Bioresponsive materials

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Abstract | 'Smart' bioresponsive materials that are sensitive to biological signals or to pathological abnormalities, and interact with or are actuated by them, are appealing therapeutic platforms for the development of next-generation precision medications. Armed with a better understanding of various biologically responsive mechanisms, researchers have made innovations in the areas of materials chemistry, biomolecular engineering, pharmaceutical science, and micro- and nanofabrication to develop bioresponsive materials for a range of applications, including controlled drug delivery, diagnostics, tissue engineering and biomedical devices. This Review highlights recent advances in the design of smart materials capable of responding to the physiological environment, to biomarkers and to biological particulates. Key design principles, challenges and future directions, including clinical translation, of bioresponsive materials are also discussed.

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Pioneering studies using engineered materials for dosage and for spatially and/or temporally controlled drug release were carried out in the 1970s[1–3]. More recently, there has been a growing interest in the development of stimuli-responsive, 'smart' materials for a range of biomedical applications, including drug delivery, diagnostics, tissue engineering and biomedical devices[4–7]. A major research focus is to design biocompatible materials capable of responding to specific biological triggers either for interacting with biological objects or for actuating the release of therapeutics[8]. These biological triggers include innate biological signals and pathological abnormalities.

In drug delivery, the treatment efficacy of therapeutics is directly related to the administration method[9–12], which requires the development of advanced materials to achieve precision drug release (BOX 1); the improvement of medical diagnostics demands non-invasive or minimally invasive approaches based on stimuli-responsive materials that allow for real-time monitoring; the growing desire for tissue engineering and regenerative medicine leads to urgent needs for matrices endowed with the ability to communicate and interact with cells; while in the development of medical devices, the incorporation of high-performance biocompatible materials is crucial for improving the antibacterial and anti-inflammation capability and preventing the formation of biofilms, as well as fibrosis[13].

In general, bioresponsive materials can be deconstructed into functional motifs with biological sensitivities, which can be built into the desired formulations, scaffolds or devices in a controlled manner using appropriate fabrication methodologies. We describe general rules for designing bioresponsive materials, especially for drug delivery and tissue engineering, with the intention of circumventing challenges that currently hinder clinical translation. We concentrate on examples of the current state of the art that apply these principles for creating and tailoring materials, with a focus on the underlying design rationale.

Sensitivity to physiological environment

Variations in physiological parameters are often important hallmarks for distinct types of diseases, such as cancer, autoimmune disorders, degenerative diseases, infections and cardiovascular diseases, rendering them attractive targets when designing bioresponsive materials[4,14]. In general, physiological triggers can be classified into three main categories: triggers at the organ level; triggers related to pathological conditions[15–17]; and cellular compartment-specific triggers (FIG. 1; TABLE 1).

pH

Materials that are pH-responsive are often capable of physical or chemical changes, such as swelling, shrinking, dissociation, degradation, or membrane fusion and disruption[15,18,19] (BOX 2). The pH-sensitivity can be attributed to either the protonation of ionizable groups or the degradation of acid-cleavable bonds[4].

For intracellular delivery, the acidification of endosomes and their subsequent fusion with lysosomes create an ideal pH gradient for intracellular drug release. At the organ level, the pH gradients along the gastrointestinal tract enable organ-specific release of orally administrated drugs. The local acidification commonly found at cancerous or inflammatory sites has also been frequently used for disease-specific controlled drug delivery. Classic examples are polymers polymerized from acrylic acid, methacrylic acid, maleic anhydride and *N*,*N*-dimethylaminoethyl methacrylate[20,21]. In the pharmaceutical industry,

aminoalkyl methacrylate copolymer (Eudragit E), a US Food and Drug Administration (FDA)-approved cationic polymer with increased solubility in acidic environments, has been applied for taste masking through the suppression of burst drug release in the oral cavity[22].

The design and choice of pH-responsive materials also depend strongly on the nature of the cargo molecules. For example, for acid-degradable drugs, such as proton pump inhibitors and some proteins, prevention from gastric degradation is crucial. Anionic polymers containing carboxyl groups have a higher solubility at basic pH and thus could be used for shielding acid-sensitive drugs for intestine targeted delivery[23,24]. For example, microspheres composed of poly(itaconic acid-co-*N*-vinyl-2-pyrrolidone) (poly(IA-co-NVP)) were evaluated for the controlled release of model protein therapeutics triggered by basic pH[25]. Polycations are especially appealing for non-viral gene delivery owing to their easy complexation with negatively charged nucleotides through electrostatic interaction. FDA-approved polyethylenimine remains the gold standard for evaluation of new polymers intended for delivery of nucleic acids, although its efficiency and safety has been surpassed by other candidates[26]. For example, a high-throughput screened library of different poly(β-amino ester) chemistries is used to guide the construction of polycations[27]. Acetal-based acid-labile crosslinkers or pendent chains of polymers were encapsulated through crosslinked microgels or emulsion-based particles for the pH-triggered release of therapeutic protein[28]. The 'particle replication in non-wetting templates' (PRINT) process has been used to incorporate pH-sensitive silyl ether crosslinkers into microparticles to construct acid-degradable smart devices[29]. Recently, doxorubicin (Dox) was conjugated to the side chains of poly(lactic-co-glycolic acid) (PLGA) by means of an acid-cleavable hydrazine linker, to evade excretion by drug efflux pumps[30]. Moreover, polyion complex micelles formed through the self-assembly of oppositely charged amphiphilic block copolymers represent another family of pH-responsive formulations[31–34]. In another example, pH-responsive peptide amphiphiles have been used for pH-triggered reversible self-assembly into nanofibres[35]. In a DNA-assembled nanoclew, decreased pH within the endosome triggered the release of encapsulated DNase, which attacked the DNA nanoclew for the eventual intracellular Dox delivery[36]. In this case, the endosome acidification served as an indirect trigger to induce drug release, which can be considered as a progressively activated system (BOX 1).

Although organic materials are still predominantly used, pH-responsive inorganic materials have recently emerged as alternatives for drug delivery applications, among which acid-degradable materials such as calcium phosphate and liquid metal might be appealing because of their biodegradability and the non-toxic or low-toxicity metabolism products[37,38]. For example, in a liquid-metal-based drug-delivery system, the metallic cores (composed of gallium–indium alloy) of the nanoformulation were capable of fusion and degradation upon the attack of protons[38]. In a recently developed pH-activatable contrast agent, the degradation of calcium phosphate within acidic solid tumours freed confined Mn^{2+}, which then bound to proteins for increased relaxivity during magnetic resonance imaging[39].

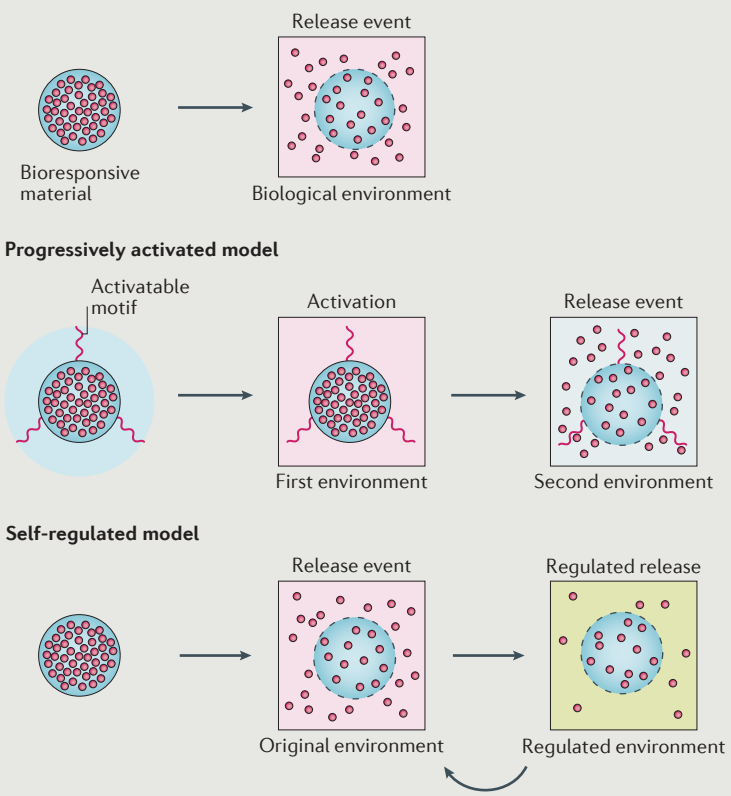
In addition to directly inducing cargo release, physiological pH gradients can also be used to achieve site-specific delivery of drug carriers in a sequential manner[40]. In some cases, nanocarriers decorated with pH-responsive motifs undergo charge conversion in the mildly acidic tumour environment, leading to upregulated endocytosis by the cancerous cells. The charge-

Box 1 | Bioresponsive modalities for controlled drug release

Most bioresponsive systems for controlled drug delivery can be classified according to three models: directly activated, progressively activated and self-regulated (see figure parts **a**, **b** and **c**, respectively).

In a directly activated model, the material responds directly to the target biological cue, promoting drug release from the system. In the progressively activated model, the material switches to an activated mode upon exposure to the first type of biostimulus, which leads to exposure to the secondary stimulus and eventual release. This bioresponsive modality is often referred to as a sequential model, the realization of which relies on successful step-by-step responses towards each stimulus[40]. An application of this model involves targeted delivery of therapeutics in which the targeting ligands can be originally shielded and finally activated in the tumour microenvironment[236].

A self-regulated system, also known as a signal feedback control system, functions in a continuous and self-regulated manner based on a feedback-responsive modality. In a classical self-regulated drug-delivery system, the drug released upon the environmental trigger subsequently influences the surrounding environment to generate a feedback, which further regulates drug release from the responsive system to achieve homeostasis. The glucose-responsive closed-loop insulin delivery systems (artificial pancreas) can be described using this model[84].



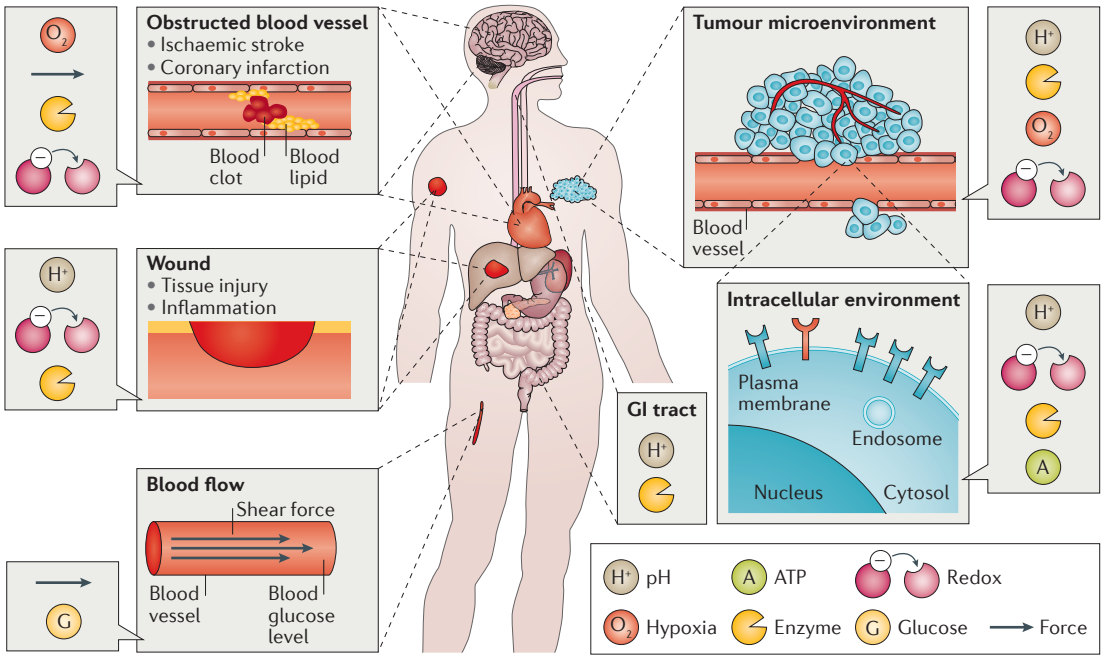


Figure 1 | **Typical physiological environments with associated biological stimuli.** Variations in physiological parameters exist at the organ, tissue and cell levels, and are closely associated with various pathological conditions, such as cancer, cardiovascular disease, diabetes, stroke and chronic wounds. ATP, adenosine triphosphate; GI, gastrointestinal.

converting strategy has also been used for *in vivo* cancer imaging for improved cancer diagnosis[25]. Engineered pH-sensitive cell-penetrating peptides (CPPs), which can be activated by the local acidification at the tumour site, facilitate cellular uptake for enhanced tumour accumulation. pH (low) insertion peptides (pHLIP) capable of reversibly folding and inserting across cell membranes upon pH changes were used for targeting acidic tissues[41]. For example, pHLIP was attached to antisense oligomers for enhanced cellular uptake at the mildly acidic tumour microenvironment[42]. Localized acidification can also be exploited for cancer theranostics, for example, by using an ultrasensitive fluorescent nanoprobe that is activated by the mild acidicity of the tumour microenvironment[43]. In a recent study, dendrimer-conjugated platinum prodrugs were released site-specifically within tumour tissue as a result of amide bond cleavage within the mildly acidic environment[44]. Other pathological-associated pH gradients, such as the site acidification at chronic wounds and inflammatory sites, have also been reported as biological targets for pH-responsive drug delivery[45].

Recently, researchers took advantage of pH-sensitive supramolecular gels that were stable in acidic environments but soluble at neutral pH values to construct stomach-resident devices[46]. The enteric elastomer was constructed using poly(acryloyl 6-aminocaproic acid) (PA6ACA) and poly(methacrylic acid-co-ethyl acrylate). The terminal carboxyl groups enabled the formation of intermolecular hydrogen bonds in acidic environments, resulting in an elastic water-containing supramolecular network. By contrast, in neutral environments, the supramolecular gels underwent rapid dissociation due to the deprotonation of carboxyl groups. Devices constructed from this smart gel displayed prolonged gastric retention in a pig model.

In addition to the construction of smart drug-delivery systems, pH-responsive hydrogels have been exploited for regenerative medicine[47]. For example, dimethylaminoethyl methacrylate-based scaffolds capable of altering oxygen and nutrient transport by expanding in an acidic environment were used to generate a pro-healing effect for tissue regeneration[48].

Redox

Differences in redox potential exist at both the tissue and cellular level. For example, the glutathione/glutathione disulfide couple has been verified as the most abundant redox couple in animal cells, where glutathione is found at a level that is two to three orders of magnitude higher in the cytosol than in the extracellular fluid[49]. Further, studies with a rodent model have revealed a higher glutathione concentration in tumour tissues compared with that within normal tissues[50]. In addition to the reducing conditions, reactive oxygen species (ROS) are also associated with distinct pathological conditions including cancer, stroke, arteriosclerosis and tissue injury.

Disulfides transform to thiols in the presence of reducing agents, including glutathione, and the resulting thiol groups can reversibly reform disulfide bonds on oxidation. The mild reaction conditions of thiol–disulfide exchange also render it an appealing approach to construct disulfide-containing materials[51]. Disulfides have also been incorporated into material systems in the form of disulfide-containing crosslinkers[52,53].

Another redox-responsive motif used for engineering redox-sensitive materials is the diselenide linkage[54,55]. In a recent study, micellar aggregates self-assembled from a diselenide-containing block copolymer displayed high sensitivity to both oxidants and reductants[56]. In addition, the library of reduction-sensitive materials has recently been expanded with the development of functional groups such as *cis,cis,trans*-diammine-dichlorodihydroxy-platinum(IV) (DHP) or *cis,cis,trans*-diamminedichlorodisuccinato-platinum (DSP) and trimethyl-locked benzoquinone (TMBQ)[57,58].

Oxidation-responsive materials mainly target ROS such as hydrogen peroxide (H_2O_2) and hydroxyl radicals. A major class of oxidation-responsive materials is sulfur-based. Researchers copolymerized oxidation-convertible poly(propylene sulfide) (PPS) with polyethylene glycol (PEG) to form amphiphiles capable of self-assembling[59]. In addition, efficient gene delivery has been achieved with thioketal-containing materials[60]. Ferrocene-containing materials have also been heavily investigated owing to the redox-sensitivity introduced by ferrocene[61]. Moreover, emerging responsive motifs

Table 1 | **Summary of typical physiological stimuli**

Body part or biological stimulus	Details
pH	
Plasma	Normal pH range: 7.38–7.42
Gastrointestinal tract	Saliva: 6.0–7.0; gastric fluid: 1.0–3.5; bile: 7.8; pancreatic fluid: 8.0–8.3; small-intestinal fluid: 7.5–8.0; large-intestinal fluid: 5.5–7.0
Urinary tract	Urine of pH-balanced body: 6.5–8.0
Vagina	Normal pH range: 3.8–4.5
Eye	Ocular surface: ~7.1; healthy tear: 7.3–7.7
Pathological microenvironment	Inflammation-associated acidic pH: 7.2–6.5 for extracellular pH in tumour; down to pH 5.4 in inflamed tissue; down to 4.7 in fracture-related haematomas; down to pH 5.7 in cardiac ischaemia[237]
Intracellular compartments	Early endosome: 6.0–6.5; late endosome: 5.0–6.0; lysosome: 4.5–5.0; Golgi complex: 6.0–6.7 (REFS 106,238,239)
Redox	
Reducing species	Glutathione: intracellular, 10 mM; extracellular fluids, 2–10 μM
Oxidative species	Elevated reactive oxygen species levels are associated with inflammation and tissue injury
Enzyme	
MMPs	Overexpression of MMPs is associated with various cancers and colorectal disease. For example, the plasma MMP-9 level in a healthy human body is about half of that found in patients with non-small cell lung cancer[240]. Moreover, evidence suggests that MMPs are important regulators for inflammatory and wound-healing processes[241]
HAase	Breast cancer: elevated HAase levels in metastases compared with the primary tumour[242]; prostate cancer: 3–10-fold elevation in HAase expression of cancerous tissue compared with that of normal adult prostate[243]; bladder cancer: 5–8-fold higher urinary HAase levels in patients with grade 2 and 3 bladder tumour than those of normal individuals[244]. Note: the tissue HAase levels usually correlate with tumour grade[243]
Phospholipases	Typical plasma levels of type II secretory phospholipase A2 (sPLA2) in healthy individuals are 5.8–12.6 ng ml^{-1}; elevated sPLA2 levels are associated with potential artery diseases[245]
PSA	The lower threshold of PSA was established to be >4 ng ml^{-1} in a PLCO trial[246] and >3 ng ml^{-1} based on the ERSPC trial[247]; elevated PSA levels are often associated with prostate cancer
Glucose	
Diabetic[84]	Blood glucose level: >180 mg dl^{-1} (hyperglycemia); <70 mg dl^{-1} (hypoglycemia)
Non-diabetic	Blood glucose level: 70–100 mg dl^{-1} (normal fasting blood glucose level); <140 mg dl^{-1} (normal blood sugar level, 2 hours post-eating)
Physical stimulus	
Temperature	Normal body temperature: 36.5–37.5 °C
Pressure and shear force	Normal range of mean arterial pressure: 70–105 mmHg. The average shear stress in healthy coronary arteries is found to be around 1.5 Pa; in constricted vessels, it increases to above 7 Pa (REF. 250)
Others	
ATP	Intracellular environment: 1–10 mM; extracellular environment: <5 μM (REF. 248)
Hypoxia	Hypoxemia (abnormally low blood oxygen level): <60 mmHg Hypoxia (low oxygen levels in tissues): critical oxygen partial pressure is 8–10 mmHg on a global tissue level[249]; for example, regions with low oxygen partial pressures (down to zero) often exist in solid tumours[249]

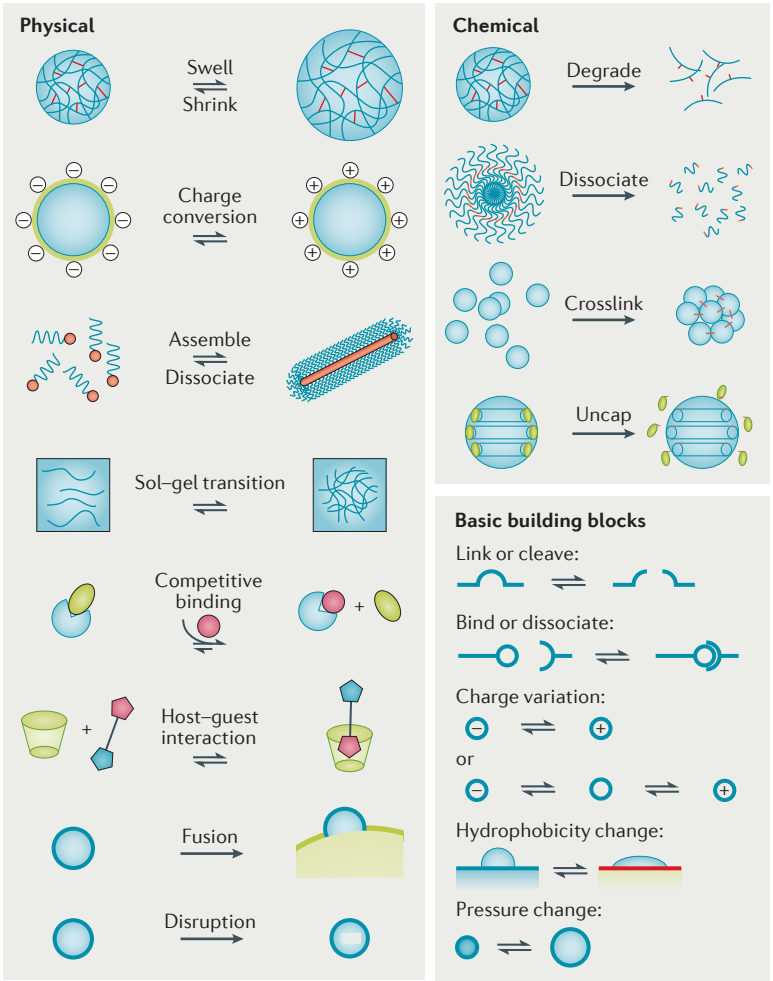
ATP, adenosine triphosphate; ERSPC, European Randomized Study of Screening for Prostate Cancer; HAase, hyaluronidase; MMP, matrix metalloproteinase; PLCO, Prostate, Lung, Colorectal, and Ovarian cancer screening trial; PSA, prostate-specific antigen.

such as boronic ester groups and phenylboronic acid (PBA) derivatives have also attracted considerable attention[62–65]. For example, arylboronic esters were modified at the hydroxyl groups of dextran as well as the lysine residues of RNase A for H_2O_2-triggered protein release and activity recovery, respectively.

In a recently reported anti-inflammatory drug-delivery system targeting osteoarthritis associated with H_2O_2, the PLGA hollow microsphere carrier was encapsulated with an anti-inflammatory drug, an acid precursor (composed of ethanol and $FeCl_2$), and a bubble-generating agent, sodium bicarbonate[66]. The material was designed to allow H_2O_2 diffusion through the microspheres allowing for ethanol oxidation to establish an acidic milieu, in which sodium bicarbonate decomposed to generate CO_2 bubbles, disrupting the shell wall of the microspheres and leading to the release of the anti-inflammatory payload.

Monitoring localized ROS levels has the potential to improve the diagnosis and treatment of a wide variety of diseases, ranging from cardiovascular diseases to drug-induced organ failure. Incorporating ROS-responsive materials represents an appealing approach for developing enzyme-free ROS sensors. A recently developed biosensor that uses a thin film of a hydrogel polymer containing ROS-degradable thiocarbamate linkages in its backbone was capable of detecting drug-induced liver injury by monitoring the oxidative stress in the blood[67].

Box 2 | **Typical bioresponsive actions**



Bioresponsive materials can be integrated with formulations, scaffolds or devices to act differently towards biological triggers. Most of these materials can be described as 'transformable' because they are often capable of morphology changes upon exposure to environmental stimuli. Choosing appropriate stimuli-responsive mechanism(s) is critical for achieving desired applications. The ideal bioresponsive behaviour should be both highly selective and sensitive, which requires target-specific responses. As summarized in the figure, the stimuli-triggered responses can be based on physical changes, on chemical changes or on a combination of both, all of which are generally based on the basic building blocks. Target items, such as therapeutics, can be further incorporated into these formats for stimuli-triggered delivery.

Enzymes

Owing to the varied roles that enzymes have in different biological processes, disease-associated enzyme dysregulations have recently become an emerging target for medications. For example, ester bonds are often incorporated for targeting phosphatases, intracellular acid hydrolases and several other esterases; amides, although relatively stable to chemical attack in physiological environments, are vulnerable to enzymatic digestion and have been used for constructing materials sensitive to hydrolytic proteases, such as prostate-specific antigens; and materials containing cleavable azo linkers can target bacterial enzymes in the colon for site-specific drug release. Here, we illustrate several typical enzymatic triggers.

Matrix metalloproteinases (MMPs) are closely associated with tumour invasion and metastasis. The upregulated expression of MMPs within the tumour microenvironment can serve as site-specific biological cues for activating bioresponsive materials[68–70]. Activatable CPPs (ACPPs) with blocked cellular interaction were constructed by fusing CPPs with an anionic inhibitory domain[71,72]. ACPPs can be activated by overexpressed MMPs at the tumour site through the cleavage of the linker connecting the cationic and anionic domains. This strategy has been applied for visualizing tumours during surgery. In addition to the tumour microenvironment, MMP upregulation is also associated with other inflammatory diseases such as asthma and inflammatory bowel diseases, providing a potential drug-delivery target[73,74]. In a recent study, a negatively charged hydrogel was anchored to the surface of the inflamed colon with upregulated MMP expression, where it released anti-inflammatory drugs only upon enzymatic digestion[73]. In addition, being a natural habitat of a series of bacteria that constantly secrete various enzymes including several polysaccharidases, the colon is a suitable target for site-specific drug release using polysaccharide-based materials. Biocompatible polysaccharides, such as chitosan, pectin and dextran, have been used for colon-specific drug delivery via the oral route in various forms including tablets, capsules, hydrogels and drug conjugates. Polysaccharides have also been used as crosslinkers to form lysozyme-cleavable nanogels, which were further incorporated into contact lenses for sustained release of glaucoma drugs[75]. Another

class of enzymes whose expression is often elevated at the tumour site is hyaluronidase (HAase). In a gel–liposome nanoformulation[76], the core–shell structured nanocarrier was designed to have a cell-penetrating peptide-modified liposome core for chemotherapeutic loading and a hyaluronic acid-based crosslinked shell for the encapsulation of tumour necrosis factor-related apoptosis inducing ligand (TRAIL), a cytokine that can bind to the death receptors on the plasma membrane. In the tumour microenvironment, the hyaluronic acid shell was digested by the overexpressed HAase, leading to the release of TRAIL, followed by the sequential release of Dox inside cells. In addition to triggering cargo release, the HAase has also been used for the *in situ* construction of extracellular drug-delivery depots for sustained local cargo release[77].

Furin — a member of the pro-protein convertase family — has a crucial role in tumour progression, metastasis and angiogenesis. In one study, furin-cleavable peptide crosslinker was incorporated into drug-delivery carriers, which could be degraded gradually to release cargo protein along their cellular uptake pathway[78]. Recently, a graphene-based co-delivery system took advantage of the transmembrane activity of furin to cleave the furin-degradable substrate for the exposure of TRAIL toward the membrane[79]. In addition, intracellular enzyme protein kinase Cα (PKCα) is crucial for cancer cell proliferation[80]. PKCα is hyper-activated in various cancer cell lines but displays low activity in normal cells. To take advantage of the cancer-specificity of PKCα, researchers have designed polymers equipped with PKCα-specific peptide substrates for targeted gene delivery. In another study, caspase 3-cleavable polymeric nanocarriers that were crosslinked by the caspase 3 substrate-based peptide crosslinker were developed to deliver caspase 3 for promoting apoptosis of cancer cells in a 'self-degradable' manner[81].

Several phospholipases also function in the extracellular microenvironment when selected as therapeutic targets[82]. In a hydrogel-based closed-loop system designed to be responsive to blood coagulation, heparin release was triggered by the cleavage of thrombin-degradable peptide when the blood thrombin reached a high level; the released heparin then inactivated thrombin to inhibit further drug release[83].

Glucose

At present, blood sugar monitoring and insulin injection ('open-loop' treatment) is still the primary management of type 1 and advanced type 2 diabetes[84]. Apart from being both painful and inconvenient, it is extremely challenging to tightly control blood glucose levels (BGLs) in this way, which leads to a high risk of diabetes complications[17]. Moreover, hypoglycaemia can result in fatal insulin shock. Therefore, there is a tremendous desire for glucose-responsive 'closed-loop' medications that mimic the function of the healthy pancreas and work in a self-regulated manner[17].

The first glucose-responsive insulin delivery system (GRIDS) was developed[3] in 1979, and used concanavalin A (ConA), a member of the saccharide-binding lectin family. Free glucose can dock within the specific binding sites of the ConA–polymer complex, causing the dissociation of the complex and subsequent insulin release[85]. Enormous efforts have been invested in this area[17,84], focusing in particular on achieving a fast response, ease of administration and excellent biocompatibility. In general, there are two types of GRIDS based on the mechanism of controlling the BGL. In one type, such as GRIDS based on ConA or synthetic boronic acids[3,86–88], a high BGL serves as the direct trigger for insulin release (that is, a directly triggered model). In other systems, which apply the glucose oxidase (GOx)-based enzymatic reaction, a high BGL induces a decrease of local pH or oxygen level, which subsequently promotes insulin release (that is, a progressively activated model)[89].

The saccharide-sensitivity endued by the well-established boronic acid–diol interaction renders boronic acid-containing polymers potential candidates for constructing glucose-responsive materials. PBA with electron-withdrawing moieties is commonly used[87,90]. In a recent study, researchers linked small molecules containing both an aliphatic moiety and a PBA moiety to insulin. Such conjugation afforded binding to serum albumin, or other hydrophobic components in serum, for prolonged circulation half-life as well as glucose-responsive release of insulin[90]. In another case, polymersomes constructed from polyboroxole block copolymers showed on-demand insulin release upon high BGL[91].

GOx converts glucose into gluconic acid in the presence of oxygen, resulting in a decreased local pH value[89,92]. This action can enhance the solubility of lysine-modified insulin[92], which triggers the swelling or collapsing of hydrogels[89,93–96] or the dissociation of nanoformulations[97], leading to insulin release. An example of this is the glucose-dependent swelling and deswelling of GOx-immobilized hydrogels constructed with cationic copolymers[89,98]. In addition to the localized acidification, researchers have recently taken advantage of enzymatically generated local hypoxia (induced by elevated BGL) to create glucose-responsive microneedle-array patches (smart insulin patches)[99]. Rapid glucose-responsive insulin release can be achieved through vesicles assembled from 2-nitroimidazole-conjugated hyaluronic acid.

The application of glucose-responsive materials is not limited to GRIDS. For example, in a recent study, hydrogel formulations composed of PBA derivatives showed potential as both the delivery carrier for protein therapeutics and substrates for 3D cell culture[100]. The hydrogel exhibited self-healing (rapid structural recovery) based on the dynamic interaction between PBA and diols. A nanostructured surface constructed by grafting a PBA-containing brush from an aligned silicon nanowire array captured and released cells in response to changes in pH values and glucose concentration in an AND logic manner[101]. In addition, in a recently reported microneedle-based cancer immunotherapeutic delivery system targeting melanoma, GOx converted blood glucose to localized acidification for triggering sustained release of anti-PD1 antibody with enhanced retention in the tumour site[102].

In addition to drug-delivery systems, glucose-responsive materials are also used for long-term glucose monitoring.

For example, single-walled carbon nanotubes (SWNTs) functionalized with a glucose analogue were developed for glucose sensing[103,104]. The SWNTs forms aggregations in the presence of saccharide-binding ConA or PBA, quenching the fluorescence signal. By contrast, the dissociation of such aggregates owing to the competitive binding of glucose leads to the recovery of the fluorescence. Fluorescent polyacrylamide hydrogel beads fabricated from monomers containing glucose-recognition sites and fluorogenic sites have shown potential for continuous BGL monitoring[105].

Ions

Ionic strengths vary from one type of biological fluid to another. For example, each gastrointestinal site has a specific ionic concentration; thus, materials sensitive to ionic strength are of particular interest as oral delivery carriers[106]. Moreover, gradients in ionic concentration also exist in the blood, and in interstitial and intracellular compartments, corresponding to other drug administration approaches, such as intravenous injection.

A large family of physical ion-responsive materials is ion-exchange resins, which are frequently used for taste-masking, counterion-responsive drug release, and sustained drug release[107]. These resins are usually insoluble polymers composed of a crosslinked polystyrene backbone with side chains containing ion-active groups such as sulfonic acid and carboxylic acid. Upon oral administration, the counterions in the saliva and gastrointestinal fluids promote drug release, which is governed by an equilibrium exchange reaction. For example, cationic polymers containing quaternary ammonium groups display sensitivity towards ions in the saliva[108]. Polymers exhibiting a lower critical solution temperature (LCST) also display certain sensitivity towards ionic strength[109]. The LCST can be shifted, normally to a lower temperature, in the presence of salt, following the Hofmeister series[109]. Polyion complex micelles represent another major family of ionic strength-sensitive materials. Reversible formation and dissociation of polyion complex micelles through a change in salt concentration (and thus ionic strength) have been used for controlled cargo release[110].

In addition to responding physically to changes of ionic strength, materials can also respond to specific ion types, typically by forming complexes. In a recently reported metal-ion-responsive adhesive hydrogel, modified with β-cyclodextrin and hydrophobic 2,2′-bipyridyl moieties, the chemically selective adhesion property could be switched by controlling the inclusion of inhibitory metal ligands to host moieties[111].

ATP

Adenosine-5′-triphosphate (ATP), which is often referred to as the 'molecular unit of currency' of intracellular energy transfer, is found at higher concentration intracellularly than in the extracellular environment because of its immediate relationship with cell metabolism.

ATP-controlled drug-delivery systems often use ATP-targeted aptamers as 'biogates' to achieve on-demand cargo release[112]. In recent years, various formulations, such as mesoporous silica, polyion micelles, aptamer-crosslinked DNA microcapsules, tubular structures assembled from proteins and nanogels composed of DNA complexes, have demonstrated the ability to release therapeutics or restore fluorescence signals on exposure to relatively concentrated intracellular ATP[113–116]. In these cases, ATP either competitively binds to drug loading sites to trigger cargo release or fuels conformational changes, which generate structure-disrupting forces. For example, DNA aptamers were incorporated into a Dox-loaded DNA duplex[115]. The competitive binding of ATP molecules to ATP aptamers in an ATP-rich environment resulted in the dissociation of the duplex for targeted drug release. In another design[114], a protein nanotube assembled from barrel-shaped chaperonin units shielded cargo molecules from biological degradation, but upon exposure to the intracellular hydrolysis of ATP, the induced conformational change of the chaperonins led to the disassembly of the tubular structure and the release of the guest molecules. Instead of functioning solely, ATP can serve as part of a combinational trigger with other stimuli[117].

Hypoxia

Hypoxia is associated with various diseases including cancer, cardiomyopathy, ischaemia, rheumatoid arthritis and vascular diseases[118].

Tumour hypoxia is generally considered as a negative prognostic because of its central role in tumour progression and therapy resistance, and has been extensively exploited for engineering diagnostic agents and therapeutics[119]. Nitroaromatic derivatives that can be converted to hydrophilic 2-aminoimidazoles under hypoxic conditions with a relatively high sensitivity are among the most widely exploited functional motifs for hypoxia imaging and the design of bioreductive prodrugs. Similarly, azobenzene, another well-established, hypoxia-sensitive motif previously used as an imaging probe, has been incorporated in the form of a bioreductive linker for targeted siRNA delivery[120]. Recently, researchers also used the idea of engineering smart materials containing oxygen-sensitive groups as substitutes for hypoxia-responsive small molecules or transition metal complexes to improve the sensitivity and specificity for *in vivo* imaging[121,122]. To achieve ultrasensitive detection of cancer cells, a water-soluble macromolecular imaging probe with hypoxia-sensitivity and near-infrared (NIR) emission was synthesized by conjugating a phosphorescent iridium (III) complex to a hydrophilic polymer, poly(*N*-vinylpyrrolidone) (PVP)[122]. Similar approaches might be of interest for enhancing imaging for the diagnosis and real-time monitoring of other hypoxia-associated diseases, such as stroke and ischaemia[123,124].

Temperature

Polymers that exhibit a LCST typically undergo an abrupt phase transition near the LCST, which can be easily tuned by adjusting the ratio of hydrophobic and hydrophilic components or by replacing the end groups[125]. When the LCST of a polymer is between room temperature and body temperature, the polymer is endowed with inherent sensitivity towards physiological temperature.

Poly(*N*-isopropylacrylamide) (PNIPAM) undergoes a sol–gel transition at its LCST of 32 °C, and this value can be further optimized to be closer to body temperature through copolymerization with hydrophobic monomers or the introduction of hydrophobic groups[126]. The application of PNIPAM for thermoresponsive drug delivery was developed in the 1980s[127,128]. In some hybrid systems, the LCST of PNIPAM-based materials was varied by incorporating inorganic materials, such as gold nanoparticles[129–131]. To accelerate the thermoresponsive transition process, researchers have developed controllable, activated nanogels as crosslinkers for the construction of thermoresponsive hydrogels. The resulting hydrogels displayed rapid and reversible responsive characteristics while maintaining high elasticity[132]. Homopolymers and copolymers of *N*-acryloyl pyrrolidine (APy) and 2-hydroxyethyl methacrylate (HaEMA) have also been synthesized to achieve temperature-regulated insulin release through the tuning of permeability[133,134]. Furthermore, the temperature-sensitive coiled-coil domains of proteins have been complexed onto soluble polymers to generate thermoresponsive hybrids[135].

Other thermoresponsive materials include several classes of synthetic polypeptides, among which elastin-like polypeptides (ELPs) have attracted considerable attention. ELPs are genetically encodable polypeptides composed of repeating Val–Pro–Gly–X–Gly (X ≠ Pro) sequences. These polypeptides with controllable composition and length exhibit a LCST[136] that can be fine-tuned within the range of 0–100 °C to comply with different applications. With a LCST lower than body temperature, ELP-therapeutic conjugation can form a tumour-resident drug depot after local injection, through temperature-induced coacervation[137]. In a similar strategy, ELPs were fused to protease-cleavable oligomers of glucagon-like peptide-1 (GLP-1) to obtain an injectable drug depot[138]. In addition, ELPs have also been applied for tissue engineering to form matrices *in situ*[139].

Mechanical cues

The narrowing or obstruction of blood vessels results in a significant variation in fluid shear force between healthy and constricted blood vessels. To target diseased blood vessels with obstruction, using the abnormally high shear stress at the blockage site as a trigger has recently emerged as an appealing strategy.

For example, spherical liposomes are highly stable to shear forces whereas lenticular liposomes[140] preferentially release encapsulated cargo when subjected to high shear forces owing to transient pore formation, which enables disease-targeted release. Another strategy is to form micrometre-sized aggregates that are stable under static conditions yet are disrupted on exposure to high shear stress[141]. Platelet-shaped micro-aggregates composed of several nanoparticles underwent a disassociation at sites with abnormally high shear stress. The resulting nanoparticles adhered more efficiently to the walls of blood vessels because they experienced relatively low drag force compared with larger structures. This design led to drug enrichment at diseased locations, minimizing off-site drug release.

Another design strategy that involves *in vivo* pressure gradients is the fine-tuning of the material size on the nanoscale to take advantage of the 'enhanced permeability and retention' effect[142]. It has been shown that elevating the mean arterial blood pressure upgrades this effect and thus enhances tumour accumulation[143].

A wearable, tensile-strain-sensitive device composed of stretchable elastomer film with embedded drug-encapsulated PLGA microspheres was recently developed[144]. On application of strain, the mircoparticles underwent surface enlargement and compression, thereby releasing the drug. In another example, a pressure-sensitive quantum tunnelling composite was coated onto the surface of a battery to lower the potential external electrolytic current if accidentally swallowed[145].

Nucleic acids

Nucleic acids, including RNA and DNA, have recently emerged as important biological triggers because of their various roles in different biological processes as well as their unique hybridization features.

Alterations of microRNAs (miRNAs) have been revealed to be involved in the initiation and progression of cancer, rendering them potential targets for cancer therapy[146]. In light of this, multicomponent nucleic acid enzymes (MNAzymes) were functionalized to the surface of silica-coated gold nanorods[147]. In this design, an inactive DNA motif is formed from two MNAzymes, which are activated by the conformational rearrangement that occurs in the presence of the target miRNA. The activated MNAzymes then cleave and release fluorescent probes for intracellular imaging, while the conformational change of the DNA motif serves as an uncapping mechanism, triggering the release of the encapsulated chemotherapeutics. Mesoporous silica nanocarriers gated with DNA aptamers specifically release Dox upon exposure to target miRNA[148]. Additionally, a biomimicking nanosystem loaded with endoribonuclease used DNA oligonucleotides as a recognition motif to achieve site-specific cleavage of target RNA[149].

DNA enables physicochemical control over nanoparticle-based systems with high precision. This is exemplified by the assembly of gold nanoparticles mediated by the specific interactions of DNA oligonucleotides[150]. The recent breakthrough in DNA-controlled colloid bonding, in which inorganic nanoparticles act as analogues of atoms and form crystal-like structures with the guidance of DNA strands, has gained considerable attention[151]. In another dynamic colloidal nanoparticle system, DNA was used to control the morphology of gold nanoparticles to either hide or expose cell-targeting folic acid ligands, thereby regulating the particle–cell interactions[152]. Moreover, an alginate depot was developed that used oligodeoxynucleotide-mediated binding to realize drug refilling through blood[153].

To control the activity and minimize the side effects of therapeutic aptamers during treatment, researchers have developed matching oligonucleotides that specifically neutralize the activity of the

therapeutic oligonucleotides[154]. Furthermore, the sequence-independent interaction between polymers and proteins or aptamers has also been exploited to enable universal antidotes that counteract the activity of circulating aptamers[155,156].

Sensitivity to biological particulates

In addition to creating materials that can respond to physiological signals, an emerging trend in bioengineering is to engineer materials that can interact with biological particulates, including eukaryotic cells, bacteria and viruses. Current design strategies mainly include chemical engineering (synthesis and modification) approaches as well as bioengineering approaches (FIG. 2).

Scaffolds and surfaces

The ultimate goal for regenerative medicine is to engineer replacements for diseased biological tissues as alternatives to other treatment approaches such as organ transplantation[157]. There is an inherent need for engineered materials capable of fulfilling the native behaviour of naturally occurring biological components[47,158,159]. In addition to maintaining desirable physical properties, bioactive ligands are often incorporated for building bioresponsive materials[160,161] (FIG. 2). Ideally, the materials should be able to instruct cell behaviour, including trafficking, attachment and proliferation, and, in the case of stem cells, should also have a key role in guiding stem-cell differentiation[162].

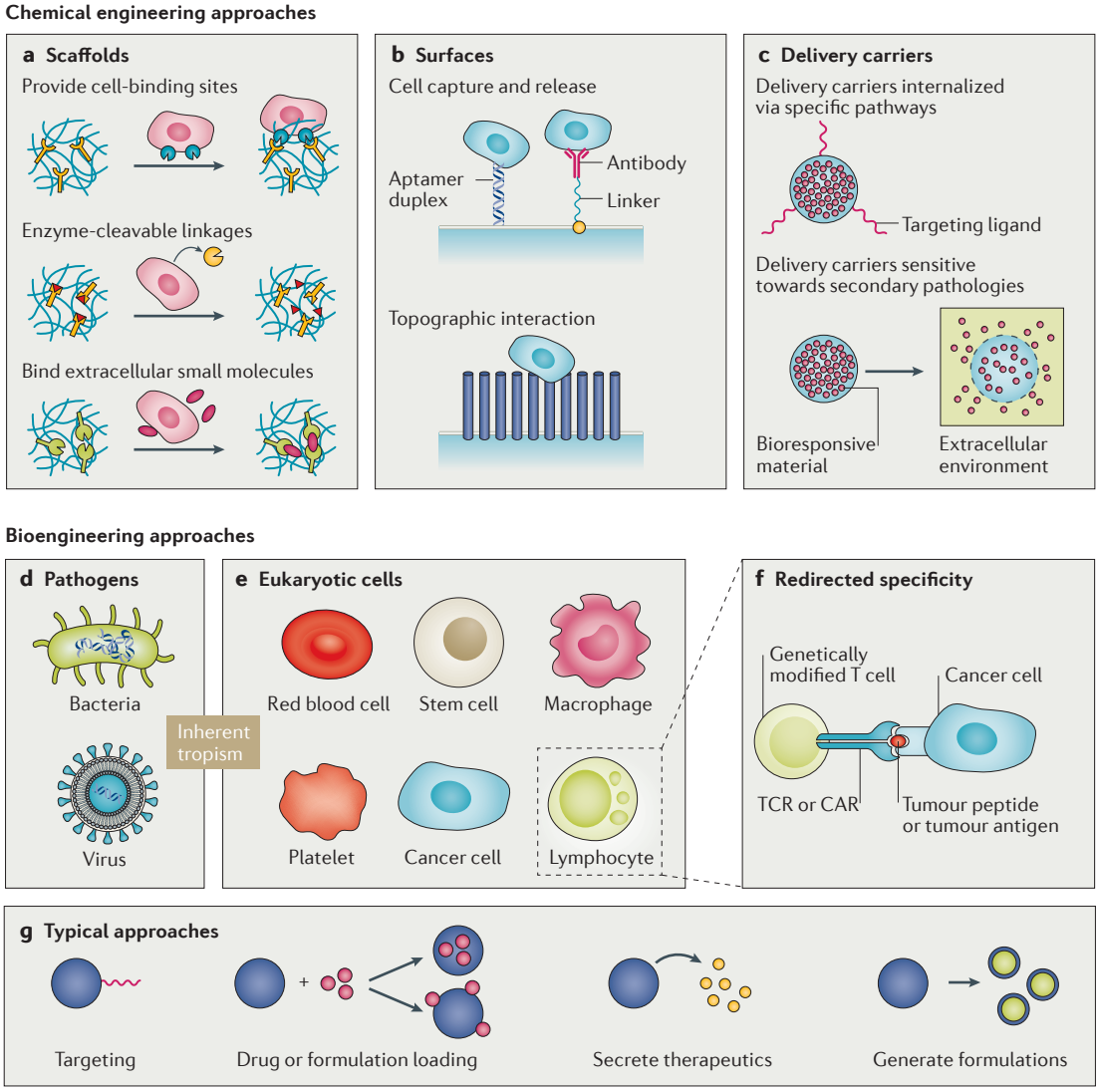


Figure 2 | **Materials sensitive to biological particulates.** There are two major approaches for constructing smart materials capable of communicating with biological particulates: chemical engineering (panels **a**–**c**) and bioengineering (panels **d**–**g**). **a** | Cell-responsive scaffolds can have a range of useful properties. **b** | Surfaces can be functionalized with cell-binding ligands or designed to have fractal structures for the reversible capture and release of cells. **c** | Delivery carriers with a specific internalization pathway and nanoparticles sensitive towards cell-induced environmental variations. The different bioengineering approaches include the use of pathogens (panel **d**), eukaryotic cells (panel **e**) and the genetic redirection of T-cell specificity (panel **f**), which is an emerging strategy for cancer immunotherapy. **g** | Typical approaches are shown schematically. CAR, chimeric antigen receptor; TCR, T-cell receptor.

A reasonable strategy is to take advantage of the major functional components derived from the natural extracellular matrix (ECM)[163]. In one study, porous, injectable gelatin cryogels could rapidly resume their original shape after subcutaneous injection[164]. The resulting cell-adhesive, gelatin scaffolds could then be degraded by MMPs. In addition to the inherent bioactivity of gelatin, the microgrooved surfaces of these fibres promoted cell encapsulation and adhesion to induce cell alignment. Besides, protein hydrogels have also attracted considerable attention owing to their biocompatibility and ease of incorporating bioactive ligands.

Compared with natural scaffolds, synthetic scaffolds have several advantages, including predefined physical and chemical properties, and relatively low cost. One of the most widely applied strategies is assisting tissue regeneration by mimicking the invasion of the natural ECM mediated by MMPs[165]. In light of this, both integrin-binding sites and MMP substrates are required to provide the synthetic networks with cell-specific degradability. MMP-responsive matrices were developed and have been used for constructing cell-responsive drug-delivery systems and synthesizing injectable matrices for tissue regeneration[165]. Through *in situ* addition reactions, a hydrogel can be formed that combines a structural component (PEG) and bioresponsive oligopeptides, whereby the matrix can be degraded by cell-surface proteases to create 3D pathways for cell invasion[166]. In a PEG-based MMP-degradable matrix, a bioactive peptide, thymosin β4 (Tβ4), was co-encapsulated with human umbilical vein endothelial cells (HUVEC)[167]. After encapsulation, the matrix can be considered to have a built-in signal-amplification modality. Tβ4 can stimulate MMP-2 and MMP-9 secretion from the encapsulated HUVEC, and the released MMPs can further degrade the MMP-sensitive substrates, triggering the release of Tβ4.

In addition to purely natural or synthetic materials, hybrids have also been applied to imitate the functions of the ECM[168,169]. Instead of directly modifying the matrices, researchers have recently incorporated kartogenin (a differentiation-inducing agent)-encapsulated PLGA nanoparticles into hyaluronic acid hydrogels for cartilage regeneration[170]. In a recent study, PEG-based microgels crosslinked by an MMP-substrate were further annealed into a microporous particle gel through transglutaminase-catalysed amide formation[171].

Cell adhesion ligands are crucial components of natural ECM and thus are commonly incorporated into scaffolds to provide cells with proper biophysical cues. For this purpose, natural adhesion proteins and peptides, such as collagen and Arg–Gly–Asp (RGD) peptides, have been widely applied to mimic the native extracellular microenvironment. In addition, studies have shown that DNA aptamers can be functionalized onto hydrogels for specific cellular adhesion with minimal sacrifice of scaffold mechanical properties[172,173]. Moreover, synthetic matrices chemically functionalized with small-molecule moieties have been used to direct stem-cell differentiation[174].

The strategy of incorporating cell adhesion ligands into scaffolds has been extended to intelligent surfaces on medical devices that can specifically catch and non-destructively release cells such as lymphocytes and circulating tumour cells[175]. A 3D network composed of repeating DNA aptamer domains selectively captured and released cancer cells with high efficiency[176]. Similarly, antibodies can bind cells with high efficiency. The available substrate materials range from soft organic materials, such as polystyrene, to rigid inorganic formulations, including gold nanostructures and silicon nanowires[177]. In addition to topographic interactions, hydrophobic interactions realized by a thermoresponsive PNIPAM coating have been used in combination with antibodies for efficient cell capture[177]. It is worth noting that it is crucial to control the physicochemical properties and bioactivities of hydrogels in both space and time. One of the emerging approaches to achieve the spatiotemporal control over hydrogels is photopatterning[178,179]. Photochemical techniques have enabled the remote and precise control over hydrogel properties via light triggers[180,181].

Another emerging application of cell-responsive materials is in the creation of artificial tumour microenvironments *in vitro* and *in vivo*, with the intention to alter the immune system to achieve improved outcomes for immunotherapy[182]. For example, immunotherapy can be further integrated with bioactive materials that are able to regulate the tumour microenvironment for enhanced therapeutic efficacy[182].

Synthetic carriers

Nanoformulations represent another format of materials that are responsive to biological particulates, especially bacteria. The main strategies for fabricating bacteria-responsive materials fall into two major classes: direct bacteria targeting, such as microorganism recognition based on specific uptake pathways, and targeting infectious microenvironments[183,184]. Bacteria-associated secondary biological cues include toxins, bacterial enzyme overexpression and local acidification.

A family of maltodextrin-based imaging probes were synthesized to target bacteria directly[185]. These probes are efficiently internalized through the bacteria-specific maltodextrin transport pathway to achieve the localized accumulation inside the bacteria. The uniqueness of this bacteria-targeting mechanism is its independence of the host response and secondary pathologies.

Over 70 years of abusing of antibiotics has created 'super bacteria', which exhibit multiple resistance towards traditional treatments. Compared with traditional therapy, anti-virulence approaches exert less selective pressure, and this delays the development of bacterial resistance[183]. For some severe infectious conditions, targeting the toxin becomes an appealing strategy. For example, gold mixed-monolayer protected clusters can recognize and stabilize peptide α-helices[186]. Plastic antibodies were also developed using copolymeric *N*-isopropylacrylamide:*N*-*tert*-butylacrylamide (NIPAM:BAM) nanoparticles[187]. Furthermore, a new type of plastic antidote — protein-sized polymeric

nanoparticles with satisfactory binding affinity and selectivity — was synthesized by combining molecular imprinting with a functional monomer optimization strategy[188].

Moreover, a carrier–drug conjugate was developed that can be cleaved by a specific enzyme, penicillin G amidase (PGA), from *E. coli* cells containing the PGA gene, thereby releasing the drug molecule and a fluorescent probe[189]. This carrier lowers the drug dosage required to kill the bacteria in addition to providing a route for targeted combination therapy[189]. Extracellular lipases are particularly abundant at sites of bacterial infection, as indicated by high amounts of anti-lipase in anti-sera obtained from cystic fibrosis patients suffering from *Pseudomonas aeruginosa* infection. Taking advantage of this bacterial enzyme overexpression, researchers developed nanogels composed of mannosyl ligands conjugated to the shell of a PEG-armed and polyphosphoester core-crosslinked nanogel, which could be degraded by the active phosphatase or phospholipase produced by the bacteria[190]. Such bacteria-targeted drug release can also be achieved by directly conjugating antibiotics to PEG via lipase-sensitive linkages[191].

Targeting bacteria-induced local acidification has also emerged as an appealing approach to fight bacterial infections[192]. For example, polymeric nanoparticles that underwent a charge conversion under acidic pH were developed for bacteria-wall-targeted antibiotic delivery[192].

Antibacterial medical devices capable of preventing infection and suppressing biofilms are of notable clinical significance because indwelling device infections are often life-threatening and attributed to biofilm tolerance to antibiotic treatments. For example, lytic-peptide-immobilized surfaces have been shown to sense bacteria adhesion and kill attached bacteria, and are thus suitable as antibacterial surfaces of medical implantations[193].

Engineered biological particulates

In the past decades, a considerable number of engineered biological particulates have been developed for targeted therapy, with some of them successfully entering clinical practice[194].

For mucosal-targeted delivery, recombinant *Lactobacillus acidophilus* was engineered to express the protective antigen of *Bacillus anthracis*, which was further fused with dendritic-cell-targeting peptide to recognize and bind to mucosal dendritic cells[195]. Additionally, it has been revealed that certain strains of bacteria specifically colonize tumour cells, exhibiting a natural tumour-targetability. Making use of their natural tumour tropism, these bacteria have been genetically modified to express protein therapeutics for cancer treatment[196]. Recently, researchers programmed a bacteria-based circuit to lyse and release anticancer toxins at the tumour site upon achieving the threshold population[197].

Similar to bacteria, viruses have also evolved into natural carriers with both specificity and efficiency. Cell-targeted carriers constructed from engineered viruses mainly take advantage of their natural tropism with a range of targets. For example, virus-like particles are particles self-assembled from virus-derived capsid or envelope proteins, whereas virosomes are spherical virion-like lipid bilayer vesicles containing virus-derived surface glycoproteins[194]. These vesicles have inherited the capability to specifically recognize and interact with target cells from their parental viruses. Despite their potency, up to now the clinical use of these pathogen-based carriers has been limited to vaccine delivery. The potential immunogenicity has hindered their clinical translation[198].

Stem cells also possess tumour tropism and thus have been genetically engineered to express anticancer proteins specifically at tumour sites[199]. Owing to the capability of cells to endocytose nanoparticles or to absorb nanoparticles onto their surfaces, it is also possible to use stem cells as tumour-targeting carriers for delivering nanoparticles[200]. An important feature of cancer cells is homotypic tumour cell adhesion. In light of this, cancer cell membranes were coated onto the surface of PLGA nanoparticles for source-cell-targeted delivery[201]. Natural RNA transport vesicles, such as exosomes, have been genetically modified with targeting peptides for gene delivery[202]. Red blood cells (RBCs) are promising drug-delivery candidates that possess several appealing features, such as their long circulation time. In addition, their unique transporting characteristics enable RBC-based delivery targeting RBC-eliminating cells, such as reticuloendothelial system macrophages. Apart from directly using intact RBCs, RBC membranes have also been coated on PLGA cores for different applications, such as toxin absorption[203]. Moreover, synthetic nanoparticles have been coated with platelet membranes to target MRSA252 bacteria[204] and circulating tumour cells[205,206]. As an essential component of the immune system, macrophages also display an inherent tendency to harbour diseased tissues attributed to the cellular secretion of signalling molecules, such as cytokines, and thus are natural vehicles for targeted drug delivery. Similar to nanoparticle-containing stem cells, nanoparticles can also be loaded into macrophages by means of phagocytosis[207].

The interaction between immune cells and target cells has been extensively explored for constructing bioresponsive vehicles. For example, the interactions among lymphocytes of the immune system have been used for developing a whole-cell sensing system[208]. In a recently developed method, live T cells expressing lymph-node-homing receptors were used as active carriers for delivering chemotherapeutic-loaded nanoparticles to cancerous lymphoid tissues[209]. T-cell therapy suffers from relatively low *in vivo* persistence and rapid function decline, and thus often requires co-administration of adjuvant drugs[210]. Using this strategy, adjuvant-loaded nanoparticles were conjugated onto the surface of T cells to enhance the efficacy of T-cell therapy[211]. By contrast, T-cell specificity could be effectively redirected through the genetically engineered expression of chimeric antigen receptors (CARs) on the surface of T cells[212]. In CAR-T-cell therapy, the engineered CAR T cells are cultured and expanded in the laboratory and then infused into the patient after a desired population has been achieved[213]. These 'living drugs' then multiply *in vivo* and

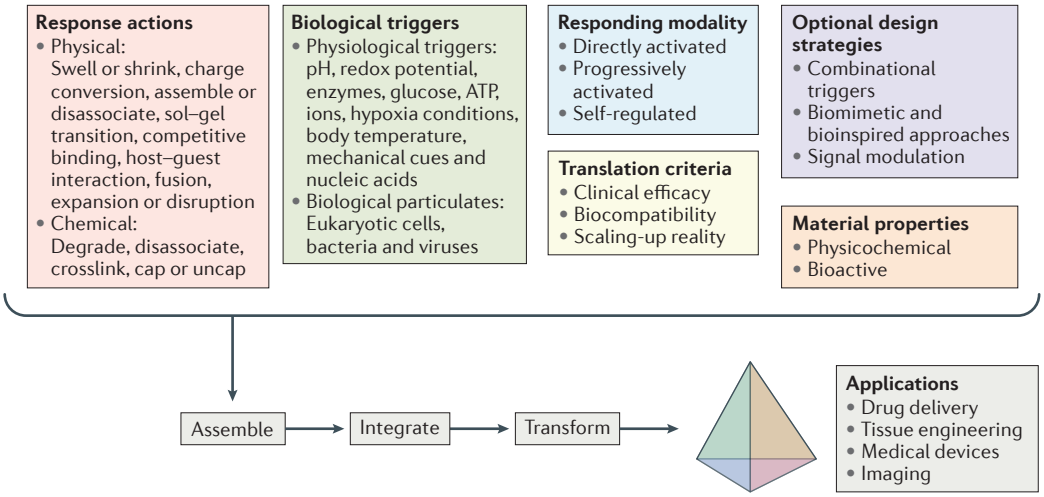


Figure 3 | **General design rationale of bioresponsive materials.** Multiple perspectives, including the responding modality, biological triggers, response actions, material properties, design strategies and translation criteria, serve as 'building blocks' for engineering bioresponsive materials for different applications.

recognize and kill cancer cells that harbour the antigen on their surfaces under the guidance of their engineered receptor[214].

Conclusion and outlook

The past decade has witnessed extensive exploration of bioresponsive materials accompanied by the confluent advances in materials science, molecular pharmaceutics and nanobiotechnology[5,215]. Despite the enormous efforts invested and the booming growth in scientific publications, few technologies have been successfully commercialized or have even entered clinical trials[11,15]. In the case of anticancer drug delivery, Cerulean Pharma's pH-responsive cyclodextrin-based nanocarrier[216] (CRLX101, ClinicalTrials.gov identifier: NCT01612546) has completed phase II trials, and its collaboration with FDA-approved poly ADP ribose polymerase (PARP) inhibitor LYNPARZA is now in phase I and II clinical trials. Several smart materials for diagnostic applications have entered clinical trials, including tumour-targeting silica nanoparticles equipped with a NIR fluorophore and radiolabelled peptide (ClinicalTrials.gov identifier: NCT01266096) for the detection of melanoma and malignant brain tumours. For diabetes treatment, Merck's smart insulin with glucose-sensitivity (MK-2640, ClinicalTrials.gov identifier: NCT02269735) is currently in phase I clinical trials. Most recently, SEL-212 from Selecta Biosciences (ClinicalTrials.gov identifier: NCT02648269) designed for gout treatment has just started clinical trials.

Generally, the success of technology commercialization relies on the feasibility of therapeutic scale-up manufacturing and the demonstration of robust clinical safety and efficacy, allowing for regulatory approval. Surveying the commercialized smart materials, such as aminoalkyl methacrylate copolymer (Eudragit E)[22], and several types of liposomes has revealed one commonality: a simple structure with a defined response mechanism of action makes these relevant formulations or devices highly attractive for industrial production and possible commercialization. The translation of bioresponsive materials is often restricted by their structural and/or mechanistic complexity. Innovation of bioresponsive materials design for biomedical applications should be based on translational feasibility, instead of decorating sophisticated structures and/or incorporating new methodology. Most 'overdesigned' systems are highly challenging with multiple mechanisms of action, prohibiting future exploration beyond preclinical demonstrations.

In FIG. 3 and BOX 3, we summarize the design rationale as well as highlight several guidelines with an emphasis on accelerating the potential translation of bioresponsive materials. To fulfil a successful construction process, several steps should be assembled and integrated with each other, including the choice of appropriate modality (BOX 1), determination of the target biological cue (TABLE 1) and choice of suitable responsive building blocks (BOX 2 and Supplementary information S1 (table)). Two important basic criteria should be followed: response efficacy (basic performance) — with high selectivity, high sensitivity and precise timing response action; and translation potential (clinical performance) — with desirable stability, excellent biocompatibility and ease of scaling up.

To be more specific, from a materials perspective, the ultimate goal is to achieve and maintain stable yet effective performance in the highly complex *in vivo* milieu, with satisfactory safety profiles. In drug delivery, for example, the clinical performance is frequently impeded by systematic toxicity and immunogenicity of the formulations. Thus, there is an urgent need to use materials or formulations (including their format(s) after response) with excellent biocompatibility as the first step when conceiving the strategy[217]. In addition, advances in bioresponsive materials development require a clear

understanding of the *in vivo* behaviour of a material. It is crucial to inspect how a material interacts with the biological milieu. There is an inherent need for advances in both fundamental biophysical and biochemical studies, as well as in detecting or imaging techniques that enable real-time monitoring of the administrated materials[218,219]. For most situations, the drug formulations need to be transported to reach the response location to interact with the effective biological environment; thus, the timing for sufficient interaction is extremely important. For some programmed stimuli-responsive systems[40,220], incorporating two or more stimuli for synergistic or sequential actions requires thorough testing *in vivo* to evaluate how to achieve precise spatiotemporal control of each trigger. A combination of detailed pharmacokinetic and pharmacodynamic analysis, as well as mathematical modelling will help to refine such systems[221].

Regarding the development of new response mechanisms to achieve high selectivity and sensitivity, the vast literature available in the field of bioanalytical chemistry could be assessed to help identify innovative triggers with high performance. For example, fluorescent SWNTs were recently functionalized with nitric-oxide-sensitive DNA oligonucleotides to detect reactive derived forms of nitric oxide at inflammatory sites[198]. Integrated with an actuation component, this design could be further extended to create a closed-loop drug release system. In another recent example, water gradients were exploited as a new type of stimulus[222]. This water-responsive polymer film was constructed with a rigid component, polypyrrole, and a polyol-borate-based, flexible, water-responsive unit. The mechanical properties of the composite could be tuned with a water trigger, the action of which was mainly attributed to the hydrolysis and reformation of the borate esters. The water exchange with the surrounding environment enabled film expansion and contraction, making it a potential smart material candidate sensitive to skin moisture. The researchers further incorporated this water-responsive film with a piezoelectric film to generate electric output fuelled by a water gradient.

Another emerging design strategy is to engineer biomimetic or bioinspired systems to mimic the natural bioresponsive mechanism in the body. For example, by mimicking the structure and response mechanism of granules or vesicles in pancreatic β cells, synthetic vesicles loaded with insulin can aid in a fast response for glucose-responsive insulin release[99]. Inspired by the efficient cell penetration capability of viruses, virus-mimicking nanogels were created to achieve sequential cellular internalization and deep tumour penetration[223]. Furthermore, biological machinery could be incorporated into the system, for example, using the bacteria-mimetic CRISPR–Cas 9 (clustered, regularly interspaced short palindromic repeat–CRISPR-associated protein) system for genome editing[224]. We note that biomimicry should not be limited solely to biochemical approaches. Instead, physical properties of the natural structures, such as their shape and mechanical property, could provide inspiration for constructing smart materials[225–227]. For example, nanoparticles resembling the shape and surface biology of platelets were shown to be capable of targeting vascular injuries[228], and nanoparticles coated with high-density PEG brushes to mimic viruses were demonstrated to efficiently penetrate the mucus barrier[229].

With respect to physiological signals, appreciable variations among and within individuals hinder the translation of bioresponsive materials. For exogenous stimuli-responsive materials, such as commercialized thermally responsive liposomes (ThermoDox, Celsion Corp.) and iron oxide nanoparticles (NanoTherm, MagForce AG), the stimulus can be manually controlled. By contrast, materials sensitive to endogenous stimuli suffer from inconsistent target biological parameters among patients. Moreover, the levels of biological cues may be significantly different between animal models and humans. Therefore, detailed information associated with the targeted cue(s) should be carefully collected and evaluated. Importantly, levels of biological cues can be manually tuned, for example, through signal amplification. In a recently developed β-cell-encapsulated microneedle patch, researchers designed a hypoxia-responsive 'signal amplifier' composed of GOx, α-amylase and glucoamylase[230]. The amplifier first converted the BGL into localized hypoxia to release the encapsulated enzymes. The released enzymes then digested the previously embedded α-amylose to generate a relatively high local glucose concentration to induce the secretion of insulin for externally positioned β-cell capsules[230]. In addition, the physiological environment can also be genetically modulated, for example, to create hypoxic conditions. In some cases, physical or biochemical triggers can be generated *in situ*[231,232]. For example, researchers applied radio waves to gate the transportation of Ca^{2+} for remote control over *in vivo* insulin synthesis[231]. In another study, light was used to generate hypoxic conditions at specific positions and times, to aid in drug release from a hypoxia-responsive formulation delivered to the tumour site of a mouse model[232]. Moreover, implanted wireless biochips[233] or wearable devices[234,235] that dynamically monitor physiological signals can further generate or amplify signals for achieving precision-controlled drug delivery[8].

Box 3 | **Take-home messages for designing bioresponsive materials**

- Take two basic criteria into consideration: response efficacy (with high selectivity, high sensitivity and high spatiotemporal control) and translation potential (desired stability, excellent biocompatibility and ease of scaling up)
- Build libraries of biological stimuli as well as bioresponsive motifs, which may require a high throughput study
- Flexibly choose from the three bioresponsive modalities (see BOX 1) based on the nature of the applications
- Adopt biomimetic or bioinspired approaches to mimic natural bioresponsive processes in the body
- Investigate the interactions among materials, formulations and devices, and the biological environment to optimize the design strategy
- Combine dual or multiple stimuli (programmed systems), either physiologically based or physical, to promote responsive behaviour and enhance the final efficacy

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