling of Caco-2 cellular membranes and ZO-1 expression when in contact with nanostructured films (Fig. 3a) [85]. This phenomenon is also hypothesized to be mediated through integrin-ligand engagement, as well as dynamic claudin and ZO-1 rearrangements [54,86]. This approach was studied not just for oral delivery, but also for transdermal penetration of drugs. Using a nanostructured microneedle dermal patch with a drug reservoir, Walsh et al. demonstrated increased serum concentrations of the drug Etanercept in a rabbit model (Fig. 3b), attributed to the integrin-mediated remodeling of dermal tight junctions [87]. In another study, Uskokovic et al. used silicon nanowire-coated particles to induce similar tight junction remodeling and increased epithelial barrier permeabilization for oral drug delivery [57]. The authors also investigated the effects of particle morphology on tight junction remodeling and demonstrated that flat particles increased remodeling and permeabilization, likely owing to increased surface area contact [88]. In a recent study published by the Mullertz group, microcontainers were used for the oral delivery of insulin [89]. The authors demonstrated the importance of maintaining microcontainer proximity to the cell surface, further strengthening the hypothesis that maximizing the biointerface between the material and the biological surface is key for epithelial permeabilization. Taken together, these studies demonstrate that a combination of surface chemistry, morphology, surface topography, and dynamic materials can be used to enhance the biointerface between a drug carrier and epithelial barriers to increase drug transport.

3.1.2. Drug carriers to penetrate tissue barriers—One of the most important parameters for efficient drug delivery using engineered drug carriers is their pharmacokinetics and pharmacodynamics [90]. Depending on the administration route, for effective drug absorption and distribution, penetration across tissue barriers is the first hurdle to overcome. The skin is the most attractive route for drug administration due to its accessibility, however it is also one of the most difficult tissue barriers to overcome. Successful transdermal delivery is dependent on the penetration and disruption of the outermost layer of the skin, the stratum corneum [91]. Engineered drug carriers have been successfully used as an alternative to unpleasant and painful injections for drug delivery applications and vaccination.

Microneedles (MNs) have been widely used for transdermal drug delivery through the penetration of stratum corneum but without penetrating deep enough to stimulate nerves [91,92]. MNs are formulated to deliver small molecules, macromolecules or carriers allowing a highly localized and effective delivery [90,93,94]. McAllister et al. demonstrated an increase in *in vitro* skin permeability for macromolecules and nanoparticles up to 50 nm in radius by using solid MNs made of silicon, metal or biodegradable polymers [95]. Another interesting application of MNs is fluid flow of small molecules,

macromolecules, polymer microparticles and cells through hollow glass MNs, allowing a precise microinjection into skin [96]. Hollow glass MNs have been used to allow a flow of microliter quantities of insulin into skin to modulate successfully blood glucose levels in diabetic rats [95]. In addition to the MNs, nanoneedles (NNs) have been developed to provide an efficient intracellular delivery of small molecules and biopharmaceutics as well as an intracellular sensing. Due to its barrier penetrating properties and high transfection efficacy, NNs, made by silicon, metal or biodegradable polymers, are one of the most promising tools for efficient intracellular delivery of nucleic acids [97–100].

The BBB is an impermeable structure that limits the delivery of therapeutic small molecules or biopharmaceutics into the healthy brain. Local brain delivery of therapeutic molecules is difficult to achieve, so engineered drug carriers have been used to overcome the low brain drug bioavailability. Polymeric nanoparticles, liposomes, lipid nanoparticles, dendrimers and inorganic nanoparticles have been formulated to overcome the BBB and achieve increased brain pharmacokinetics [101]. Aiming a targeted therapy to the brain, engineered drug carriers can be modified at the surface with a ligand. Many different receptors found in the brain can be targeted for drug delivery, including the transferrin receptor, insulin receptor, low-density lipoprotein receptor, and others [102]. Active targeting to those receptors with a peptide, peptide fragment, antibody or antibody fragment could allow higher uptake into the brain, resulting in a higher drug concentration. Anraku et al. formulated a self-assembled supramolecular nanocarrier functionalized with glucose to target glucose transporter-1 in brain capillary endothelial cells [103]. This strategy allowed a higher brain accumulation of this engineered drug carrier correlated with a rapid glycemic increase after a fasting state.

In addition to receptor targeting, the morphology and surface charge of drug carriers play an important role in enhancing BBB penetration. Several studies have shown increased penetration of rod-shaped particles over spherical particles in *in vitro* BBB models, as well as in mouse models of GBM [11,104–107]. Particle size is another important morphological characteristic that influences BBB penetration, with smaller particles oftentimes penetrating faster than larger particles, although there are conflicting reports, with some studies demonstrating a peak particle accumulation at a middle size regime [104]. These conflicting results are likely due to differences in particle composition, surface charge, and in the animal models used in the studies. Lastly, surface charge interactions with the BBB influence barrier penetration. Some studies have demonstrated that positively charged particles increase penetration through the BBB, although other studies reported the penetration of neutrally charged PEGylated particles across blood-brain barriers [106,108,109]. Using a bio-inspired approach, Lee et al. fabricated gold nanorods that mimicked the size, shape, and surface properties of rabies virus capsids [110]. These rabies-inspired nanorods demonstrated significant tumor uptake in orthotopic glioma mouse models following IV injection. The authors also used the nanorods for photothermal therapy to shrink tumors in a xenograft model. Despite these innovative approaches to increase BBB penetration and treat brain tumors, further studies are needed to elucidate the permeability of the BBB in GBM patients and mouse models, and how the physicochemical properties of drug carriers can be engineered to enhance BBB penetration and therapeutic outcomes.

3.2. Biological hydrogels

Biological hydrogels are present throughout the body and pose significant barriers to effective drug delivery, as drugs and drug carriers must navigate through hydrogels prior to reaching their disease target. Similar to other hydrogel systems, biological hydrogels have inherent porosities and material properties that limit the penetration of particles through steric filtering and chemical interactions such as electrostatics [26]. In contrast to synthetic hydrogel systems, biological hydrogels are dynamic biomaterials that undergo perturbations and alterations to their chemical and mechanical properties in order to maintain homeostasis, or in response to disease or stress [15].

One of the most studied biological hydrogels is mucus. Mucus is a dynamic hydrogel barrier that prevents the penetration of toxins and pathogens from one organ to another, but also poses significant challenges for oral, retinal, lung, and vaginal delivery, as the same mucus hydrogels that prevent pathogen penetration also inhibit the movement of particle drug carriers [7,26,111]. Mucus is composed of a plethora of biomaterials including mucin protein filaments, which contain hydrophobic regions as well as heavily glycosylated anionic regions. In addition to mucin, nucleic acids, lipids, oligo and polysaccharides, and other proteins are found in mucus hydrogels. The mechanical properties of mucus vary depending on the tissue location as well as the disease state of the patient. For instance, the mucus in the lungs of cystic fibrosis (CF) patients is significantly stiffer than those found in healthy patients, in part due to a combination of factors including increased nucleic acid content from bacterial infections and increased neutrophil-mediated oxidation and disulfide formation between mucin proteins [112]. While mucus barriers restrict the penetration of drug carriers to their targets, mucus also provides opportunities for particle adhesion and increased retention times, which can have beneficial impacts in specific applications, most notably oral drug delivery. One of the main strategies to facilitate drug adsorption into the bloodstream after oral administration is through increased carrier retention within the large intestine and colon [55]. By designing material biointerfaces to increase mucoadhesive properties, prolonged colonic retention and drug release is possible.

Bacterial biofilms are another important class of biological hydrogels. Rather than living in free floating planktonic states, many pathogenic bacteria surround themselves in biological hydrogels that promote bacterial attachment and growth on surfaces and impede the penetration of antibiotics into the biofilm [113]. Through a combination of resistance mechanisms, bacterial biofilms can cause infections that are over 1000-fold resistant to antibiotics compared to their planktonic counterparts [113,114]. Biofilms have been estimated to occur in a majority of human infections and are particularly pervasive in chronic wounds, CF lungs, medical implants, and *C. difficile* infections in the colon [113]. The bacterial biofilm matrix, or “extracellular polymeric substance” (EPS), is composed of negatively charged polysaccharides, nucleic acids, and proteins [115]. Biofilm hydrogels have different porosities and mechanical properties depending on the bacteria species within the biofilm, as well as the location of the infection. In contrast to mucus hydrogels, biofilms are not only biological barriers for drug delivery, but also drug targets. Therefore, a balance must be struck between drug carrier attachment to biofilms and permeation throughout the biofilm hydrogel to achieve maximal antimicrobial activity and biofilm disruption.

3.2.1. Mucoadhesive drug carriers—Mucoadhesive materials can improve tissue retention of drug carriers and delivery efficacies. This is highly desirable for applications such as oral drug delivery, where increased retention in the GI tract can improve penetration of the drug cargo into the bloodstream [55]. Surface chemistry is one of the primary methods of biointerface engineering that has been employed in the design of mucoadhesive drug carriers [116]. As mucin fibers contain regions of dense glycosylation, electrostatic interactions are often employed to increase mucoadhesive properties. Positively charged chitosan biopolymers have been used as mucoadhesive biomaterials and are either covalently attached or electrostatically assembled onto drug carriers. By using chitosan as a mucoadhesive, researchers have demonstrated increased drug carrier tissue retention and drug delivery efficacies for numerous applications and delivery routes, including oral drug delivery of biologics and pulmonary delivery of antimicrobials to treat lung infections [41,116–120]. In addition to electrostatics, hydrophobic material coatings can play a role in increasing mucoadhesive properties, owing to the hydrophobic regions found on mucins [26,116]. To demonstrate this, Sonia et al. acylated, to varying degrees, chitosan polymers with hydrophobic aliphatic chains and found that microparticles bearing hydrophobic chitosan moieties had increased mucoadhesive properties [42]. Lastly, modification of chitosan with thiol-containing groups has been shown to increase mucoadhesive properties through the formation of disulfides with mucin strands [121]. Thus, a combination of electrostatics, hydrophobicity, and reactive chemical display can be used to increase mucoadhesion and tissue retention of chitosan-functionalized drug carriers.

In addition to chitosan-based strategies, other polymer-coated particles have been used to increase mucoadhesion. These strategies rely on physical entanglement between the protruding polymers of the drug carrier and the mucus hydrogel network. Such strategies have been employed using diverse polymers, including poly(acrylic acid), alginate, pectin, and cellulose and have seen success in oral, lung, and vaginal drug delivery [26,116]. Nanotopography can be used in a similar vein to promote mucoadhesion through increased entanglement of a drug carrier within mucus hydrogels. Fischer et al. fabricated silicon nanowire-coated microparticles and demonstrated increased gastrointestinal mucoadhesion compared to noncoated particles in canine models (Fig. 4a) [122]. The authors further characterized their systems *in vitro* by analyzing the retention of particles on mucus-coated cellular monolayers under flow. They found that not only do nanowire coatings increase particle retention, but that installing positively charged amine residues onto the nanowire surfaces using silane chemistry can further increase mucoadhesive properties. Subsequent studies investigated how material aspect ratio influenced nanostructured microparticle adhesive properties, with higher aspect ratio particles demonstrating increased adhesion [55]. Taken together, these studies highlight how surface properties of a material such as electrostatics, hydrophobicity, and surface topography can be engineered to increase mucoadhesion and subsequent tissue retention for improved drug delivery.

Nano and micromotors are a new class of drug carriers that have seen recent interest for mucoadhesion and oral drug delivery. Micromotors are dynamic materials that contain gas-producing catalysts, which drive the movement of the drug carrier through fluids and biological systems [63]. Micromotors therefore do not solely rely on traditional tumbling

mechanics or Brownian motion to facilitate transit through mucus layers. This new material property of active motion has been explored by the Zhang lab as a means to induce mucus adhesion, as micromotors can actively embed themselves into mucus barriers [124–126]. In a recent example, Wei et al. used these micromotors to deliver antigens via oral administration [123]. The authors used a magnesium microparticle core asymmetrically coated with TiO_2 to induce unidirectional propulsion via Mg reaction with water to generate hydrogen gas (Fig. 4b). These micromotors were then coated with bacterial toxins immobilized into red blood cell membranes, which were previously found to act as antigens and induce immunity to *staphylococcus* infections. In addition to these toxin coatings, micromotors were coated with a layer of chitosan followed by a final layer of an enteric coating that protected the micromotors from the acidic pH of the stomach. Using this strategy, the authors demonstrated increased drug carrier retention within the GI tract as well as increased antibody titers against *staphylococcal* toxins in the feces of mice 1-week after administration.

3.2.2. Mucus-penetrating drug carriers—In contrast to mucoadhesive drug carriers, mucus-penetrating materials have been fabricated to improve drug delivery by diffusing through mucus hydrogels to underlying targets. This approach has been explored for oral drug delivery to GI epithelial barriers, as well as for pulmonary delivery of gene editing and antimicrobial cargos [26,111,116]. In many ways, the design parameters for mucus-penetrating materials are the exact opposite as those for mucoadhesive carriers. As biological hydrogels such as mucus contain porosities with inherent size limits, engineering the morphologies of drug carriers to allow for penetration through mucus pores is critical. Mucus porosities vary depending on the tissue target, but are typically on the order of hundreds of nanometers [26]. In addition to size limits, surface chemistries need to be engineered to prevent attachment between the drug carrier and the mucus biomaterial. These two limitations typically lead to the design of mucus-penetrating particles that are negatively charged and in the 100–300 nm size range [111,116]. Such mucus-penetrating particles have been fabricated from a variety of materials, including silica, synthetic polymers, and liposomes [44,75,127,128].

In a recent study, Derbali et al. compared anionic polymeric PLGA-PEG nanoparticles to both cationic and anionic liposomes for the delivery of the antibiotic levofloxacin for treating bacterial infections of *Pseudomonas aeruginosa (PA)* [129]. PA infections are prevalent in the lungs of cystic fibrosis patients and often exists as biofilm clusters embedded within stiff CF mucus barriers [130]. Thus, CF lung infections pose particular challenges, as drug carriers must penetrate through both the lung mucus and the bacterial biofilm – as will be discussed in the next section. Derbali et al. analyzed both the stability of particles within mucus hydrogels over 48 h as well as the penetration properties of the drug carriers. Anionic liposomes displayed increased stability as well as penetration through mucus barriers when compared to cationic liposomes. Interestingly, flow cytometry revealed superior bacterial binding with cationic liposomes. These results highlight the difficulties in achieving effective navigation through multiple biological barriers coupled to specific functional outputs and could provide opportunities for dynamic drug carriers to penetrate through mucus barriers followed by a morphological or chemical change to

facilitate bacterial adhesion and uptake. In that vein, Akkus et al. recently reported on a dynamic drug carrier that permeates mucus barriers followed by phosphatase-responsive charge-switching, enabling cell uptake [131]. While the authors focused on oral delivery applications, such an approach could find use in the delivery of antimicrobials to treat CF lung infections.

In addition to surface charge, muco-inert polymeric coatings such as PEG have been widely used to increase mucus penetration of drug carriers [111,116,132]. The Hanes lab has researched multiple variations of PEGylated particles for mucus-penetrating drug delivery [111,128,133]. While mucus-penetrating particles were initially studied to drive particle transportation through mucus to the underlying epithelium, Schneider et al. demonstrated for the first time that mucus-penetrating particles can in fact increase lung retention when compared to mucoadhesive particles (Fig. 5) [134]. While this finding may seem counterintuitive, the authors hypothesized that increased mucus penetration allows for particles to embed themselves within the deeper static mucus layers and avoid mucociliary clearance pathways that remove mucoadhesive particles embedded in the upper mucus layers. As a proof-of-concept, the anti-inflammatory drug dexamethasone was loaded into mucoadhesive particles (MAPs) and mucus-penetrating particles (MPPs) and delivered into the lungs of mice. The authors observed reduced inflammation in the lungs of MPP-treated vs MAP-treated mice, further validating the concept of mucus-penetration for increased lung retention.

Topographical strategies have also been used to increase mucus penetration of drugs. In several recent examples, the Traverso and Langer labs reported on microneedle-based strategies to overcome mucus barriers and directly inject drugs onto the epithelial layer for oral drug delivery [135–137]. Microneedle injections were initiated through the fabrication of dynamic oral capsules which dissolve over time in the GI tract and actuate the injection of microneedles deep into the mucus layer for drug release along the epithelium. These devices were used for insulin delivery and demonstrated increased insulin plasma concentrations and glucose response compared to an oral bolus dose.

Diverse mucus-penetrating strategies thus show promise for increasing drug delivery across biological barriers and for the delivery of cargo via pulmonary administration. While it remains unclear as to which technologies will be successful in clinical applications, the decision between mucoadhesion and mucus-penetration must be made in the context of specific drug cargos, disease targets, and routes of administration. For drug targets that lie near mucosal barriers, such as intestinal adenocarcinomas or bacterial infections within CF lung mucosa, mucoadhesive materials may offer advantages for local retention and sustained drug delivery. In contrast, drug delivery may be improved by increasing drug penetration through mucus barriers, for instance to deliver insulin into the bloodstream following oral administration. Lastly, the combination of mucus-penetrating and mucoadhesive materials may offer benefits in the navigation of multiple biological barriers, or in the active remodeling of mucus barriers to increase drug delivery efficacies [138,139].

3.2.3. Biofilm-interfacing materials—There are many examples of micro and nanoscale materials developed for antibiotic drug delivery [140,141]. Most therapeutic

strategies to treat bacterial infections focus on planktonic bacteria, while biofilm-targeted drug delivery remains a challenge. Biofilm hydrogels prevent the penetration of antibiotics as well as drug carriers through steric filtering and electrostatic adsorption [142]. Additionally, the bacteria within biofilms are oftentimes heterogeneous in terms of metabolism and bacterial species, both of which affect the efficacy of antibiotics [113]. Advanced strategies have been developed that engineer drug carriers to interact with bacterial biofilms in controllable ways. These strategies have been used to increase particle adsorption onto bacteria, penetrate through outer biofilm layers to reach bacteria in the biofilm core, or disrupt the biofilm matrix [142–145].

Similar to mucus-penetrating and mucoadhesive strategies, the morphology and surface chemistry of drug carriers are key in driving the biointerface with biofilms. In their seminal work, Peulen and Wilkinson investigated for the first time how physicochemical properties of particles influence their diffusion within bacterial biofilms [146]. The authors found that particles consistently diffused slower through *Pseudomonas fluorescens* biofilms than through water, with smaller particles (<50 nm) diffusing faster than larger particles. Additionally, negatively charged particles diffused faster than their positively charged counterparts, likely owing to electrostatic interactions between the negatively charged biofilm matrix and the particle surfaces. Importantly, the growth conditions of the biofilm heavily influenced particle diffusion properties, highlighting the diversity and dynamic nature of bacterial biofilms. For all biofilm studies, it is therefore essential to report in detail the growth conditions and biofilm model used in each experiment, as there are many biofilm models available for both *in vitro* and *in vivo* experiments, each with their own set of strengths and limitations [147].

In an example of biofilm-penetrating materials, Li et al. reported on the surface modification of CdSe quantum dots (QDs) to increase their penetration into *E. coli* biofilms grown *in vitro* [148]. Interestingly, the authors found that by installing positively charged quaternary amines onto their surfaces, QDs were able to more effectively penetrate into biofilm hydrogels than negatively charged or neutral QDs (Fig. 6a). In addition to surface charge, surface hydrophobicity also played a key role in biofilm penetration, as the installation of a hexyl alkane chains on the quaternary amine further enhanced QD penetration into biofilms. While these results may seem contradictory to previous reports of decreased penetration of positively charged carriers, biofilm-disruptive forces may play a role in the observed results. Subsequent work published by the same research groups reported that tertiary methyl amine-coated gold nanoparticles displayed increased biofilm-disrupting properties when compared to ethylene glycol coated particles [149]. Thus, the increased interaction and disruption of biofilm matrices via positively charged particles may offer a new path forward in the development of biofilm disrupting materials. Unfortunately, positively charged gold nanoparticles displayed some cytotoxic effects, which could lead to negative side effects for therapeutic applications. New surface engineering approaches will be needed to properly balance biofilm penetration and disruption with biocompatibility.

Dynamic materials have also been used for the detection of biofilms and biofilm-targeted delivery of antimicrobials [46,141]. Most approaches rely on charge-switching behaviors, which induce negative to positive charge modulation and initiate bacterial adsorption

and increased drug delivery to biofilm targets. This strategy has been used to enhance the detection of bacterial biofilms, as well as increase delivery efficacies of diverse antimicrobials, including small molecule antibiotics and silver nanoparticles [151–153]. In addition to surface charge engineering, surface functionalization of particles with biofilm-interacting cargo may offer an alternative path to increased penetration and disruption of bacterial biofilms. Baelo et al. reported on the covalent attachment of DNase I, which is capable of degrading the DNA components of bacterial biofilms, onto the surface of PLGA nanoparticles loaded with the antibiotic ciprofloxacin (Fig. 6b) [150]. The authors used these particles to treat *Pseudomonas aeruginosa* biofilms grown *in vitro* and observed increased biofilm disruption and antimicrobial activity with combination DNase-ciprofloxacin particles when compared to antibiotic-loaded particles alone.

As the biofilm is not only a biological barrier but also a drug target, a balance must be maintained between adhesion to biofilm surfaces and penetration into the core of the biofilm network in order to effectively deliver antimicrobial agents or disrupt biofilm growth. While most studies focus on increasing either particle adhesion or penetration, next generation drug carriers offer opportunities in dynamically interacting with and remodeling bacterial biofilm matrices to not only increase particle permeation within biofilm hydrogels, but also to disrupt the matrix and increase antimicrobial activities. While morphological and surface engineering strategies dominate the field of biofilm-targeted drug delivery, surface topography may offer innovative avenues to advance the field, as surface topography has been observed to prevent bacterial adhesion and biofilm formation [154,155]. It would therefore be interesting to develop drug carriers with similar nanostructures to study the influence of material topography on biofilm penetration for increased drug delivery efficacy.

3.3. The immune system and immunogenicity

When engineered drug carriers are administered into the body the immune system will efficiently recognize them as a foreign particles and induce an immune response [156]. The first step is the formation of a particle protein corona composed by plasma proteins and then, drug carriers might be rapidly internalized by phagocytes of the innate immune system, displaying a strong immune system that might lead to the particle clearance [157]. Mononuclear phagocytic system (MPS) is responsible for particle opsonization, leading to high particle clearance rates and low efficacy treatment responses [158]. To prevent the biological function of MPS, engineered drug carriers can be designed with immune-evasive properties to avoid the nanoparticle-macrophage interactions and improve drug pharmacokinetics and pharmacodynamics. An alternative approach to immune evasion is to engineer drug carriers for designed immune system engagement to either suppress or activate the immune system for a given application.

3.3.1. Immune recognition of the drug carrier protein corona—After the administration of the engineered drug carriers, their recognition by phagocytes, either MPS or tissue-resident phagocytes, can occur via protein adsorption or via phagocyte surface receptors. Immediate host biological response of *in vivo* administration of bare nanocarriers will produce protein adsorption onto the nanocarrier, referred to as the “protein corona” [159]. The initial discovery of the term “protein adsorption” to the

nanocarrier surface occurred in the 1960s by Nangham and Vroman, demonstrating the real role of these proteins in the immunological and biological response [160,161]. Over the years, the concept of “protein adsorption” changed to “protein corona” and more recently, to “biomolecular corona” due to deeper analysis of the molecular components onto nanoparticles which are comprised of lipids, sugars, nucleic acids, hormones and metabolites. While many researchers have attempted to reduce the biomolecular corona to inhibit immune clearance, a new strategy was presented to use the biomolecular corona to target specific cells.

As a new strategy for nanomedicine field, engineered drug carriers might be intentionally designed to interact with specific plasma proteins and allow for active targeting to a specific cell type using a receptor-mediated endocytosis. Zhang et al. formulated retinol-conjugated polyetherimine (RcP) nanoparticles to immediately bind to the retinol binding protein 4 (RBP) to form a specific protein corona [162]. After the interaction of retinol-conjugated RcP particles and RBP, this complex was successfully directed to the hepatic stellate cells to deliver antisense oligonucleotide (ASO) without being eliminated by phagocytic cells. Besides cell targeting applications, the biomolecular corona might be used to improve nanocarrier biocompatibility and toxicity using a protein-mediator complex, improve drug delivery using a protein-carrier complex and lastly, may be used for disease detection using a protein-biomarker complex. In addition to the protein binding, the interaction of engineered drug carriers with blood might cause changes in the coagulation factors’ functions leading to platelet aggregation or changes in coagulation time and changing the integrity of red blood cells leading to hemolysis [156].

3.3.2. Immune-evasive materials—While the material composition of a drug carrier drives a significant portion of the immune response, the physicochemical properties of a material such as morphology and surface chemistry can also influence immune recognition. Researchers have taken advantage of these interactions to create immune-evasive materials, which are not as easily recognized by the immune system and evade MPS clearance pathways. The most common route to immune evasion is the PEGylation of drug carriers. By attaching PEG polymers onto the surface of drug carriers through noncovalent adsorption, incorporation of PEG co-polymers into material backbones, or via conjugation, PEG can help reduce macrophage recognition and immune clearance pathways, while increasing biodistribution profiles [163,164]. Yu et al. conducted a systematic evaluation of the effects of PEGylated particle size and charge on macrophage uptake [165]. Interestingly, the authors observed that highly electrostatic surfaces of both positive and negative charge had increased macrophage uptake compared to more neutrally charged materials. However, size was the dominant trait that controlled macrophage uptake, with larger particles demonstrating increased uptake. To take advantage of this effect, the authors fabricated MMP-responsive particles, which decreased in size after MMP-catalyzed cleavage of surface-displayed polymers, thereby decreasing macrophage uptake in response to the presence of MMP.

Other surface coatings have also been used to facilitate immune evasion, such as the incorporation of “self-peptides” onto drug carriers. Self-peptides signal to the immune system that a material is native to the host and thereby evades foreign-body responses

such as macrophage-mediated phagocytosis and clearance. Rodriguez et al. reported on a self-peptide that was computationally derived from human CD47 proteins [166]. When attached to 160 nm polystyrene nanoparticles, the self-peptides delayed macrophage clearance and increased biodistribution and half-lives of particles when compared to non-coated particles. This strategy was later used by Zhang et al. for the dual therapeutic and diagnostic delivery of paclitaxel and MRI contrast agents in tumor-bearing mouse models, demonstrating enhanced imaging and tumor reduction for self-peptide coated nanomicelles, when compared to PEGylated or zwitterionic coated groups [167]. In a recent study, Tang et al. developed a dual particle delivery system to first block phagocytosis with self-peptide coated liposomes and then inject therapeutic PLGA nanoparticles for increased drug delivery and therapeutic half-life (Fig. 7a) [168]. The authors found that self-peptide coated liposomes adhered to the surface of macrophages but did not undergo phagocytosis. This biointerface inhibited those macrophages from recognizing and clearing any other particles that may be in their surrounding environments. By using this strategy, subsequently injected BBB-targeted PLGA nanoparticles resisted macrophage clearance and demonstrated enhanced half-lives and BBB penetration for increased antifungal drug delivery to treat cryptococcal meningitis in mice.

Other immune evasion strategies have relied on the coating of particles with biological materials such as cell membranes [169]. In a recent example, Hu et al. isolated the plasma membranes of human platelets and coated them onto PLGA nanoparticles [170]. The authors demonstrated increased nanoparticle immunocompatibility and reduced uptake into macrophages through a CD47-mediated mechanism. The platelet-mimetic nanoparticles had increased tissue half-lives and enhanced biodistribution profiles. The authors functionalized the platelet-coated nanoparticles with vancomycin antibiotics for the treatment of systemic methicillin-resistant *S. aureus* (MRSA) infections in mouse models and showed improved bacterial reduction with platelet-coated vancomycin nanoparticles compared to vancomycin injection alone or red blood cell coated vancomycin nanoparticles. Together, these studies demonstrate that the surface chemistry of drug carriers can be engineered to modulate immunological biointerfaces and improve therapeutic outcomes for a range of biomedical applications.

3.3.3. Immune-interfacing materials—By engineering drug carrier properties, researchers can determine material interactions with the immune system by inducing either an immunostimulatory or immunosuppressive response (Fig. 7b) [171]. Engineered drug carriers have been used to improve immunotherapy by delivering cytokines, enzymes, antigen, adjuvants, checkpoint inhibitor and DNA/RNA-based formulations or using biomaterials with immunomodulatory functions. The aim of those platforms was to reprogram the immune response, where the delivery of antigens and adjuvants to antigen presenting cells (APC) can initiate a potent T cell activation and consequent antigen-specific immune response [171,172].

Nanoparticles for immunostimulation have been used to treat cancer and infectious diseases, while nanoparticles for immunosuppression have been used for inflammatory diseases like atherosclerosis, rheumatoid arthritis, diabetes, obesity, and transplantation [171]. The most common immunostimulation therapy using engineered drug carriers is achieved through

the checkpoint blockade of cytotoxic T-lymphocyte 4 (CTLA-4), programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) [173]. Despite promising expected results of checkpoint blockade immunotherapy, several studies have demonstrated a low response rate due to the immunosuppressive tumor microenvironment and low tumor immunogenicity. Feng et al. developed a prodrug nanoparticle containing oxaliplatin (OXA) and reduction-activatable homodimer of NLG919 to improve immunotherapy targeting dual modulation of tumor immune microenvironment [174]. The authors have shown both an intratumoral accumulation of cytotoxic T lymphocytes and immunosuppression by triggering immunogenic cell death. Macrophages represent another common cellular target for immunomodulatory materials. Drug carriers have been developed to release cytokines in controlled manners to stimulate macrophage polarization for applications in regenerative medicine [175,176]. In addition to the controlled release of cytokines near macrophages, recent studies have demonstrated that particle adhesion onto or uptake into monocytes and macrophages followed by cytokine release can improve immunomodulatory engineering for a variety of applications such as regenerative medicine and cancer immunotherapy [177,178].

In addition to the delivery of biotherapeutics to stimulate the immune system, several reports have shown that the surface charge of materials can impact their immune biointerface, with positively charged drug carriers inducing a higher inflammatory response compared to the anionic or neutral polymers and lipids [179]. Wei et al. studied the role of cationic nanocarriers (cationic liposomes, PEI and chitosan) to induce an inflammatory response [180]. The authors demonstrated a high rate of acute cell necrosis correlated to the interaction with Na^+/K^+-ATPase and mediated by a pathway involving TLR9 and MyD88 signaling. On the other hand, a high secretion of inflammatory cytokines like TNF, IL-12 and IFNγ, and increased expression of dendritic cells surface markers (CD80/CD86) have been correlated with cationic liposomes, showing promise as an engineered drug carrier to treat cancer due to the immunosuppressive tumor microenvironment [181,182].

For an immunosuppressive response, poly(amidoamine) (PAMAM) dendrimers have been used to inhibit the secretion of inflammatory cytokines and chemokines from macrophages and dendritic cells [183]. On the other hand, fullerene derivatives were shown to suppress immune response by quenching nitric oxide and consequently decreasing free radicals [184]. Lie et al. also showed an immunosuppressive response of specific fullerene-steroid conjugate C_{60}-dextametasone [185]. Immunosuppressive therapy thus has several advantages for treatment of inflammatory diseases due to the overstimulation of immune systems against their own healthy cells. However, special care in its use must be considered due to the potential to cause immunodeficiency, cytotoxicity and genotoxicity, opening doors for opportunistic infections.

In addition to surface chemistry, material stiffness and surface topography has also been shown to influence local immune systems [28,186]. This has been predominantly studied in the context of macrophage-material biointerfaces and macrophage polarization. The morphology and polarity of macrophages influence their physiological behavior and induce changes between pro-inflammatory and proreparative states [28,157]. Several studies have shown that installing surface topography on implanted materials can induce macrophage

morphological changes and influence subsequent cytokine production [187–190]. Various factors in surface topography can drive macrophage behavior, including the porosity of the surface, the alignment of topographical structures, as well as the dimensions and morphologies of nanostructured surfaces [28]. While the rational design of surface topography to influence macrophages has yet to be elucidated, most studies have found that nonrandom nanostructured surfaces induce proreparative behavior in macrophages, likely by stimulating the controlled polarization of macrophages adhered to a material surface [119,188,189]. While further studies are needed to better understand these interactions, it could also be interesting to determine if such topographical cues are maintained when topography is fabricated on the surface of a particle, rather than on a bulk implantable material. Additionally, most topography-immunological studies were conducted without drug-delivering materials. Thus, the combination of nanotopography with drug carriers is a new and emerging field of research, which could bring innovative approaches to enhance drug delivery and immunomodulation.

3.4. Cell uptake and intracellular trafficking

The last biological barrier to deliver therapeutic agents is the intracellular barrier. Indeed, the target site of many therapeutic agents is localized inside the cell and therefore, cellular uptake and intracellular routing are critical to successful drug delivery. Large macromolecules, small hydrophilic drugs and nucleic acids are the most challenging therapeutic agents to deliver intracellularly due to the low pH in the endosomes/lysosomes, enzymes in the lysosomes and the redox environment in the cytosol [191]. Engineered drug carriers are used and formulated to overcome these intracellular barriers by providing a higher efficacy of cellular uptake and intracellular delivery [192].

For efficient intracellular delivery, the first barrier to overcome is the plasma membrane since it is a complex barrier composed of multiple lipid and membrane proteins, limiting the entry of large macromolecules and hydrophilic molecules. Small and/or moderately polar molecules may use passive diffusion across the cell membrane to enter the cell. However, larger and/or highly polar molecules, such as, sugars, proteins, and peptides, might use the membrane transporters expressed at the cell surface to enable entry inside the cell [193]. It is well-known that drug carriers use multiple endocytic pathways to enter live cells in order to release their cargo in an intracellular target site. Uptake of foreign engineered drug carriers usually relies on endocytosis but depending on their physicochemical properties, different endocytic pathways might be used (e.g. phagocytosis, pinocytosis, macropinocytosis) [194]. Internalization of large molecules by cells such as monocytes/macrophages and neutrophils occurs using intracellular phagosomes to proceed with phagocytosis process, while macropinocytosis uses endocytic vesicles to deliver intracellularly small nanoparticles (< 1 μm) [195].

The uptake of most small organic and inorganic nanoparticles is done by clathrin-mediated endocytosis, where nanoparticles interact with extracellular receptors to be internalized into early endosomes [192,196]. Maturation of early endosomes (pH 6.5) into late endosomes (pH 6) usually translates with a decrease in intravesicular pH due to the ATP-driven transport of H^+-ions [197]. The fusion of late endosomes with lysosomes naturally occurs,

leading to the destruction of nanoparticle cargo due to the presence of lysosomal enzymes and low pH (4.5–5) [198]. This endolysosomal sequestration process is the most challenging barrier for effective intracellular delivery, therefore engineered drug carriers should be formulated with biomaterials that allow for endolysosomal escape to the intracellular environment in a timely manner.

3.4.1. Endosomal escape of drug carriers—To achieve efficient drug release, two types of engineered drug carriers have been widely used: pH-responsive nanocarriers and enzyme-responsive nanocarriers. Overall, pH-responsive drug carriers are formulated to deform or disassemble exclusively at the acidic pH of the endolysosomal compartment, resulting in an efficient intracellular delivery of loaded drug [199]. In an alternative approach, enzyme-responsive nanocarriers have been formulated for endosomal escape due to the presence of abundant digestive lysosomal enzymes including proteases, glycosidases and sulfatases [200]. The presence of cathepsins B and D has been a target to deliver peptides intracellularly. Lee et al. formulated enzyme-responsive polymersomes based on block copolymers with a peptide linker (Gly-Phe-Leu-Gly-Phe) aiming a fast-enzymatic destabilization at the lysosomal compartment for drug release. The authors showed both fast-enzymatic destabilization of polymersomes at pH 5.5, and rapid release of the model drug in the presence of cathepsin B at pH 5.5 [201].

High redox potential in the cytosol, endolysosomal compartments, and the cell nucleus have been used as targets for active intracellular drug and gene therapy due to the abundant presence of glutathione (GSH) and other reducing enzymes and agents (e.g. gamma-interferon-inducible lysosomal thiol reductase, cysteine) [202,203]. Redox-responsive nanosystems have been formulated with cleavable disulfide linkages into the polymer main chain, side chain or in the cross-linker to release cargo into the cytosol and cell nucleus more efficiently [201]. Liu et al. developed smart redox-responsive micelles composed by amphiphilic homopolymer and alternative hydrophobic disulfide and hydrophilic polyphosphates segments (HPHDP) [204]. Due to the redox environment of cell nuclei and cytosols, these redox-responsive micelles were able to deliver doxorubicin efficiently inside cell nuclei, enhancing antitumor efficacy.

In the last 30 years, the use of biologics in medicine has substantially increased and become one of the most important drug types. Therapeutic peptides, proteins, monoclonal antibodies, and RNA-based formulations for gene therapy have become a large part of the research studies in the last years for the therapeutic modulation of intracellular targets [192]. To enable efficient intracellular delivery, cationic lipids or polymers have been formulated as engineered drug carriers to interact with negatively charged membrane and deliver intracellularly biotherapeutic medicine. Cationic particles when interacting with negative endosomal membranes will induce a “flip-flop” mechanism, leading to an endosomal membrane destabilization caused by charged-neutralized ion pair [205]. A burst release of the cationic particles into the cytosol might happen due to the pore formation caused by membrane destabilization and osmotic pressure caused by constant influx of chloride ions [206]. This mechanism of endosomal escape is well-described for cationic particles composed of quaternary amine groups. In addition to the cationic liposomes, polymeric

nanoparticles composed of poly(ethyleneimine) (PEI), poly(L-lysine) (PLL), chitosan, and poly-amido amines have been used to facilitate endosome escape [207,208].

The development of RNA interference (RNAi) therapeutics for gene therapy has been strongly studied over the last years and remains a key challenge due to the escape of RNAi therapeutics from endosomes into the cytosol. Gilleron et al. developed small interfering RNAs (siRNAs)-loaded lipid nanoparticles (LNPs) and monitored their uptake in different types of cells in order to get a high transfection efficacy [209]. The presence of siRNA-loaded LNPs in different endosomal compartments was studied, where the majority of the nanosystem was found in the early endosomes after 1.5 h of uptake. The authors estimated that just 1–2% of siRNAs could escape from endosomes into the cytosol in a limited window of time. Indeed, understanding the low efficacy of engineered drug carriers to escape from endosomal compartments into the cytosol highlights the need to develop more endosomal escape strategies. Recently, Van de Vyver et al. found 56 cationic amphiphilic drugs (CADs) that strongly promoted efficient siRNA delivery from endosomal compartments into the cytosol [210]. This result might be an open door for a combinatory treatment composed of RNAi therapeutics-loaded nanocarriers and CADs adjuvants. In addition to the CADs adjuvants, Evans et al. studied the use of anionic polymer poly (propylacrylic acid) (PPAA) as another alternative to potentiate the intracellular delivery of cationic biotherapeutics and particles [211]. The pre-treatment with PPAA enhanced intracellular delivery of cationic biotherapeutics and cationic particles and provided an increase in the editing efficiency at approximately 50% in engineered Ai9 fibroblasts.

After nanocarriers are internalized, an important question to address is their intracellular fate, namely their biodegradation and elimination. One of the biggest issues in achieving efficient intracellular delivery is endosomal escape, as described above. Thus, the most used and characterized degradation pathway of nanocarriers in an intracellular context is the hydrolysis provided by acidic cellular environment and intracellular enzymes found in the endolysosome [212]. This is particularly applicable to biodegradable polyesters nanoparticles (e.g. PLGA and PLLA), where acidic pH and endosomal enzymes hydrolyze ester bonds [213]. Once polyester nanocarriers are degraded, monomers might be metabolized through the Krebs cycle or tricarboxylic acid cycle to be cleared from the body [214]. In addition to biodegradable polyester nanoparticles, the degradation of poly(alkyl cyanoacrylate) nanoparticles have been associated with enzymatic degradation via esterases as well as increased degradation at the neutral pH of the cytoplasm as opposed to the acidic endosomal environment [215]. Another parameter that influences the degradation of nanocarriers is reactive oxygen species (ROS) generation [216]. Balfourier et al. observed unexpected intracellular biodegradation of gold nanoparticles induced by ROS, where oxidation of gold nanoparticles resulted in biomineralization that created well-defined crystalline assemblies. While challenges remain in the efficient intracellular delivery of therapeutic cargo, engineering drug carriers to controllably interface with cell membranes and endosome compartments will enable substantial improvements in therapeutic drug delivery.

3.4.2. Direct cytosolic uptake of drug carriers and drug cargo—While the majority of drug delivery research focuses on inducing endosomal escape of drug carriers,

the direct cytosolic uptake of drug carriers offers an alternative approach to cellular drug delivery. Modifying the surface chemistry of drug carriers is the most studied approach to inducing cytosolic uptake of nanoparticles. This can be achieved by densely coating particles with positively charged moieties or lipophilic surfaces that interact with the cell membrane and cause direct membrane permeabilization rather than inducing endocytosis [217–220]. Many studies have reported on the surface modification of drug carriers with cell-penetrating peptides (CPPs). CPPs are typically composed of cationic peptide sequences such as poly(arginine), which owing to their positive charge, can permeabilize cell membranes and enable the transport of drug cargo or intact nanoparticle drug carriers into the cytosol [221–223]. CPPs have been used with a wide range of drug carrier types, including liposomes, inorganic particles, and biodegradable polymeric particles. One major caveat to CPP-induced cell uptake is possible cytotoxic effects caused by increased membrane permeability. It is therefore essential to carefully tune the surface charge and density of CPP coatings to enable cytosolic uptake without causing toxicity. Lastly, CPPs are nonspecific for cell type, and thus additional targeting strategies may benefit the use of CPPs and circumvent some of the off-target cytotoxicity associated with their use.

Another method to overcome endosomal escape and gain direct access to the intracellular space is through the use of nanoneedles (NNs). The use of NNs to intracellularly deliver biotherapeutics such as nucleic acids, proteins, and engineered drug carriers with high transfection rates has been studied (Fig. 8a) [224,225]. Overcoming the fate of endosomal compartments, NNs have been proposed to provide a direct traffic of biotherapeutics into the cytoplasm where NNs traverse the plasma membrane with minimal toxicity [226,227]. However, other reports have indicated that NNs rather than facilitating direct cytosolic access, alter the standard endolysosomal uptake mechanisms to hasten endosomal uptake and subsequent cytosolic cargo release [97,225,228]. Several in-depth analytical studies described that NNs cause perforations and cell deformations, influencing mechanosensitive cell behavior [229,230] and can lead to the formation of intracellular scaffolding structures that are correlated to clathrin or caveolae-mediated endocytosis [224,231]. To better understand the contribution of endocytosis with NNs, Gopal et al. studied endolysosomal trafficking of porous silicon nanoneedle-injected siRNA and quantum dots to understand the role of endocytosis on NN-mediated drug trafficking [225]. The authors demonstrated improved intracellular delivery of siRNA using nanoinjected siRNA targeting GAPDH (Fig. 8b). Regarding endolysosomal trafficking, nanoinjected-siRNA was colocalized into the endolysosomal pathway with a frequency 62 ± 16%, implying that the remaining 38% of siRNA was trafficked in an alternative pathway, likely via direct cytosolic uptake. It therefore appears that surface topographical strategies such as nanoneedles can bypass endocytosis to induce direct cytosolic uptake of drugs or modulate cellular uptake mechanisms to hasten drug delivery into the cytosol. By using advanced imaging and cellular analytical techniques, researchers can better elucidate the mechanisms of topographical nanoinjection into cells and better apply these systems to advance therapeutic drug delivery.[232]

4. Conclusions

Drug delivery strategies offer a wealth of opportunities to improve drug efficacy and tissue targeting to reduce side effects. However, biological barriers throughout the body prevent effective drug delivery by erecting physical and chemical barriers to drug penetration, clearing drug carriers via the immune system, and degrading drug cargo prior to reaching its intracellular target. By rationally designing drug carrier properties to interface with biological systems, researchers can overcome these barriers and improve drug delivery. This can be achieved by engineering drug carrier morphologies, surface chemistries, topographies, and installing dynamic responsive behaviors. These strategies can improve the adherence or penetration of drug carriers through tissue and hydrogel barriers, remodel and permeabilize barriers, escape or modulate the immune system, and increase cellular uptake and intracellular trafficking. For all these applications, it is important to study the biological barrier of interest not only as a biological system, but also as a dynamic biomaterial, as the biointerface is a two-way relationship between how the drug carrier interacts with the biological barrier and vice versa.

While we have highlighted many innovative examples of drug carrier biointerface engineering to improve drug delivery, challenges still remain in the field. Biological barriers are difficult to study, as they are dynamic systems that not only change in response to local perturbations, but also can be damaged during analysis and lead to an imperfect understanding of the barrier properties. As more advanced and nondestructive analytical techniques are developed to study the micro and nanoscale architectures of biological barriers, rational design approaches to biointerface engineering will improve. Clinical translation of nano and microscale drug carriers is an overarching challenge in the field of drug delivery [1,2,11]. Improvements in study reproducibility, material scale-up, and preclinical models will all be necessary to advance the translation of micro and nanotechnology into the clinic. Off-target effects and toxicity studies are especially important for the translation of drug carriers that interact with and remodel biological barriers, as any perturbation to homeostasis could have severe consequences. Thus, drug carrier biodistributions and half-lives, immunogenicities, and in-depth analyses of the material biointerface in relevant animal models must be thoroughly studied prior to clinical translation.

Next generation drug carriers could offer significant improvements in overcoming multiple biological barriers and dramatically improving therapeutic efficacies. As we have seen, drug carriers must oftentimes navigate multiple barriers prior to reaching their biological targets. As the field of dynamic and responsive materials advances, researchers should incorporate new and innovative designs into drug carriers to allow for dynamic and sequential interactions with multiple biological barriers. This approach could allow for a single drug carrier to not only penetrate through mucus barriers, but also initiate tight junction remodeling and evade immune system clearance and immunogenicity. Lastly, researchers should look to biology for inspiration in how to overcome biological barriers. Both bacteria and mammalian cells have evolved ways to dynamically remodel biological hydrogels such as mucus in order to travel across and through these barriers. Bioinspired materials that mimic these strategies through advanced synthetic chemistry and materials

engineering could therefore improve drug transport and targeting for numerous biomedical applications. Throughout these new approaches, the biointerface between a drug carrier and a biological system must be treated as a dynamic and tunable relationship, one which could facilitate improved therapeutic outcomes and enhance approaches to overcome key biological barriers to drug delivery.

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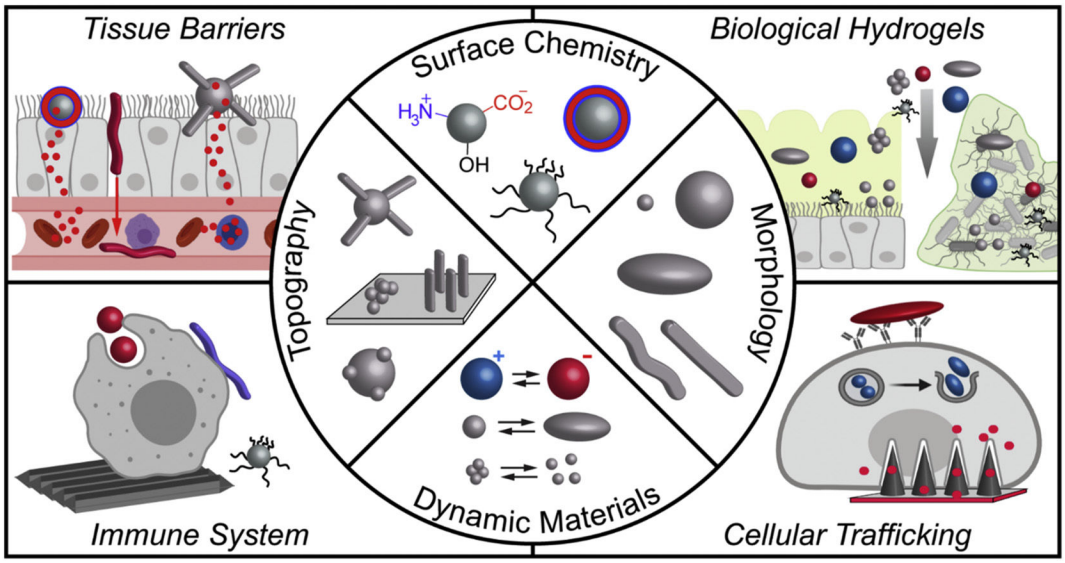

Fig. 1.

Strategies to engineer drug carrier biointerfaces to overcome biological barriers to drug delivery. Drug carrier morphologies, surface chemistries, topographies, and stimuli-responsive behaviors can be adjusted to influence biointerfaces and overcome biological barriers. Such strategies can 1) facilitate transport of carriers across tissue barriers and improve their permeabilization, 2) navigate carriers through biological hydrogels such as mucus and bacterial biofilms, 3) enable the evasion and engineering of the immune system, and 4) promote cellular uptake and intracellular trafficking of drug carriers.

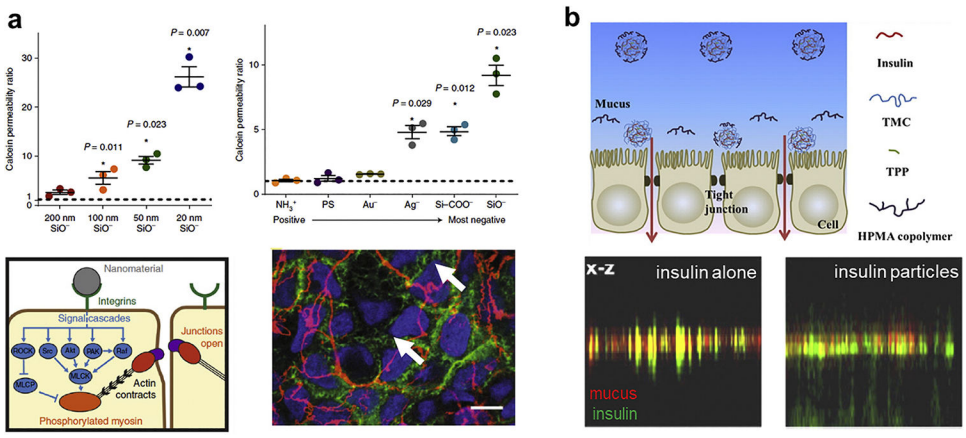

Fig. 2.

Influence of drug carrier surface chemistry and particle morphology on tight junction remodeling and drug penetration across epithelial barriers. (a) Nanoparticles displayed size and charge dependence in promoting calcein permeability across epithelial barriers. Anionic silica nanoparticles remodel TJs through integrin-mediated mechanisms and alter ZO1 morphology (stained red) in Caco-2 monolayers to increase drug permeability (actin stained green; nuclei stained blue). Scale bar, 10 μm. Images adapted from [75] (b) Dynamic chitosan and HPMA drug carriers increase mucus permeation until binding to epithelial barriers and undergoing chitosan-mediated tight junction remodeling for increased insulin permeation. Insulin (green) displayed increased permeability through mucus barriers (red) and across epithelial barriers below the mucus layers. Images adapted from [80].

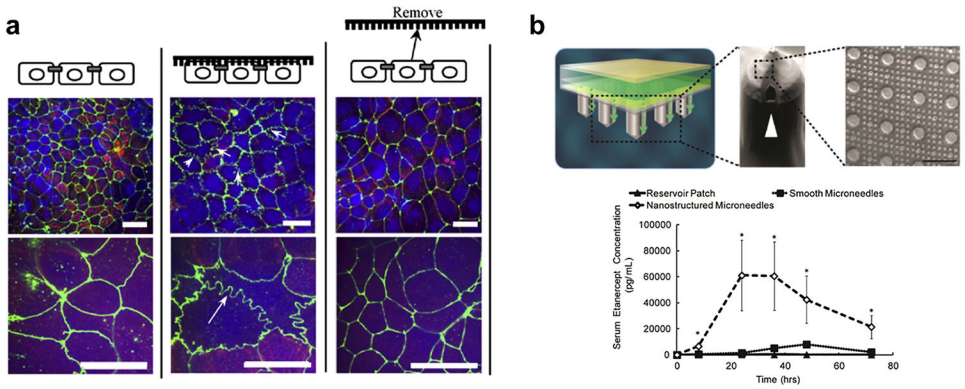

Fig. 3.

Nanotopographical surfaces for tight junction remodeling and increased drug transport. (a) Nanostructured thin films reversibly remodel TJs and cause morphological ruffling of ZO1 proteins (green). Scale bars for top and bottom images, 10 μm and 20 μm, respectively. Images adapted from [85] (b) Transdermal drug reservoirs containing nanostructured microneedles increase the serum concentration of Etanercept in rabbit models, when compared to reservoirs with smooth microneedles. Scale bar, 3 μm. Images adapted from [87].

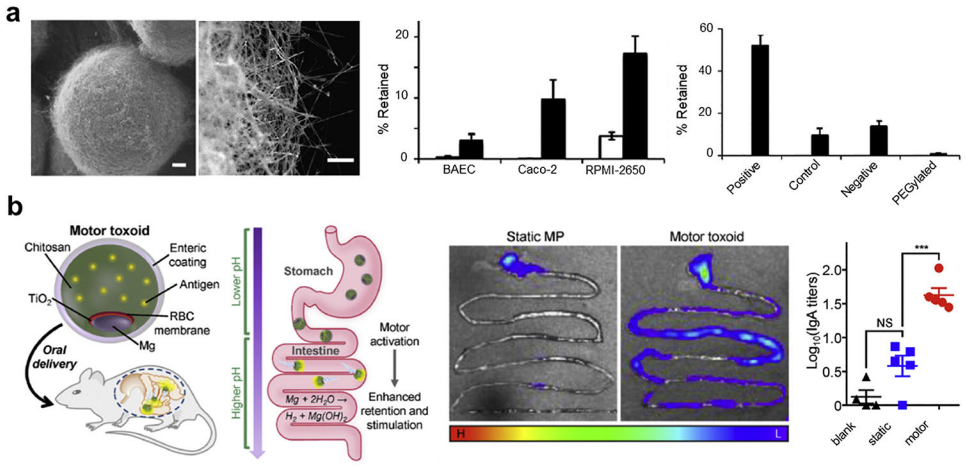

Fig. 4.

Surface topography, surface chemistry, and dynamic materials in the design of mucoadhesive drug carriers. (a) Nanowire-coated microparticles utilize nanotopography to induce mucosal binding and increase tissue retention. Attachment of positively charged moieties onto the nanowire surfaces increases particle retention on mucus hydrogels under flow. Scale bars, 2 μm (left) and 20 μm (right). Images adapted from [122] (b) Micromotors increase GI tissue retention through actively embedding into mucosal barriers via Mg-catalyzed microparticle propulsion. Using this strategy, bacterial toxin antigens were delivered with higher efficacy to mouse mucosa compared to static microparticles. Images adapted from [123].

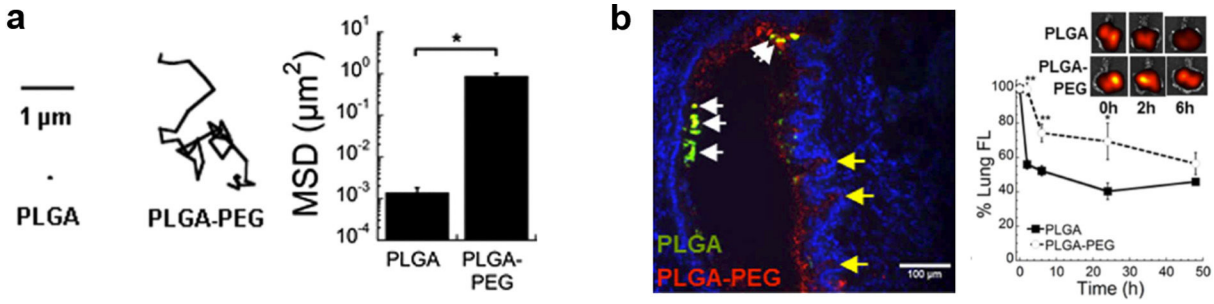

Fig. 5.

Design of mucus-penetrating particles for enhanced lung retention and drug delivery. (a) Multiple particle tracking (MPT) studies revealed the trajectories of mucoadhesive and mucus-penetrating particles. PLGA nanoparticles displayed mucoadhesive properties, while PEGylated PLGA nanoparticles facilitated movement through CF mucus. This was further quantified via median mean square displacement (MSD) values over 1 s of movement. (b) Mucus-penetrating PLGA-PEG particles had more even and prolonged lung distribution in mice when compared to mucoadhesive PLGA particles. Images adapted from [134].

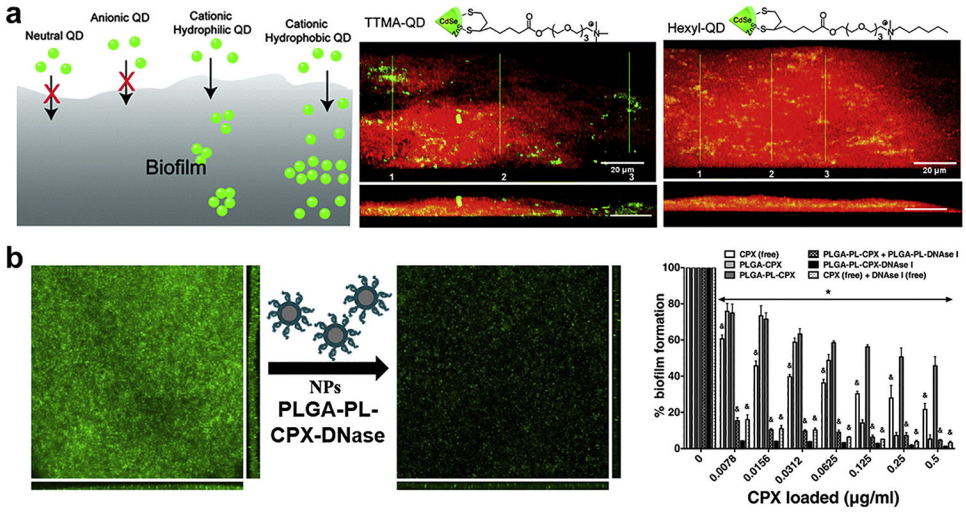

Fig. 6.

Engineering the biofilm-material interface to drive biofilm permeation and disruption. (a) Surface charge and hydrophobicity influence biofilm penetration of quantum dots (QDs). Tertiary tetramethyl amine (TTMA) and hexyl tertiary amine coated QDs display increased biofilm penetration over neutral and anionic particles. Images adapted from [148] (b) DNasecoated PLGA nanoparticles increase biofilm disruption and antimicrobial activity of antibiotic ciprofloxacin in *Pseudomonal* biofilm cultures. Each biofilm field was 455 × 455 μm. Images adapted from [150].

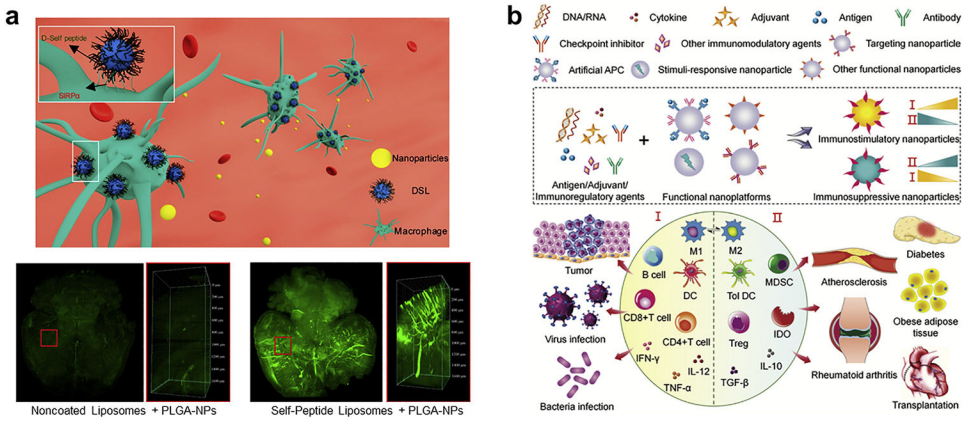

Fig. 7.

Immune-evasive and immune-interfacing materials for drug delivery. (a) Self-peptide coated liposomes (DSLs) block phagocytosis and enable the immune evasion and subsequent BBB penetration of drug-loaded BBB-targeted PLGA nanoparticles. Images adapted from [168] (b) Biological response and applications of immunostimulatory and immunosuppressive nanoparticles used in immunotherapy. Images adapted from [171].

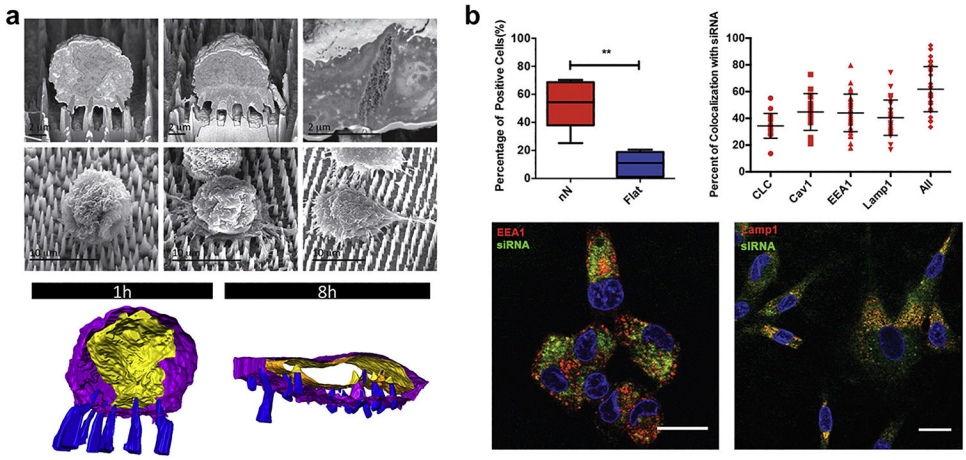

Fig. 8.

Nanoneedles for enhanced cellular uptake and drug delivery. (a) Nanoneedles interface with cell membranes, imaged via focused ion beam – scanning electron microscopy. Cell membranes and nuclear envelopes were observed to undergo remodeling when in contact with nanoneedle surfaces. Images adapted from [224] (b) Porous silicon nanoneedles enhances siRNA delivery. The percentage of cells with siRNA uptake was significantly increased using nanoneedle injection. The colocalization of nanoinjected Cy3-siRNA in endocytic carrier protein (CLC, Cav-1), endosomes (EEA1) and late endosomes/lysosomes (Lamp1) as well as their combination (All) were quantified to reveal a combination of endolysosomal and direct cytosolic uptake. Scale bars, 20 μm. Images adapted from [225].