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Personalizing Biomaterials for Precision Nanomedicine Considering the Local Tissue Microenvironment

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New advances in (nano)biomaterial design coupled with the detailed study of tissue–biomaterial interactions can open a new chapter in personalized medicine, where biomaterials are chosen and designed to match specific tissue types and disease states. The notion of a "one size fits all" biomaterial no longer exists, as growing evidence points to the value of customizing material design to enhance (pre)clinical performance. The complex microenvironment in vivo at different tissue sites exhibits diverse cell types, tissue chemistry, tissue morphology, and mechanical stresses that are further altered by local pathology. This complex and dynamic environment may alter the implanted material's properties and in turn affect its in vivo performance. It is crucial, therefore, to carefully study tissue context and optimize biomaterials considering the implantation conditions. This practice would enable attaining predictable material performance and enhance clinical outcomes.

1. Precision Medicine: From Drugs to Materials

Biomaterials have been increasingly used in the medical field for myriad applications including sensing,[1–4] cell scaffolds for tissue engineering,[5–8] immunomodulation[9–12] and targeted drug delivery.[13–16] Such materials are programmed to perform a specific action on their biological environment. The development and characterization of material platforms is often conducted in vitro without adequate simulation of the intended clinical application. These studies are complemented by basic in vivo subcutaneous biocompatibility studies in murine models. Although many materials, especially those with embedded therapeutics, are eventually tested for efficacy in a more realistic disease model, most material optimization occurs during earlier stages of development.[17–19] This approach may not be sufficient to fully understand contextual material performance.[20,21] Different implantation sites and disease states exhibit variations that may have profound effects on local tissue chemistry, immune state, cell biology and mechanics. These variations may alter the pre-programmed material performance. Hence, predictive studies of material behavior must examine the material in a meaningful context, followed by material optimization for a given application (**Figure 1**).

For the past two decades, advances in panomics and systems biology allowed clinicians to envision personalizing the practice of medicine in a data-driven manner: drugs could be tailored precisely to the individual's condition based on their genetics and disease state. In a parallel of drug development, materials must be evaluated based on both 'material dynamics' and "material kinetics" in vivo. These roughly correspond to how the material affects the tissue and how the tissue affects the material. Material dynamics is usually studied in detail, where the therapeutic effect of a material system is evaluated to understand its biocompatibility and efficacy. However, material kinetics—understanding how the tissue microenvironment affects material properties—has long been neglected. Tissues and materials interact in a dynamic and complex manner, with significant influence imparted in both directions. Furthermore, we believe that interpersonal heterogeneity in disease etiology and pathogenesis should be considered in material design. As such, materials should be built from versatile building blocks that allow for application-specific optimization. Modular material platforms can thus be readily modified to sense and report on the dynamic local environment that would then trigger the most appropriate therapeutic outcome (**Figure 2**).

Evidence for tissue-dependent material performance was apparent in a study that followed the degradation of gelatin-based matrices subsequent to murine implantation in the subcutaneous, intramuscular or intraperitoneal spaces.[22] Degradation kinetics were significantly modified in different tissues owing to varying amounts of fluid present in each location. In another study, adhesion strength of a biological glue was tissue-dependent and varied between the lung, liver, heart and

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duodenum,[23] with each tissue presenting graded availability of binding sites. In addition, the effect of two disease models, inflammation and neoplasia, on adhesive material efficacy was recently examined.[21] It was shown that disease type (colitis or colon cancer) and state (graded colitis severities) substantially modify the interaction of the adhesive material with its surrounding tissue. Additionally, tissue responses to this adhesive material were altered. Modification of adhesive material behavior was driven by the tissue immune state and biochemistry, reiterating the importance of examining materials under (pre)clinically relevant conditions, as will be explained in detail in Section 3.2.

The era of precision medicine is just beginning, but there is a growing recognition of the potential for substantial improvements in patient care that can be achieved by tailoring drug therapies for the individual.[24–26] Biomaterials scientists must now accept the challenge of translating these insights into the complex world of material-tissue interactions, where subtle differences in tissue type and disease state can have substantial effects on material properties and clinical efficacy. This perspective explores the rational design of biomaterials to control a wide range of properties with an eye towards developing patient-specific materials. First, we will provide a brief overview on how to design platform materials with appropriate functionalities for facile tuning, as discussed in Section 2. We demonstrate how tissue-interacting materials can be used to probe and report on tissue state, and how this can be used for rational design of biomaterials in Section 3. Then, we will address the importance of matching tissue and biomaterial mechanical properties to provide the appropriate mechanical stability and adequate tissue function, as detailed in Section 4. Functionalizing materials with agents to allow for in situ diagnosis and targeted therapies adds a further level of sophistication. Materials can be doped with different nanoscale materials (organic and inorganic nanoparticles) and conjugated to a range of biomolecules (drugs, proteins, DNA/RNA, antibodies or dyes) as described in Section 5. This approach to multifunctional material design will pave the way for the development of precision materials with improved therapeutic effect.

2. Methods for Biomaterials Design

Material properties hinge on their chemical structure. Chemists and material scientists can now join forces to design diverse materials to meet specific clinical needs. With appropriate design, biomaterials can be tuned to confer the desired degradability, mechanics, and environmental sensitivity. A wide choice of chemical conjugation strategies provides powerful tools to create such materials (**Table 1**). The listed conjugation strategies can be used for a variety of purposes, from hydrogel curing to introducing new functionalities.

2.1. Degradation Rate

Biodegradable materials play a prominent role in biomaterials designed for drug delivery, sensing, and tissue engineering applications. The degradation rate is dependent on

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Shimon A. Unterman was awarded his Ph.D. in biomedical engineering from Johns Hopkins University in 2012. His research focused on the combination of natural and synthetic polymers to create materials with defined biological, mechanical, and rheological properties. Since then, he has worked as a postdoctoral researcher at the Institute for Medical Engineering and Science in the Massachusetts Institute of Technology. His research focuses on designing multifunctional nanocomposite hydrogels for drug delivery and tissue engineering applications.

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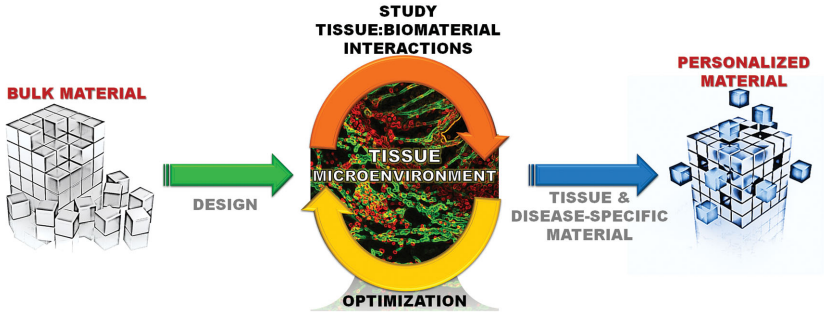


Figure 1. Biomaterials' interactions with tissues must be studied in light of specific tissue microenvironment conditions and optimized based on pathological alterations to achieve personalized materials that are tissue- and disease-specific.

the hydrophilicity and chemical structure of the polymer. Hydrophilic materials tend to follow bulk degradation modes, while hydrophobic materials are more likely to follow surface erosion.[33] While naturally derived polymers such as proteins and polysaccharides are mainly subject to enzymatic degradation, synthetic materials are susceptible to both enzymatic degradation and hydrolysis. Chemical bond type can further control degradation rate, e.g., ester bonds are stable up to a few months.[34] When more stable materials are in need, amide and urethane bonds featuring half-lives of 2 years are employed, due to their higher resistance to hydrolysis.[35] Material choice and chemistry can be rationally selected to impart the desired degradation profile for specific applications. In this context, the actual degradation rate should not be determined solely based on in vitro degradation, but following consideration of physiological and pathophysiological conditions of the implantation site, such as water content, pH, and enzyme concentrations.

2.2. Mechanical Properties

Mechanical properties vary considerably from tissue to tissue, from hard and stiff (cortical bone; up to 20 GPa in compression)[36] to soft (adipose tissue; 10–20 kPa in compression).[37] Biomaterial platforms should therefore exhibit a wide range of mechanical properties. Similar to degradation rate, mechanical properties can be substantially tuned by chemical modification. Increasing polymer molecular weight or introducing crosslinks between polymer strands can significantly increase strength and elasticity.[38] Alternatively, control over intermolecular interactions such as hydrogen bonding or molecular packing can be employed to tune the mechanical properties.[39,40] Furthermore, mechanical properties can be significantly improved by physical addition of nanofillers including carbon nanotubes, clay, and silica into polymeric matrices, as will be discussed in detail in Section 4.

2.3. Curing Rate

An important property of hydrogels is their capability to form in situ following injection.[41] Rapid, high yield reactions

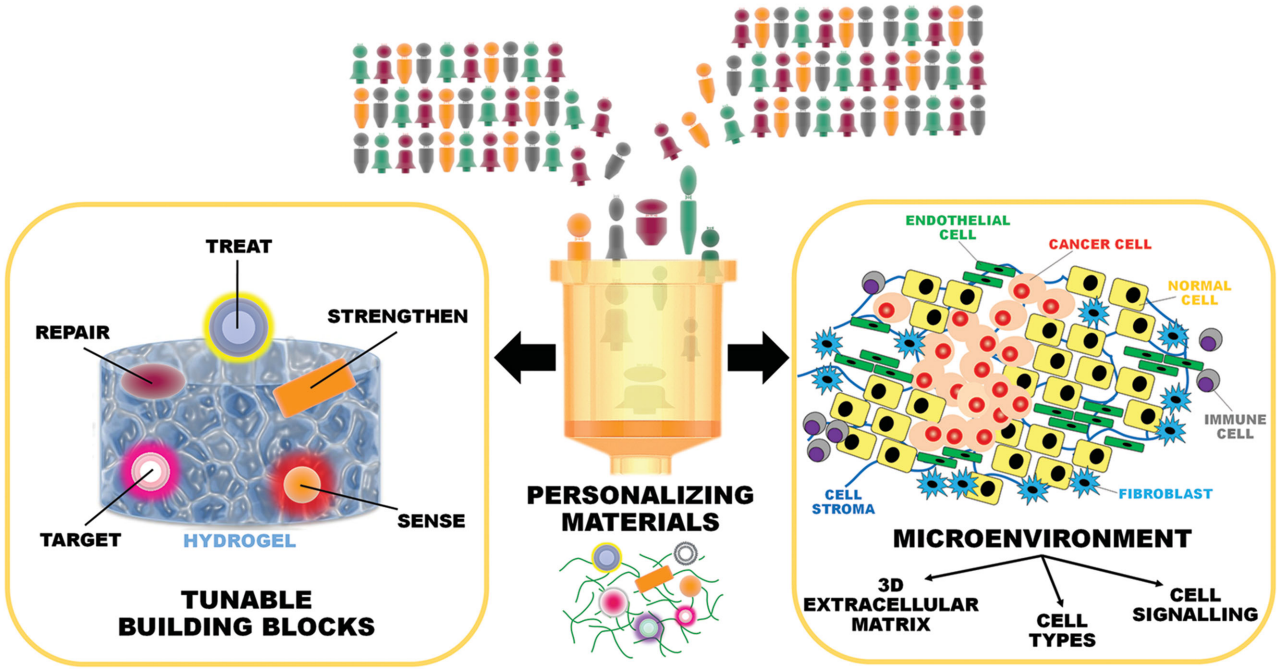


Figure 2. Biomaterials for medical applications are in need of patient-by-patient personalization that matches the application and the target site. Versatile biomaterial design can be achieved by addition of tunable building blocks for sensing, repairing, treating, targeting and strengthening.

Table 1. Summary of chemical conjugation strategies to introduce new chemical functionalities.

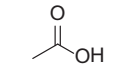
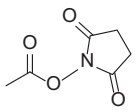
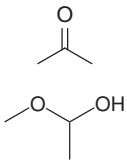
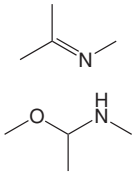
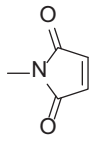
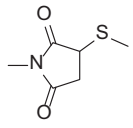
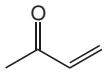
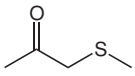
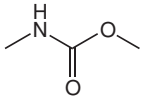
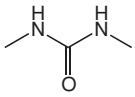
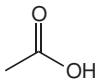
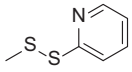
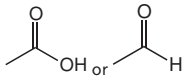
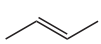
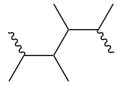
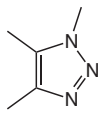
Conjugation Chemistry	Conjugating Group		Final Group	Comments
Carbodiimide		—OH		1. Both EDC and DDC can be used for common organic solvents, while only EDC is suitable for aqueous systems. 2. NHS helps to form a stable intermediate and lower the chance of hydrolysis.
		—NH_2		
Imine/Amine Chemistry	—NH_2			1. Click reaction between aldehydes and amines.[23] 2. Hydrazide usually replaces amines to react with ketones due to its high reactivity.[27] 3. Hemiacetals have a highly reactive hydroxyl group that can easily react with amines to generate secondary amines.[28]
Michael Addition	—SH			1. Strong nucleophiles such as thiol groups can be easily added onto α, β-unsaturated carbonyl compounds such as acrylate or maleimide. 2. More violent reaction conditions or catalysts are necessary for weaker nucleophiles such as amines.[29]
				
Isocyanate/Isothiocyante	–N=C=O	—OH		1. Due to the high reactivity of isocyanates, an aprotic system is required. 2. With relatively lower reactivity, isothiocyanates can react with those functional groups in the same manner but are suitable for aqueous systems.[30]
		—NH_2		
				
Redox Chemistry	—SH			1. Thiol groups and disulfide bonds are the basic concept underlying redox sensitive materials.[31] 2. With proper choice of oxidant and catalyst, hydroxyl groups can be oxidized to aldehydes/ketones or carboxyl groups. 3. Periodate can oxidize vicinal diols to provide two aldehyde groups.[23]
	—OH	Oxidant		
Free Radical Chemistry		Initiator		1. Free radical chemistry is commonly applied for alkene containing materials. 2. Initiators are crucial in this chemistry. Most commonly used initiators are photoinitiators and peroxide/persulfate.[7]
Alkyne/Azide "Click" Chemistry	—N_3			1. Both alkyne and azide are easily introduced onto existing chemicals. 2. This reaction can be conducted in various conditions, a wide range of solvents (including water), and various temperatures. 3. Catalyst free "click" chemistry has been well established recently.[32]

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Table 2. Summary of stimuli able to trigger structural/chemical changes in biomaterials with correspondent stimulus-sensitivity.

Stimulus	Mechanism	Examples
Thermo	Solubility of polymer changed below or above upper/lower critical solution temperature	Poly (*N*-isopropylacrylamide)[48]
pH	1. Hydrophilic side chains leads to different swell ratio at certain pH ranges.	Poly (L-Histidine)[58]
		Poly (methyacrylic acid)[59]
	2. Hydrolysable bonds have different hydrolysis rates under different pH.	Chitosan[60]
Redox	Chemical bonds can be cleaved/conjugated by oxidizing or reducing agent.	Disulfide bond containing materials[61]
Enzyme	Chemical linkage can go through enzymatic cleavage.	Peptide sequence
		4-hydroxymandelic acid containing materials[62,63]
Photo	Chemical structure can be cleaved/conjugated under different wavelengths.	Coumarin, maleimide, or cinnamate containing materials[64]
Magnetic	Material accumulation under magnetic fields.	Iron oxide (Fe_3O_4, γ-Fe_2O_3)[47,65]
Ultrasound	Materials have structure disruption under ultrasound of a given frequency.	Liposome[66,67]

in mild reaction conditions are preferable for this application. This approach can be utilized to form 3-dimensional crosslinked structures in a short period of time, usually within one minute.[7] However, exothermic reactions (self-polymerization of cyanoacrylate), nonselective reactions (isocyanate), and toxic catalysts (alkyne/azide reaction) should be avoided for in situ applications. For these reasons, aldehyde-amine reactions forming imine bonds, Michael addition of thiol groups, and free radical crosslinking are of high interest owing to their mild reaction conditions, high yields, and versatility (see Table 1). Previously, we have shown that the combination of linear functionalized polymers with multifunctional branched polymers results in efficient crosslinking owing to minimal steric hindrance and the availability of multiple reactive groups.[42]

2.4. Stimulus Sensitivity

Stimuli such as pH, temperature, magnetic fields, light, and the presence of small molecules are able to trigger structural/chemical changes in appropriately designed biomaterials (see **Table 2**). Those changes can be utilized to accomplish special tasks such as on demand drug delivery[43] and theranostics[44,45] for personalized medicine. Chemical structures that are responsible for these stimulus-sensitivities can be incorporated into materials in a modular manner, allowing for an additional level of precision in material targeting and drug delivery. Although stimulus-responsive materials are fairly rare in the clinic, the FDA has approved the use of a thermosensitive liposome with hyperthermia-triggered release of chemotherapeutics for prostate cancer treatment,[46] and significant interest exists in the development of further applications. Numerous promising magnetic,[47] thermo,[48] pH,[49] ultrasound,[50] and light[51,52] sensitive materials have been studied for disease treatment and diagnosis. In addition to externally applied stimuli, differences between diseased and healthy tissues can be used as a local stimulus for triggered release. Previous research shows that, compared to healthy tissue, tumors embody a more acidic microenvironment,[53] and have at least four-fold higher concentrations of a reducing agent (Glutathione, GSH).[54] In addition, specific enzymes are overexpressed in disease tissues.[46] Therefore, pH sensitive, redox-sensitive, and enzyme sensitive materials have been extensively studied for on demand drug delivery for cancer treatment.[55] Hanson et al. developed a redox-sensitive green fluorescent protein[56] that serves as a powerful probe for cancer cell imaging. Materials with dual sensitivity can impart multiple functionalities. Redox/pH dual sensitive nanogel was studied for its controlled drug release under varying stimuli.[57] Wu et al. developed a thermo and pH sensitive system for controlled drug delivery, pH sensing, and cancer cell imaging.[53]

These chemical tools allow for the development of widely tunable platform materials with defined degradation, mechanics, curing, and stimulus sensitivities. In the next section, we will explore how to use these material platforms to probe the tissue microenvironment and optimize material-tissue interactions.

3. Rational Material Design Guided by Microenvironment Characterization

The design of personalized materials requires the study of the interactions between the microenvironment and the material in order to predict its behavior in a particular setting. In order to do so, it is crucial to develop a deep understanding of both material and microenvironment individually to be able to predict outcomes when they are combined. We will be focusing on adhesive hydrogels to describe this novel concept, as these materials are suitable candidates to probe the tissue microenvironment.[23,42,68] Moreover, this subtype of hydrogels relies on the intimate interaction between material and tissue, promoting integration and leading to improved drug release, cell infiltration and tissue formation. We will first introduce general concepts of adhesion chemistry and will then examine optimization of tissue-material interactions using a case study with dextran aldehyde and dendrimer amine.

3.1. Strategies to Control Biomaterial Integration with the Surrounding Tissue

When designing adhesives for medical applications, interactions between the material and the target tissue are of vital importance. These interactions are driven by physical or

Table 3. Summary of current adhesive hydrogel approaches classified based on the tissue- and biomaterial-reacting groups.

Biomaterial reacting chemical group	Tissue-reacting chemical group	Tissue chemistry type	Ref.
Aldehyde (i.e., glutaraldehyde, oxidized dextran)	Amine	Schiff base	[22,42,69–76]
NHS (i.e., chondroitin sulfate-NHS, hyaluronic acid-NHS)	Amine	Amide formation	[71,77–80]
Cathecol (i.e., PPO-PEO-cathecol copolymer, PEG-DOPA, MAPs-DOPA)	Amine/Thiol	Cathecol oxidation/π–π interactions	[81–84]
Maleimide (EPL-PEG-MAL)	Thiol	Sulfide-Maleimide addition	[85]
Radical-reacting components (i.e., *N*-isopropylacrylamide, PEG-diacrylate, Poly(AAc-co-MBA)	Unsaturated bonds	Free radical	[86–88]

chemical processes. They define material performance at the interface (adhesion strength), which then propagates into and affects the properties of the bulk biomaterial (cohesion strength and degradation rate). **Table 3** briefly summarizes current approaches and chemistries used to promote the formation of adhesive bonds between hydrogels and tissues. The availability of surface chemical groups in tissue limits the variety of adhesive chemistries to five broad categories: Schiff base reactions, amide formation, cathecol coupling, thiol-maleimide addition and free-radical reactions. Limitations arise from the fact that functional groups in the adhesive hydrogels need to spontaneously react with the tissue chemical groups at physiological conditions, while simultaneously reacting internally to form the bulk of the material. The following chart summarizes the different chemistries that can be used to promote tissue adhesion.

The vast majority of the hydrogel-based adhesive materials rely partially or completely on amine density on tissue surfaces to impart adhesion (Table 3). A smaller subgroup relies on thiol conjugation or on non-specific radical coupling with tissues. We will focus on amine-reactive adhesive hydrogels and their interactions with tissues under different conditions, and will use dextran-aldehyde and dendrimer-amine as a model platform to demonstrate the design of personalized biomaterials. Concepts

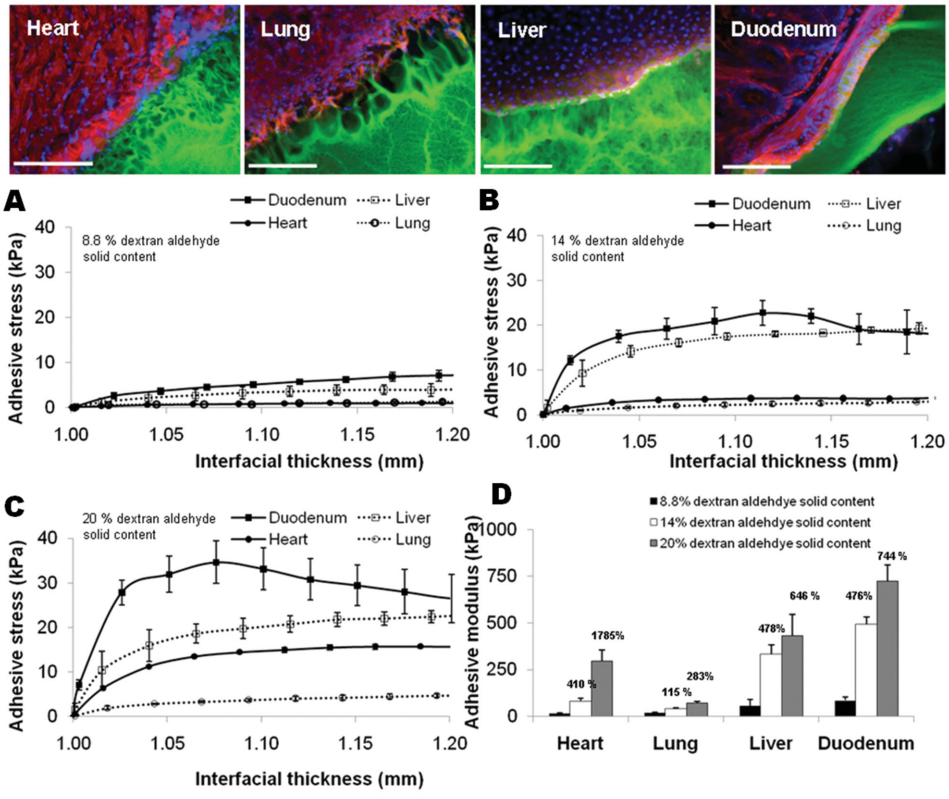

Figure 3. Interfacial morphology of PEG-amine and dextran-aldehyde adhesive hydrogel (green) following application to varying tissues (red and blue)—heart, lung, liver, and duodenum. Differential levels of interaction with tissue surfaces lead to varying adhesion strength, as showed by adhesive stress-strain measurements for A) 8.8%, B) 14%, and C) 20% dextran aldehyde solid content. The increase of dextran aldehyde content increases the amount of interactions with the tissue, leading to higher adhesion strengths. D) These trends are also observed in the adhesive moduli. Reproduced and adapted with permission [23]. Copyright 2009, John Wiley and Sons.

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learned from these studies can be applied to any biomaterial in the broad category of amine-reactive adhesives.

3.2. Personalizing Materials Based on the Microenvironmental Context

Dextran-aldehyde and dendrimer-amine cohesion and adhesion strengths are tissue-dependent. The two components react internally to form an imine-bond providing internal cohesion, while dextran aldehyde reacts with tissue amines to provide tissue adhesion.[42] Given a particular tissue with a specific surface amine density, dextran aldehyde interaction with the tissue will differ, thus changing the number of aldehydes available for cohesive reactions. Aldehyde to amine ratio can be tuned to control material properties and tissue interaction.[73] This was exemplified by the differential adhesion and cohesion strengths achieved following the application of a specific material formulation to the heart, liver, lung or duodenum in a murine model.[23] It can be inferred that there are critical differences between tissues that affect material adhesion, and that these differences rely on the chemical groups available to react with the material (**Figure 3**). Hence, measuring the amine density on the surface of various tissues of interest is essential to predict material properties.[23,42] Interestingly, these measurements correlated with mechanical testing data, proving that the variation in tissue amine density is a critical parameter defining material performance.

Understanding the healthy tissue microenvironment is the first step to successful prediction of in vivo material performance. Most biomaterials for medical applications, however, are used in patients with underlying pathologies that may alter the microenvironment, and in turn biomaterial response and behavior. Using the dendrimer:dextran model material, we studied how two different gastrointestinal diseases, cancer and inflammation, affected material performance.[21] The two diseases affected amine density in opposite manners: while neoplasia resulted in an increase in amine density provided by extra deposition of collagen-I, inflammation led to a decrease owing to collagen-I degradation. Understanding the biological phenomena underlying these variations is key to enabling predictive performance and generalization under conditions other than cancer and inflammation. Here, collagen-I content linearly correlated with amine density, enabling prediction of material adhesion to tissues in any clinical state through an understanding of collagen dynamics.

This detailed analysis of tissue-biomaterial interactions allows for an iterative design process to rationally enhance material performance and increase the likelihood of clinical translation. In the dendrimer:dextran platform, increasing the solid content of dextran aldehyde from 10 to 25% in an inflammatory setting increases the adhesion strength to a level comparable to that of the original formulation when applied to healthy tissue. Moreover, because tissue surface amine density, collagen-I content and adhesion strength correlate, a predictive model can be built to calculate adhesion strength of a particular formulation based on a rapid screen for tissue amine density. Thus, when patients present clinically, evaluating patient-specific disease severity can allow for selection of an optimized material formulation to enhance clinical performance.

This illustrates the beginning of a new field of personalized biomaterial design and development. We have shown that the microenvironment of a specific tissue site and disease state must be taken into consideration, since it plays a key role in the process of material development. Such practice would increase the likelihood of failure in late stages of clinical trials, where materials are no longer used in healthy patients, but rather in pathological environments that would alter material performance. By then, the economic burden associated and time invested in material development would be very high, and therefore an iterative optimization process is less likely to take place.

The following sections will focus on how nanotechnology can improve material personalization by tuning of modular materials on a patient-by-patient basis.

4. Designing Tunable Mechanical Responses Using Nanomaterials

While many biomaterials are of potential interest, we will continue to focus this review on hydrogels, as these emerging polymers possess remarkable properties that are required when materials encounter the biological environment. Hydrogels are versatile and facile platform material systems that can readily be personalized to match specific tissue chemistries, providing controlled local drug delivery, improved targeting and more. These advantages, however, come at a price. Their high water content provides most hydrogels with modest mechanical properties.[89] Hydrogel elastic moduli typically range from 10–200 kPa, far lower than the stiffness of many biological tissues. In addition, hydrogels are often fairly brittle, developing cracks or rapidly disintegrating upon loading.[90–92] This mismatch in mechanics between the material and surrounding tissue can lead to interfacial failures that limit their regenerative potential. In some challenging implantation environments, such as orthopedic or cardiovascular tissues, the stresses and strains experienced in vivo can easily dislodge or destroy an inappropriately designed material. Improving adhesion at the implant-tissue interface can limit this issue, however cohesive failure within the hydrogel is still a significant concern. During cyclical shearing in a closed space such as a joint compartment, the development of wear particles from a brittle material can even worsen the underlying pathology.[93]

Therefore, the role that mechanics plays in successful personalized material design cannot be understated. When considering the implantation environment, it is important to estimate the magnitude, frequency, and loading mode of the forces likely to be experienced by the material. In vitro characterization performed under non-physiological conditions may yield misleading data and a lack of mechanistic insight. Furthermore, pathological states often lead to loading states that are very different from healthy tissues,[94] so the effects of the individual's disease state in modifying the mechanical environment should be studied in detail. Degradable materials are likely to change their mechanical response over time, so it is important to ensure that mechanical stability of the implant will not be

compromised as it matures, and that wear particles will not have negative effects on the surrounding tissue.

The rheological properties of the polymer solutions prior to gelation is often an overlooked aspect of hydrogel design that should be considered[92,95] because it has important practical ramifications in the clinic. Polymer solutions need to be appropriately fluid to facilitate their easy application; however, after injection into complex geometries or wet environments, it is important that materials remain in the implantation site.

4.1. Hydrogel Reinforcement with Nanomaterials

A variety of existing strategies can be employed to improve hydrogel mechanical properties. The simplest approach is to change polymer size and crosslinking as discussed in Section 2.[89,92] These modifications can tune mechanical properties across a narrow range, but may have adverse effects on hydrogel properties such as pore size, ligand density, and degradability.[92,96] Alternative approaches are to change polymer choice and network design for further tailoring for specific applications.[90,97–100] While these approaches provide remarkable improvements in mechanics, they often involve the use of less biologically relevant or biocompatible polymers, and may require formation in vitro prior to implantation due to complex or harsh gelation conditions.

Given these challenges and limitations, researchers utilize nanocomposite materials to enhance hydrogel mechanical properties.[101] Composite materials are comprised of a soft (hydrogel) material doped with a stiffer component to provide improvements in mechanical properties while retaining the advantageous properties of hydrogels. Mesoscale and microscale particles and fibers made out of stiffer polymers such as polyesters or crystalline minerals such as calcium phosphate were used.[102,103] These materials tend to increase mechanical stiffness significantly, but only at relatively high loading ratios of filler to hydrogel. This limitation of microscale materials stems from its relatively low surface area to volume ratio, resulting in relatively low polymer-filler interactions.

Nanomaterial fillers come in a wide variety of geometries and chemistries, but share a common characteristic: when well dispersed throughout a polymer phase, they can provide dramatic improvements in elastic modulus and ultimate strength with only modest additions of material. This stems from the high surface area available for interaction between the nanomaterial and the polymer phases. Nanomaterial-reinforced hydrogels are a promising way to tune mechanical properties with the caveat that suitable integration into the polymer network is essential for mechanical reinforcement.[104,105] Of particular interest are nanocomposite hydrogels incorporating nanoscale particles, fibers or tubes, and platelets (see **Table 4**).

Platelet or sheet-like nanocomposite materials with high aspect ratio such as clays and graphene are of great value. These materials, when appropriately integrated into the surrounding polymer matrix, can dramatically improve elastic moduli of materials both through noncovalent polymer-filler interactions as well as filler-filler interactions.[112,113] Intriguingly, platelet nanocomposites also tend to improve the fracture resistance of materials; the aspect ratio and relative stiffness of the nanofillers support a tortuous crack propagation through the material, resulting in toughness.

The broad range of mechanical properties attainable using nanocomposite materials opens up new horizons for the applications of hydrogel biomaterials. Using nanomaterials to manipulate the mechanical properties of hydrogels, in conjunction with a detailed study of the physiological and pathological mechanical environment, allows the development of robust hydrogels tailored to the tissue and disease state.

5. Personalizing Hydrogels via Multifunctional Nanomaterials

An emerging approach to introduce valuable functionalities to hydrogels relies on the incorporation of nanoparticles within the polymer network. Such an approach enables engineers to impart unique magnetic, electrical, catalytic, and optical properties to hydrogel-based systems, as well as remote control actuation.[114] Nanomaterial-hydrogel conjugates consisting of inorganic nanomaterials[115] (gold,[5,116,117] iron oxide magnetic,[118] silica,[119] quantum dots,[115] carbon nanotubes,[120]

Table 4. Examples of commonly used approaches to nanocomposite design for mechanical enhancement.

Filler Type	Materials used	Mechanical properties	Comments	Ref.
Nanoparticles	Nanoscale bioglass in collagen	≈300 kPa (E′ in DMA)		[106]
	Nanoscale hydroxyapatite in PLEOF	≈45 kPa (shear modulus)		[105]
	Silica nanoparticles in PDMA	≈200 kPa (compression)	Yield stress ≈400 kPa	[107]
Nanofibers	Cellulose nanorods in dextran and carboxymethylcellulose	≈7 kPa (G′ in rheology)	Very low filler loading	[108]
	Single walled CNTs in alginate	1400 kPa (tensile)		[109]
	Multiwall CNTs in gelatin methacrylate	40 kPa		[110]
	Electrospun PCL in gelatin	20 kPa	sixfold increase	[111]
Nanoplatelets	Organoclay in NIPAAm	Tensile strength > 100 kPa	>1000% extensibility	[104]
	Synthetic clay in zwitterionic copolymer	Tensile strength 50–100 kPa	Elongation at break ≈2000%	[112]
	Graphene oxide in polyacrylamide	Tensile strength ≈300 kPa	Elongation at break > 3000%	[113]

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and graphene)[121] and organic nanomaterials (polymeric,[122] liposomes,[123] micelles,[124] dendrimers)[125] embedded in a hydrogel scaffold have already been proposed for drug and gene delivery systems (**Figure 4**).[122,126–128] Sophisticated material designs can combine multiple phases that mimic both the physical and biological properties of tissues. The combination of nanomaterials with robust hydrogels allows for the design of multifunctional, tunable materials that can target, sense, and deliver therapeutics in a manner sensitive to the tissue microenvironment.[122,129]

Hybrid hydrogels and nanogels doped with organic and inorganic nanoparticles usually represent a new functional scaffold with the capacity to deliver multiple biomolecules, such as drugs, proteins, peptides and nucleic acids (DNA/RNA). The great majority relies on a two-step controlled release using poly(ethylene glycol) (PEG),[130–132] polyacrylamide,[133] poly(amine-ester),[134] chitosan,[135] dendrimer,[136,137] dextran,[22,23,138] or gelatin,[139] particularly for cancer applications. Hydrogel systems are further decorated with appropriate nanomaterials to develop stimuli responsive matrices determined by the type of nanoparticles embedded within the polymeric network. Temperature and pH responsive hydrogels are the most commonly studied types of stimuli-sensitive hydrogels and are favored for biomedical applications due to the crucial roles that temperature and pH play in physiological processes.[114,140]

5.1. Temperature-Responsive Hydrogel Nanomaterials for Tunable Delivery

Some of these tunable hydrogel nanomaterials are designed to release drugs in response to a change in temperature[141] that can be caused by applying an external laser light source to heat up materials. This effect is usually achieved by using plasmonic gold nanomaterials (ie. nanorods, nanoshells, nanocages and nanospheres). This technique combines two key components: a) a light source such as lasers with a spectral range of 650–900 nm for deep tissue penetration, and b) irradiation of gold nanomaterials which release heat (on a picosecond time scale), inducing photothermal ablation.[142] Smart thermoresponsive hydrogels significantly and synergistically reduce tumor cell survival, with an excellent anti-tumor activity, when compared to free drug.[137,141] In one enlightening study, docetaxel-loaded thermoresponsive conjugated linoleic acid-coupled Pluronic F-127 (Plu-CLA) nanoparticles that were incorporated in poloxamer hydrogels were reported to present a markedly stronger anti-tumor effect in the suppression of gastric cancer metastasis (**Figure 5**).[141]

Gold-polymer nanoshell,[143] gold-silica nanoshell,[144] and magnetic NPs[145–147] have also been developed for the purpose of photothermally modulating drug delivery. Locally generated heat from exposure to NIR is used to trigger swelling/dwelling of the hydrogel network and results in the release of entrapped therapeutic payloads. Usually these platforms use materials that display a lower critical solution temperature (LCST), which is slightly above the physiological temperature. Stronger polymer-NP interactions that can be induced by the attachment of gold reactive groups (e.g., thiols) to the hydrogel are able to tune thermosensitivity and swelling behavior.[144]

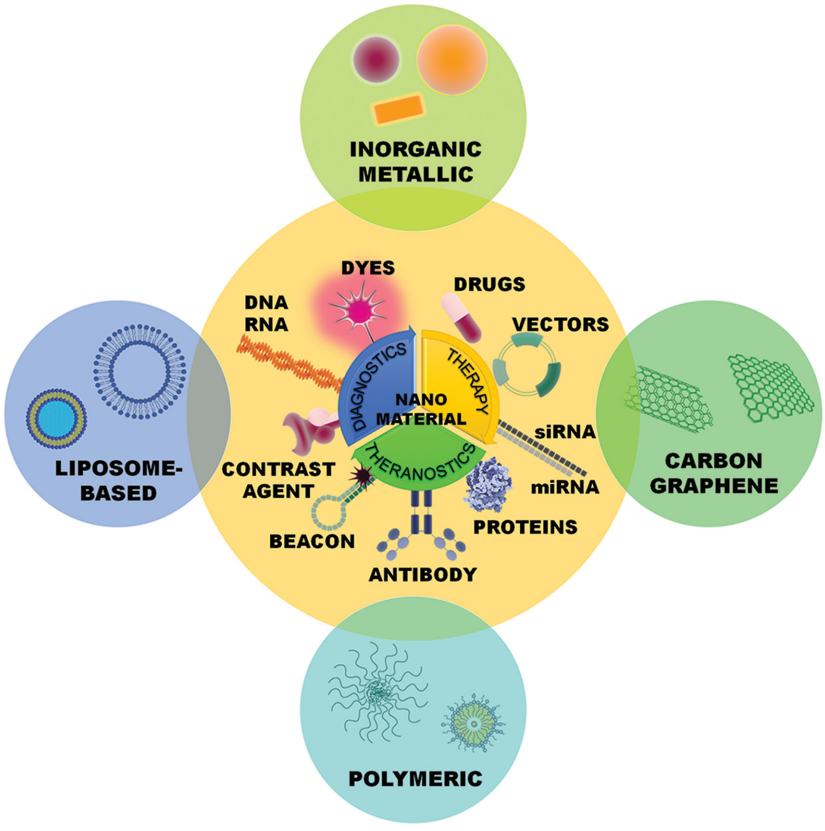

Figure 4. Tuning multifunctional nanomaterials. Inorganic (gold, iron oxide magnetic, silica, quantum dots, carbon nanomaterials) and organic nanomaterials (polymeric and liposome-based) can be tuned to include multiple functionalities like nucleic acids such as RNA (siRNA, miRNAs) and DNA (molecular beacons, plasmid vectors) used for gene silencing approaches or anti-cancer drug molecules for delivery to the target cell/tissue/organ. Responsive nanomaterials can also trigger a response following external stimuli through the introduction of smart polymers or peptides. Multifunctional systems can carry fluorescent dyes that are used as reporter molecules for tracking and/or contrast agents.

5.2. pH-Responsive Hydrogel-Nanomaterials for Drug Delivery

pH-responsive hydrogels are typically composed of a swollen ionic network containing either acidic or basic reactive groups, which can ionize and develop fixed charges on the polymer matrix. These ionic materials possess significant pH and ionic strength

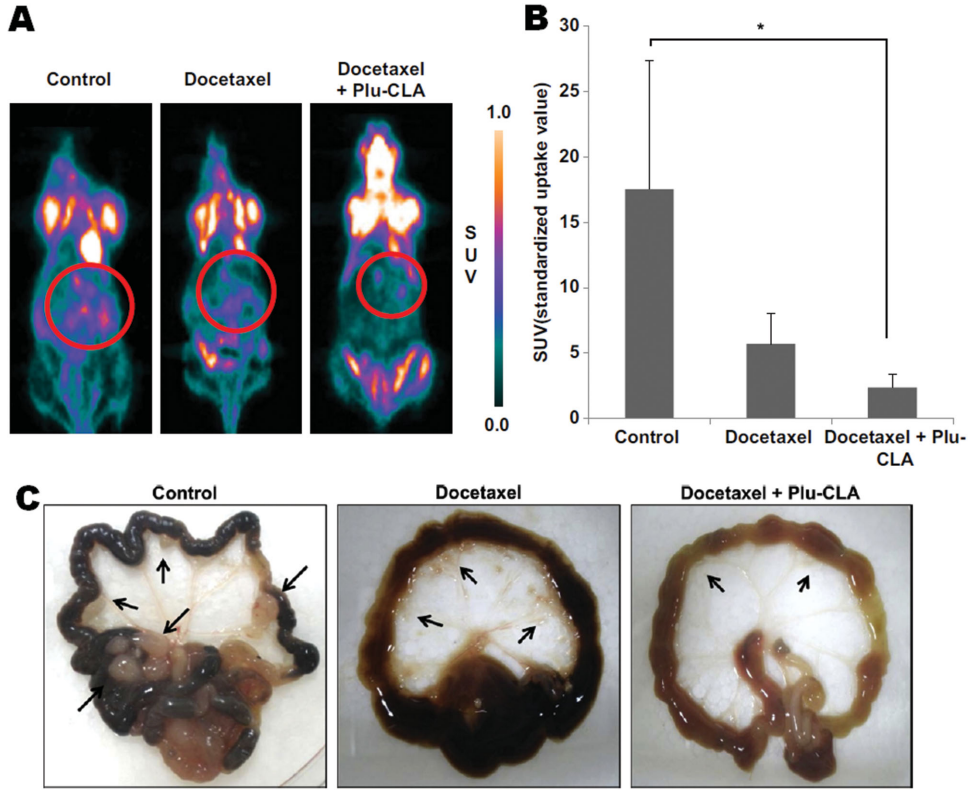

Figure 5. Docetaxel-loaded thermoresponsive conjugated linoleic acid-incorporated poloxamer hydrogel for the suppression of peritoneal metastasis of gastric cancer. A) Comparison of intra-abdominal 18F-FDG uptake (red circle) in mice, based on microPET images. B) Comparison of 18F-FDG SUV uptake in the control, docetaxel and docetaxel Plu-CLA treatment groups. $*P < 0.05$. C) Macroscopic appearance of peritoneal tumors (indicated by arrows). Markedly fewer peritoneal metastases were found in mice treated with docetaxel Plu-CLA. Reproduced with permission.[141] Copyright 2013, Elsevier.

sensitivity, with dramatic changes to swelling properties when compared to non-ionic materials. Reactive groups like carboxylic acids and sulphonic acids or other basic functional groups such as ammonium salts can act as proton acceptors or donors.[122,129]

The majority of release studies showed that pH-responsive-hydrogel carriers released the nanoconjugate at neutral pH conditions (with minimal/residual release in low pH conditions) using two-step pH experimentation. These hydrogels are capable of triggering the release of a loaded therapeutic agent when it passes from the stomach (low pH) to upper small intestine (neutral pH).[148,149] More sophisticated hydrogels may also be used to respond with greater precision to the tumor milieu.[150] These hybrid nanogels are able to detect and image cancer cells, sense the environmental pH change, and adjust the release of an anticancer drug.[151,152]

5.3. Photosensitive Hydrogel Nanomaterials for Theranostics

Near infrared (NIR) has been considered as an ideal external stimulus for in vivo detection and photothermal therapy because its absorption by tissue is often minimal, allowing for deep tissue penetration.[153] Therefore, there is a tremendous interest in developing systems for diagnostics and photomediated therapy including controlled drug release using NIR as an external stimulus.

Photosensitive hybrid hydrogels loaded with upconversion nanoparticles (UCNPs) have been proposed as promising alternatives to organic dyes and quantum dots in the field of biomedical imaging and triggered release.[154] A continuous-wave NIR light may be used to induce a gel–sol transition and release "on demand" proteins and enzymes entrapped in the hydrogel. Although no in vivo experiments have been reported to date using hybrid UCNP–hydrogels, the use of the multiphoton effect of up-converting NPs to trigger structural variations in photosensitive hydrogels constitutes a highly attractive strategy.[155,156]

To enhance material photosensitivity, carbon nanomaterials can also be excellent candidates for incorporation into hydrogels.[157] Carbon nanomaterials including graphene and carbon nanotubes (CNT) exhibit excellent physical, mechanical, and electrochemical properties which have been widely studied in the past decade.[121,158] Many studies have suggested that the integration of carbon nanomaterials improve electrochemical and optical properties of hydrogels that might also provide facile tunability for personalized therapy.[159,160]

Carbon nanomaterials exhibiting semiconductor behavior, such as single-walled carbon nanotubes (swCNTs) and graphene, absorb and emit in a NIR region and have been widely used for diagnostics and drug delivery.[161–164] Due to their excellent optical properties and photostability, carbon nanomaterials have been desirable for the design of in vivo sensing tools for the detection of disease or bioimaging.[165–168] To enhance their

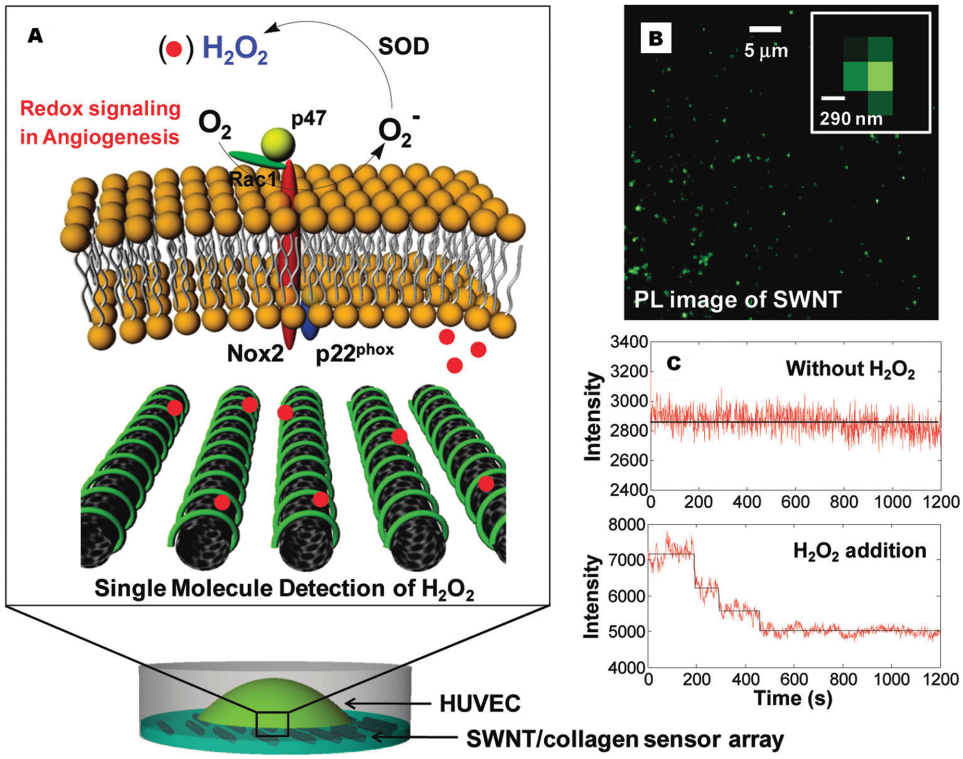

Figure 6. A) Schematic diagram of H_2O_2 production in angiogenesis and sensing platform. B) NIR fluorescence image of a swCNT/collagen sensor array showing emission from single isolated SWNT sensors. Inset: diffraction-limited spot corresponding to a single swCNT. C) Representative fluorescence time-traces (red) in PBS with and without H_2O_2, showing clear stepwise fluorescence quenching. Reproduced with permission.[172] Copyright 2011, American Chemical Society.

selectivity, carbon nanomaterials are often functionalized with biological receptors including antibodies, peptides, aptamers, DNA and enzymes as recognition/targeting elements.[167,169–171] Strano and co-workers reported a swCNT/collagen sensor array for the single-molecule detection of H_2O_2 (**Figure 6**).[172] The H_2O_2 influx during angiogenic signaling in endothelial cells was successfully monitored by measuring NIR fluorescence from a swCNT/collagen hybrid matrix.

There is tremendous interest in developing systems for controlled drug release to amplify the efficiency of drugs using NIR irradiation as an external stimulus.[173,174] Although the photothermal effects of carbon nanomaterials can be applied to induce direct damage to cells for thermotherapy,[175–177] its application to controlled drug release is more promising.[162,163] Kim et al. successfully demonstrated the development of a nanocarrier for photothermally triggered cytosolic drug delivery via endosomal disruption using reduced graphene oxides (rGOs).[153] The doxorubicin (DOX) loaded on rGOs by π–π stacking interaction was released by stimulation by NIR and glutathione (GSH), which further facilitated endosomal escape (**Figure 7**).

5.4. Hydrogel Nanomaterials for Gene Therapy

Gene therapy is receiving growing attention and, in particular, RNA interference (RNAi), small-interference RNA (siRNA) and microRNAs[178] show significant potential for sequence-specific post-transcriptional gene silencing in diseased cells.[179,180] This field can benefit from advances in materials science that can now facilitate the development of a safe, efficient, specific and nonpathogenic vehicle for gene delivery.

RNAi nanomaterials[181–186] can potentially overcome the drawbacks associated with using naked siRNAs, which show low enzymatic and chemical stability. Moreover, siRNAs and microRNAs must avoid the immune system, prevent renal clearance and guarantee effective cellular uptake and successful incorporation into the RNAi machinery.[187–189]

Injectable or implantable hydrogel scaffolds can be used to locally deliver therapeutic siRNAs in a sustained manner. Local delivery of siRNA using smart material design can facilitate high transfection efficiency and reduce the toxicity and off-target effects associated with systemic administration.[179,190] Hydrogels can prevent siRNA from inactivation during circulation while avoiding premature release. Consequently, gene delivery and RNAi-based hydrogels were extensively reported using hydrogels composed of dextran-PAMAM dendrimer,[138] PEG,[130,191,192] polyethyleneimine-poly(organo phosphazene),[193,194] fibrin,[195,196] chitosan/alginate[192] for siRNA delivery or pullulan (polysaccharide polymer)[197] and hyaluronic acid for DNA plasmid delivery.[198] Although several studies reported the use of either hydrogel nanoparticles that enhance cancer cell sensitivity to chemotherapeutic agents[199] or successful siRNA silencing,[200] the majority of these studies reported only in vitro results.

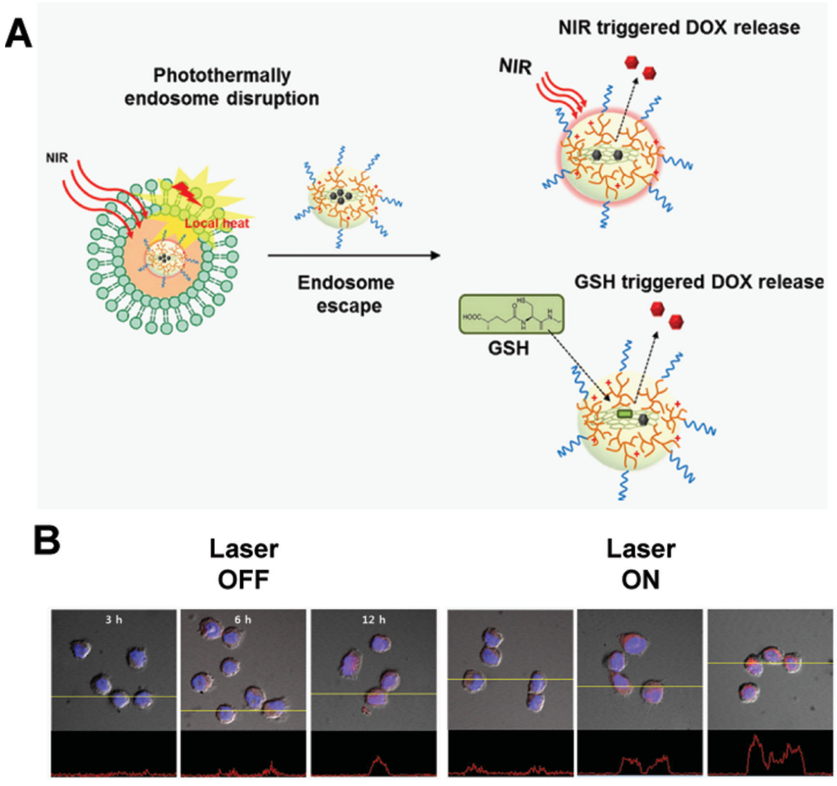

Figure 7. A) Schematic illustration of the mechanism of cytosolic drug release by NIR and GSH following photothermally induced endosome disruption. B) Confocal microscopy images of PC-3 cells treated with PEG-BPEI-rGO/DOX complexes in the dark (top) and under NIR irradiation (bottom) after various incubation times (3, 6, 12 h). Nuclei were stained with DAPI (blue), DOX has specific light emission (red). Reproduced with permission.[153] Copyright 2013, American Chemical Society.

A recent study reported on the use of the aforementioned adhesive material (Section 3) based on dendrimer and dextran for the embedding of siRNA encapsulated in oligopeptide-terminated poly(β-aminoester) (pBAE) nanoparticles (**Figure 8**) in vivo. Sustained delivery of the siRNA was achieved in a breast cancer mouse model owing to the protection of the nanoparticles within the hydrogel, enhancing their stability. This system presented with improved transfection efficiency in vivo even when compared with commercially available RNAi transfection reagents.[138] The cell compatibility and tunability of the hydrogel scaffold together with the high transfection efficiency of the oligopeptide-modified poly(β-aminoester) nanoparticles make it an attractive platform that can either complement or in some cases replace systemic delivery.

Dextran-PAMAM dendrimer hydrogels can also be used for dual therapy, that is, gene therapy in combination with drug delivery, as was exemplified by reversing multidrug resistance in cancer prior to chemotherapeutic drug release. With a single local application of a hydrogel scaffold embedded with a two-pair FRET/NSET (Fluorescence Resonance Energy Transfer/NanoSurface Energy Transfer) gold nanobeacons (also known as dark-gold nanobeacons), we were able to

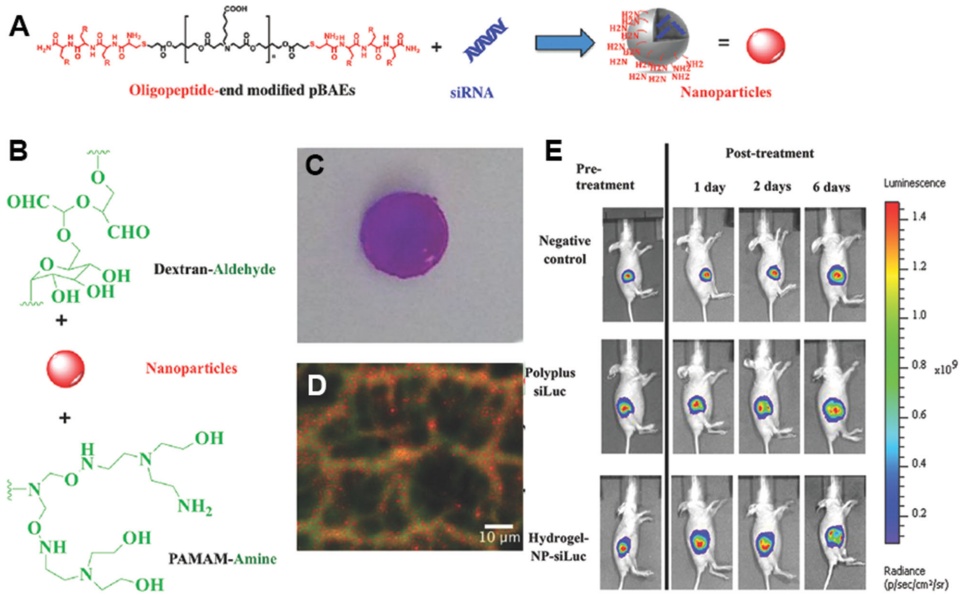

Figure 8. Hydrogel doped with nanoparticles for local sustained release of siRNA in breast cancer. A,B) Schematic representation of sustained siRNA release from siRNA-loaded nanoparticles embedded in a polymeric scaffold C) 6 mm diameter, 3 mm thick fluorescently labeled hydrogel. D) Amplified fluorescent microscopy image of hydrogel (green) doped with siRNA (red) encapsulated into arginine-modified pBAEs nanoparticles. E) Silencing of luciferase expressing tumors was achieved 24 h post-treatment and maintained until 6 d post-treatment. Reproduced with permission.[138] Copyright 2014, John Wiley and Sons.

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overcome drug resistance by detecting and silencing a multi-drug resistance protein (MRP1) prior to chemotherapeutic drug delivery in vivo. This approach enables regaining drug efficacy in a drug-resistant tumor and serves as an ON/OFF molecular nanoswitch triggered by the increased MRP1 expression within the tumor tissue microenvironment.[201]

6. Looking Forward: The Future of Precision Biomaterials

Personalized medicine, as originally conceived, was applied mostly to the design and administration of pharmaceuticals. Detailed pharmacokinetic and pharmacodynamic studies characterize the fate and effects of administered drugs to establish detailed dosing regimens tailored to the patient's physiology.

We propose that the same paradigm should be applied to biomaterial design and administration. Materials can no longer be considered as "one size fits all" for a broadly defined indication, but should take into account the unique tissue microenvironment of each patient. Studying real-time material kinetics and dynamics in realistic in vivo environments using new imaging techniques would allow for iterative improvements in biomaterial design to optimize material properties. Care must be taken to rigorously quantify disease-driven tissue modifications, to prompt the identification of critical material properties that are most susceptible to alteration by tissue microenvironmental changes. The resultant material designs must be based on tunable "platforms" that can be readily modified to meet subtle changes in physiology and disease state. Advances in material design and characterization techniques now allow for substantially more sophisticated tuning of biomaterial properties than previously imagined, and the addition of new and exciting functionalities in targeting, delivery, and sensing.

It is the responsibility of biomaterials scientists to accelerate this transition through innovative and thoughtful design, keeping in mind the implantation context. Personalized materials will reduce product failures in pre-clinical and clinical testing and usher in a new chapter in precision medicine.

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