CHEMICAL REVIEWS

pubs.acs.org/CR

Review

Bioadhesive Technology Platforms

Published as part of Chemical Reviews virtual special issue "Wearable Devices".

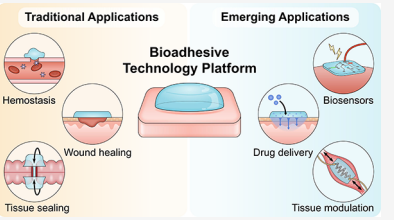
Sarah J. Wu* and Xuanhe Zhao*

Cite This: *Chem. Rev.* 2023, 123, 14084–14118

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: Bioadhesives have emerged as transformative and versatile tools in healthcare, offering the ability to attach tissues with ease and minimal damage. These materials present numerous opportunities for tissue repair and biomedical device integration, creating a broad landscape of applications that have captivated clinical and scientific interest alike. However, fully unlocking their potential requires multifaceted design strategies involving optimal adhesion, suitable biological interactions, and efficient signal communication. In this Review, we delve into these pivotal aspects of bioadhesive design, highlight the latest advances in their biomedical applications, and identify potential opportunities that lie ahead for bioadhesives as multifunctional technology platforms.



CONTENTS

Received: July 5, 2023
Revised: October 24, 2023
Accepted: October 25, 2023
Published: November 16, 2023

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084–14118

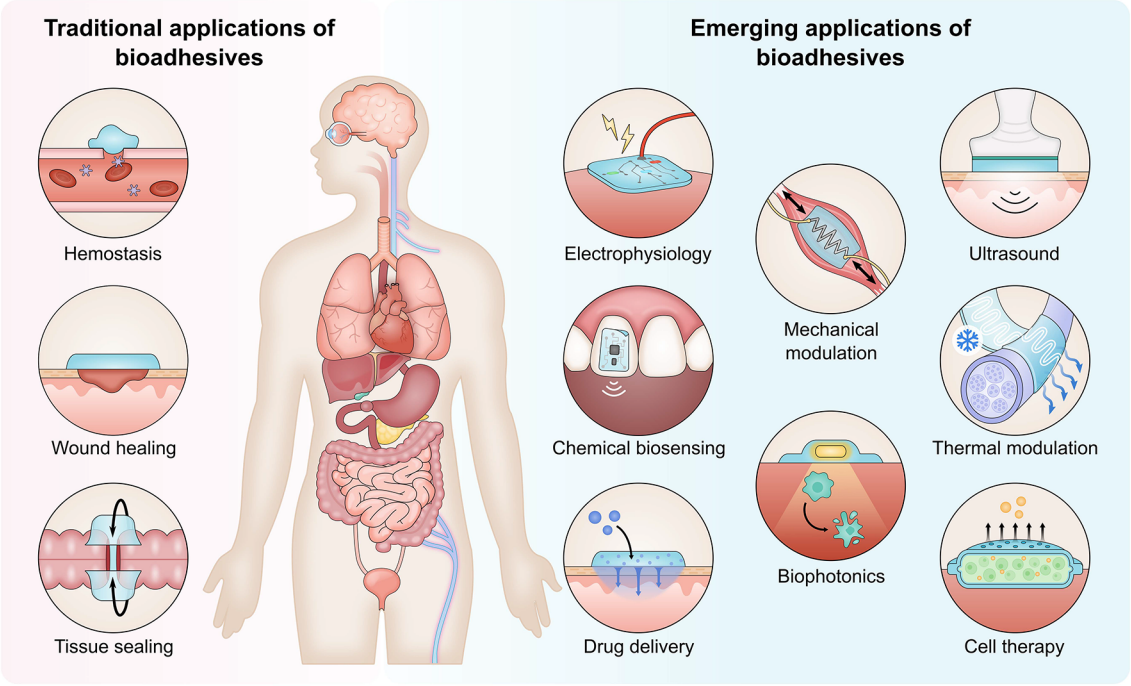


Figure 1. Examples of diverse applications of bioadhesives. Traditional applications, including hemostasis, wound healing, and tissue sealing, revolve around tissue repair and reconnection. Emerging applications, employing bioadhesives as a technology platform for various modes of healthcare monitoring and therapy, require further design and engineering of multifunctional properties beyond tissue bonding.

1. INTRODUCTION

Modern medicine is impossible to imagine without the ability to repair and reconnect tissues. Since the era of ancient civilizations, humans have found innovative methods to close wounds, from using ant jaws and thorns to bone needles and intestines.[1,2] These primitive forms of tissue closure formed the basis for surgical sutures, which continue to be regarded as the gold standard today. Despite their extensive use, sutures suffer from notable limitations. For instance, suturing is time-consuming and demands a high level of surgical skill, which is problematic in time-sensitive and anatomically complex procedures, such as hemorrhagic injuries or minimally invasive surgeries. To expedite wound closure, surgical staplers were adopted throughout the late 1900s, offering rapid application and facilitating less invasive procedures.[3] Nonetheless, staplers also have their share of disadvantages, including a high incidence of device malfunctions and adverse effects such as leakages and tissue tearing.[4,5] Moreover, the pointwise, tissue-penetrative modality of both sutures and staples is intrinsically damaging to tissues and can result in poor healing.

Bioadhesives, referring to materials that can form adhesion with biological tissues, present a promising alternative to the traditional tissue attachment techniques.[6−9] These materials offer numerous advantages, including ease of application, minimal tissue trauma, and tissue-specific tunability. Moreover, compared with the discrete mechanical anchors provided by sutures or tacks, bioadhesives can establish conformal and intimate interfaces, positioning them as attractive tools for bridging biomedical devices with tissues. First-generation bioadhesives, such as fibrin and cyanoacrylate glues, were primarily developed for achieving hemostasis and serving as adjunctive support to surgical sutures.[10−12] Recent years have seen significant efforts dedicated toward improving their adhesion performance, as well as realizing advanced properties such as reversible adhesion, self-healing behavior, and electrical conductivity.[13−16] Along with the development of advanced capabilities, the applications of bioadhesives have expanded beyond wound repair and tissue sealing, holding promise for diverse tissue-interfacing technologies such as electrophysiological recording and stimulation, drug delivery, mechanical modulation, and deep tissue imaging, among others (Figure 1).

Amid these exciting developments, bioadhesive technologies face many open questions and challenges. How can we design bioadhesives that work reliably in different environments, especially in the presence of biological fluids and dynamic tissue movement? What are the practical considerations of bioadhesive production to enable its widespread adoption in clinical practice? How can we tailor the properties of bioadhesives to unlock their multifunctional roles in advanced biomedical applications? These and other challenges provide a stimulating interdisciplinary research landscape for the development of bioadhesives in the years to come. While there have been several excellent reviews on the topic of bioadhesives for hemostasis, wound healing, and tissue sealing, limited discussion has been provided around the broader scope of bioadhesives as technology platforms for biointegrated devices, as well as the growing significance of multifunctional design considerations beyond tissue adhesion.[9,8,17−23]

In this Review, we survey the latest advances in bioadhesives, with a particular focus on their emerging roles in biomedical devices and the corresponding properties that should be considered in their design. We begin by examining the fundamental mechanisms and implementation strategies of tissue adhesion to provide the context and background for the discussions that follow. Next, we highlight key challenges and strategies related to the interactions between bioadhesives and the biological environment. The main section of this Review provides a perspective on the potential applications of bioadhesives in technologies dedicated to monitoring, modulat-

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

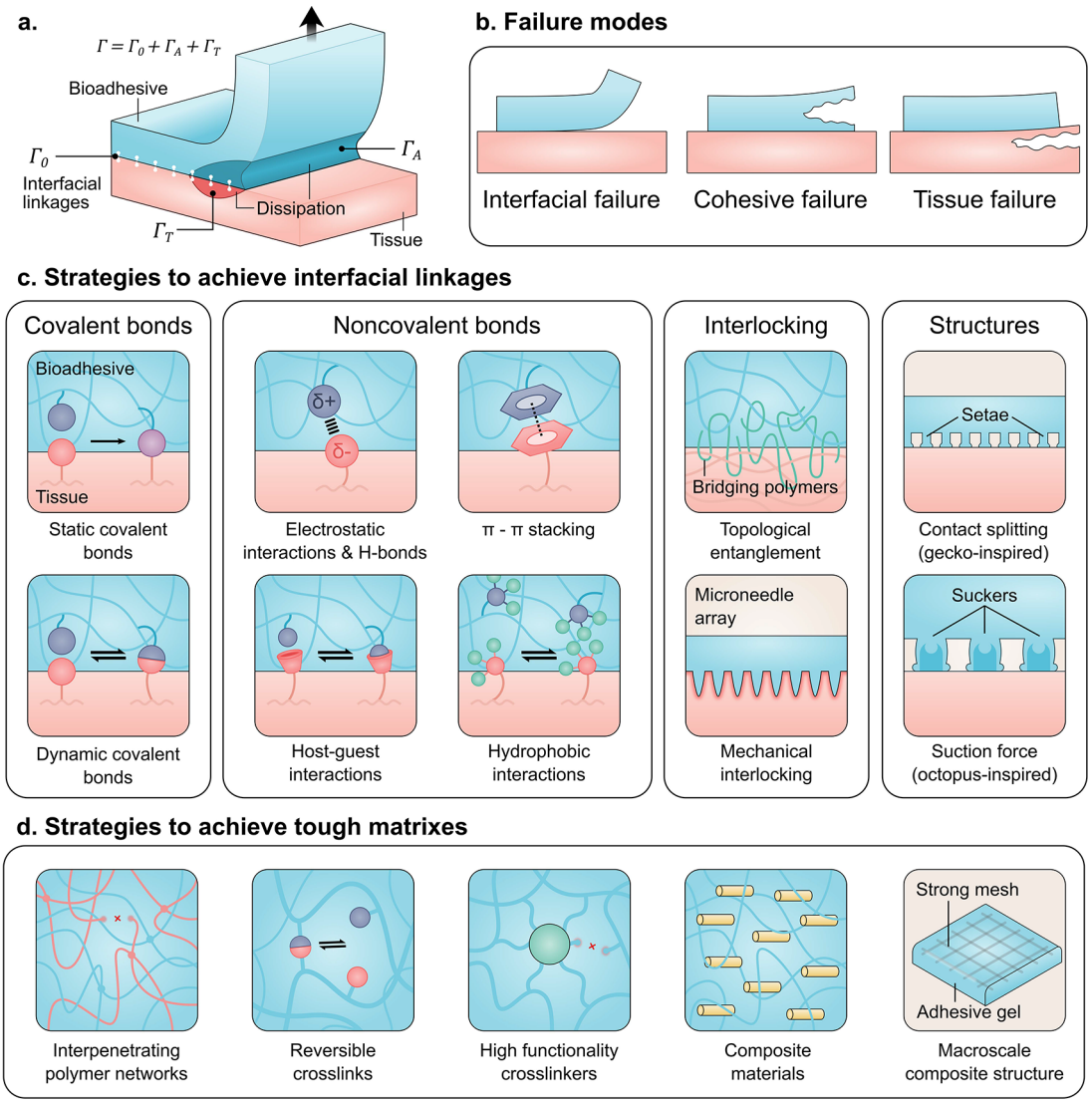


Figure 2. Design strategies for tissue adhesion. (a) The interfacial toughness of an adhered system depends on Γ_0, the intrinsic work of adhesion due to interfacial bonds; Γ_A, the energy dissipated in the bulk adhesive; and Γ_T, the energy dissipated in the tissue. Adapted with permission from ref 27 (Copyright 2021 Elsevier). (b) Three possible adhesion failure modes: interfacial failure, cohesive failure, and tissue failure. To design for tough adhesion, both strong interfacial linkages and a dissipative bioadhesive matrix are desired. (c) Representative strategies to achieve interfacial linkages and increase the interfacial work of adhesion. (d) Representative strategies to achieve tough bioadhesive matrixes by incorporating energy dissipation mechanisms.

ing, and enhancing physiological functions and pathologies. Through a systematic discussion, we explore state-of-the-art applications and identify future prospects for bioadhesive technology platforms. Lastly, we consider additional practical considerations underlying the usability and sustainability of bioadhesive technologies throughout their lifecycle.

2. TISSUE ADHESION MECHANICS

Tissue adhesion is a complex process involving physical and chemical interactions between the bioadhesive material (the adhesive) and the biological tissue of interest (the adherend) as well as each of their bulk properties. In this section, we outline various guiding principles and implementation strategies for achieving tissue adhesion.

From the basis of fracture mechanics, debonding between two adhered substrates involves the initiation and propagation of a crack along the interface (adhesive failure) or in either material (cohesive failure; Figure 2). The energy required for interfacial fracture is described by the *interfacial toughness* Γ (also called the *interfacial fracture energy* or *practical work of adhesion*), which is given by,

$$\Gamma = G_c = -\frac{dU}{dA} \quad (1)$$

where U is the total potential energy of the system, A is the undeformed crack area, and G_c is the critical energy release rate.[24−26] Note that unlike tensile toughness, which is measured in units of energy per volume, the unit for interfacial toughness is energy per area or J m^{-2}.

Most bioadhesives and biological tissues are soft materials (10^2−10^6 Pa in elastic modulus), which dissipate energy under deformation. The contribution of mechanical dissipation plays a large role in the resulting interfacial toughness. Quantitatively, the total interfacial toughness can be expressed as the summation of three components (Figure 2a): Γ_0, which is the intrinsic work of adhesion due to interfacial bonds; Γ_A, the

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

mechanical energy dissipated in the bulk adhesive; and Γ_T, the mechanical energy dissipated in the tissue:[22,26]

$$\Gamma = \Gamma_0 + \Gamma_A + \Gamma_T \quad (2)$$

In view of eq 2, tough adhesion can be achieved by incorporating strong interfacial linkages to confer a high Γ_0, along with energy dissipation mechanisms in the bulk adhesive to increase the contribution from Γ_A. Γ_T is determined by the mechanical properties of the native tissue and is therefore less readily tunable, although it is worth noting that Γ_T may change depending on the dimensions of the adhesive-tissue interface and the amount of energy absorbed by the bioadhesive. Because Γ_0 and Γ_A can be directly adjusted, we focus on strategies for tuning these two terms.

The strength of interfacial interactions and the mechanical properties of the bioadhesive and the tissue altogether determine the failure mode of adhesion (Figure 2b). If the bioadhesive matrix or the tissue is weak or brittle, cohesive failure in one of the substrates is likely to occur. Otherwise, failure at the interface due to disrupted interfacial linkages is the dominant mode.

2.1. Design Strategies for Interfacial Linkages

Interfacial interactions between bioadhesives and tissues are significantly influenced by both the chemical composition of the materials involved and the geometrical characteristics of the interface. Intermolecular interactions play a dominant role in determining the intrinsic work of adhesion (Γ_0), which is a measure of the energy required to separate two surfaces per unit area of contact without any external forces acting on them. In general, a higher intrinsic work of adhesion indicates stronger and more stable interfacial bonding, leading to an improved adhesion performance. Beyond intrinsic adhesion, physical attributes of the interface, such as surface roughness and architected protrusions, can have a profound effect on the overall adhesion behavior. In this section, we provide an overview of the primary strategies employed to modulate the interface in bioadhesive systems: intermolecular interactions, polymer entanglements, mechanical interlocking, contact splitting, and suction force (Figure 2c).

2.1.1. Intermolecular Interactions. Proteins comprising tissues contain chemical functional groups such as amines, carboxylic acids, hydroxyls, and thiols (also called sulfhydryls), which can form intermolecular interactions with reactive groups in bioadhesives.[28] These interactions can be covalent or noncovalent in nature, depending on the specific functional groups involved. Covalent interactions, which possess high bond dissociation energies relative to noncovalent interactions, are often targeted as the primary strategy for achieving strong and stable tissue adhesion.[9,29−31] Typical reactive groups that can be incorporated into bioadhesives to form covalent linkages include cyanoacrylates, isocyanates, *N*-hydroxysuccinimide (NHS) and NHS esters, and catechol groups. For example, cyanoacrylates can react rapidly with tissue surface nucleophiles such as amines and hydroxyls to form covalent bonds. Isocyanates can also react with surface nucleophiles to form covalent urethane bonds.[32] NHS can react with primary amines to form amide bonds, often with the aid of the coupling agent 1-ethyl-3-(3-(dimethylamino)propyl) carbodiimide (EDC).[33,31] Catechol groups can undergo oxidative cross-linking pathways to bond with amine and thiol groups.[34,35] The net strength of these and other reactive groups depends on the specific tissue surface and its constituent chemical functional groups.[8]

Compared to traditional covalent bonds, which are kinetically stable and require a large energy input to break, dynamic covalent bonds exhibit intermediate bond dissociation energies and can undergo exchange reactions under certain pH and temperature conditions. As a result, dynamic covalent bonds can be utilized to achieve reversible interfacial linkages.[20,36] These bonds are increasingly being incorporated into bioadhesives due to their ability to self-heal and remodel after being disrupted, which can be particularly valuable in applications where the bioadhesive is subject to continuous mechanical stress or deformation. Examples of dynamic covalent bonds include disulfide bonds, boronic ester bonds, imine bonds (also named Schiff bases), and hemithioacetal bonds.[37−40] In addition to their ability to self-heal, dynamic covalent bonds offer a tool to design bioadhesives with stimulus-responsive reversible adhesion, which can enable the retrieval or repositioning of misplaced bioadhesives without damaging the underlying tissue.[13]

Apart from covalent interactions, many bioadhesives rely on the interplay of noncovalent intermolecular interactions to adhere with tissues. Despite their relative weakness, noncovalent interactions play an important role in achieving fast interfacial bonding and contributing to adhesion stability. Noncovalent interactions in tissue adhesion include electrostatic interactions, hydrogen bonds, $\pi-\pi$ stacking, host−guest interactions, and hydrophobic interactions.[41] For example, bioadhesives possessing hydrogen bond-forming capabilities can interact with various chemical groups on tissue surfaces (e.g., amines, carboxyl, and thiol groups) and establish strong supramolecular adhesion, even without covalent linkages.[42,43]

Often, a combination of covalent and noncovalent interactions is used to impart tissue adhesion. A prime example of this approach can be seen in the adhesion strategy of the marine mussels. Mussels are renowned for their ability to adhere to a variety of surfaces and to withstand wet, dynamic environments (much to the dismay of boat owners). Their remarkable adhesive capability arises from mussel foot proteins (mfps), which contain a high proportion of phenolic residues, such as 3,4-dihydroxy-L-phenylalanine (DOPA), tyrosine, and tryptophan. These aromatic residues participate in a diverse array of bonding types, including bidentate hydrogen bonds, metal-ion coordination, $\pi-\pi$ stacking, and various covalent bonds involving quinones, the oxidized form of DOPA.[44] This repertoire of covalent and noncovalent interactions has served as inspiration for the development of mussel-inspired bioadhesives based on catechol chemistry, which continues to be a lively area of research.[45−50] For more detailed information, common chemical strategies for introducing tissue adhesive intermolecular interactions have been discussed at length in several topical reviews.[9,20,28]

2.1.2. Topological Entanglement. Topological entanglement between bioadhesive polymers and tissues provides a physical mechanism that can contribute to the interfacial work of adhesion without relying on specific reactive group chemistries. Topological entanglement refers to the phenomenon in which polymer chains diffuse into and become physically entwined with the substrate, forming a network of interlocks that can be viewed as molecular stitches.[51,52] The entanglement of bioadhesive polymer chains is governed by the molecular weight and flexibility of the polymers as well as the charge and topology of the tissue surface. Note that topological entanglement requires the adherend to have a porous microstructure to allow for the diffusion of the stitching polymers.

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

Various polymers have been employed as stitching polymers to accomplish topological adhesion with tissues. One example is poly(acrylic acid) (PAA), a water-soluble polymer that has a high density of carboxylic acid side chains, enabling the formation of coordination complexes with metal ions.[53] When PAA is dissolved in an aqueous solution and applied to the surface of a porous adherend, the polymers diffuse onto the substrate. Upon the introduction of a trivalent metal ion such as iron(III), the entangled PAA chains cross-link and form a network of stitches.[54] Other polymers that have been leveraged as stitching polymers include biopolymers such as chitosan, alginate, and hyaluronic acid.[33,54]

A drawback of the topological entanglement mechanism is the diffusion-limited rate of adhesion. Tissues with low permeability can be challenging for bridging polymers to interpenetrate, resulting in slow and weak adhesion. One potential strategy to accelerate and promote the formation of topological entanglements is to leverage an ultrasound transducer to induce cavitation and actively embed adhesive polymers into the tissue.[55,56]

2.1.3. Mechanical Interlocking. In addition to the molecular stitches described above, another physical adhesion mechanism involves the formation of mechanical interlocks between the bioadhesive and the tissue. Mechanical interlocking can occur on various scales through a number of strategies, including the use of flowable polymers to infiltrate tissue surface irregularities, the geometric design of bioadhesive surface structures, and the use of pores to promote tissue ingrowth. In general, mechanical interlocking can enhance adhesion by increasing the contact area between substrates and provoking additional energy expenditure during crack propagation.[57]

A classic example of mechanical interlocking can be seen with pressure sensitive adhesives (PSAs), which typically take the form of tapes composed of viscoelastic polymers such as acrylics and silicones.[58] When a small amount of pressure is applied, the viscoelastic polymers flow around the peaks and troughs of the adherend surface, creating mechanical interlocks. PSAs have been widely commercialized for epidermal applications by companies such as DuPont, 3M, and Elkem.[59−61] Recently, 3M unveiled a new acrylate-based PSA marketed to stick to skin for up to 28 days, expanding the previous wear time by 2 weeks.[62] Despite the commercial popularity of epidermal PSAs, their development for internal applications has been hindered by their inability to bind to surfaces coated with body fluids.[63]

To enable mechanical interlocking with the surface roughness of wet tissues, bioadhesives can be patterned with micro- or macro-scale surface features, such as microneedles and hooks.[64] The adhesion performance of these structured bioadhesives is heavily reliant on the geometric design of their protrusions, which determine the required penetration force and the pull-out force.[65] Anchoring architectures, such as barbed or swellable microneedle tips, can be employed to increase the adhesion strength, especially in shear.[66−68] This anchoring effect physically impedes crack propagation while simultaneously increasing the contact area between the adhesive and the tissue. Moreover, these surface features not only enable adhesion but also can also create microchannels through the tissue surface, facilitating the efficient delivery of drugs, vaccines, and cosmetics.[69−73] The mechanical and geometrical properties of microneedles and barbs should be evaluated to ensure that they maintain their structure during skin insertion.[74] It may also be important to account for variations in tissue properties across different body regions and individuals, as they can impact the desired adhesion performance and therapeutic effects of microneedle-type bioadhesives. To this end, numerical simulations have been employed as tools for predicting skin penetration behavior. Still, the specific contributions of microneedles and similar structures to adhesion energy have received limited attention in the literature. Elucidating how certain geometrical parameters might impact crack propagation and overall adhesion would offer a more thorough understanding of the adhesion mechanisms.

From a different approach of mechanical interlocking, self-adhesive implantable devices have been designed by crafting porous surfaces on implants, allowing for soft tissue ingrowth and interdigitation.[75−77] For example, titanium alloy implants have been modified using methods such as electron beam manufacturing, sandblasting, and acid etching to produce penetrable tissue interfaces.[77,78] However, because this strategy relies on slow biological processes to achieve mechanical stability, its practical use cases are largely confined to the long-term integration of dental and orthopedic implants.[79,80]

2.1.4. Contact Splitting. The remarkable capability of geckos to cling to almost any surface has inspired a family of adhesives known as gecko-mimetic adhesives, which are being exploited for various applications including medical bioadhesives.[81,82] The working principle of these adhesives is based on the hierarchal structure of the gecko foot, which is covered with millions of tiny hairs called setae. Each seta is further divided into hundreds of branches called spatulae that interact with the surface at the molecular level via van der Waals forces.[83−85] The sum of these van der Waals interactions over millions of setae gives rise to a surprisingly large attachment force that is relatively insensitive to the surface chemistry of the adherend. The central design principle underlying gecko adhesion is the notion of contact splitting, i.e., the division of a large contact area into many finer contact areas.[86,87] Contact splitting strategically improves adaptability to surface irregularities and increases the effective adhesion force. This can be understood from the framework of contact mechanics. Following the Johnson−Kendall−Roberts (JKR) contact model, the adhesion force of a hemispherical contact F is directly proportional to its radius R.[88] Conversely, the density of these contacts per unit area is inversely proportional to the square of the radius, scaling as $1/R^2$. Consequently, by replacing a single large contact with n self-similar smaller ones, the adhesion force F' can be enhanced to[87]

$$F' = \sqrt{n}F \tag{3}$$

Another notable attribute of the gecko foot is the anisotropy of its structures, which give rise to anisotropic shear frictional forces and an adhesion energy highly dependent on the peeling angle.[89] This feature enables the gecko to achieve a strong grip in certain directions yet also detach its feet with near-zero detachment forces. For this reason, gecko-inspired adhesives are also often referred to as frictional adhesives.

Borrowing from the adhesion strategy of the gecko, researchers have fabricated adhesive surfaces with synthetic nanopillar setae. These nanostructured surfaces can be chemically functionalized, such as with a coating of oxidized dextran, to promote chemical cross-linking with tissues and further stabilize adhesion.[82] However, gecko-inspired bioadhesives generally struggle to adhere strongly to wet surfaces with reduced friction. Altering the micropillar geometry, such as by incorporating mushroom-shaped tips, has demonstrated improved adhesion performance in both dry and wet conditions.[90] Besides tuning their shape, fabricating pillars

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

with regions of different elastic moduli (e.g., a soft tip and stiff base) can be beneficial for simultaneously achieving conformal contact with rough surfaces and overall mechanical robustness.[91] However, the introduction of added geometric or material complexities poses manufacturing challenges and may limit high-volume production.[92]

2.1.5. Suction Force. Another source of inspiration from nature is the octopus, whose arms are decorated with hundreds of suckers which can grip a variety of objects underwater, from hard rocks to soft and slippery fish.[93] Interest in the utility of octopus suckers for wet adhesion has given rise to octopus-mimetic bioadhesives which rely on the formation of suction force to attach to substrates.[94−100] The strength of attachment is influenced by the pressure differentials generated by the suckers, which is dependent on their geometry and elasticity.[101] In addition to the suction provided by these protuberances, the outer part of the octopus sucker is covered with an array of soft microscale wrinkles. These wrinkles drain water at the interface and increase the contact area between the sucker and the substrate, enhancing the net adhesion force. Inspired by this anatomical feature, researchers have developed an octopus-mimetic patch containing adhesive suckers outfitted with wrinkles to drain and capture water.[102] Overall, bioadhesives based on suction force offer several unique advantages, including the ability to adapt to rough surfaces and reversibly attach to both wet and dry substrates. Nonetheless, this family of bioadhesives has been relatively less explored, possibly due to the complexity of manufacturing suction cup architectures and the easy loss of suction.

2.2. Design Strategies for Energy Dissipation

Returning to eq 2, another important factor in determining the interfacial toughness is Γ_A, the energy dissipated in the adhesive during the process of delamination. To increase Γ_A, energy dissipation mechanisms can be intentionally designed into the polymer network architecture of the bioadhesive (Figure 2d). This can take the form of fracturing sacrificial polymer chains, breaking reversible cross-links, using high functionality cross-linkers, and pulling out embedded fibers or fillers.[103,104]

2.2.1. Fracture of Polymer Chains. Short polymer chains can impart toughness to a network by providing sacrificial bonds. As the bioadhesive is deformed, the short chains around the process zone fracture and dissipate mechanical energy. To maintain strength in addition to toughness, interpenetrating polymer networks (IPNs) have been employed as strategic architectures.[105−107] An IPN generally involves the interpenetration of a long-chain and a short-chain network that are separately cross-linked. Under loading, the brittle short-chain network dissipates energy, while the intact long-chain network maintains the integrity of the material. The implementation of IPN architectures with reactive surface functional groups has produced tough bioadhesive hydrogels with exceptional interfacial toughness.[31,108,109] However, the rupturing of the short-chain network usually induces permanent damage, resulting in limited fatigue resistance.

2.2.2. Reversible Cross-Links. Another approach to introducing energy dissipation is to incorporate reversible cross-links into the bioadhesive matrix.[110] Similar to how reversible bonds, such as physical interactions and dynamic covalent bonds, can provide self-healing behavior at the interface, reversible cross-links in the bulk matrix can dissociate under loads and allow stretched polymer chains to relax, dissipating energy. Their reversibility allows for cross-links to reform after breaking, thereby maintaining the energy dissipation mechanism over multiple loading cycles. For instance, mussel-inspired bioadhesives contain catechol groups that participate in various noncovalent interactions among one another in the bulk material (e.g., hydrogen bonding and $\pi-\pi$ stacking). The dynamic formation and breakage of these noncovalent interactions provide stretchability and toughness.[111]

2.2.3. High Functionality Cross-Linkers. Functionality refers to the number of polymer chains that can be cross-linked by a single cross-linker. Conventional physical and chemical cross-linkers typically have low functionalities, meaning there is often only a single polymer chain bridging two adjacent cross-links.[103] As a result, the network can fracture when single polymer chains are ruptured under deformation and connections between cross-links are compromised. To circumvent this issue, high functionality cross-linkers (e.g., with functionalities exceeding 100) can be incorporated into polymer networks, yielding multiple polymer chains with varied lengths connecting adjacent cross-links. This design allows for the dissipation of energy through the fracture of relatively shorter chains, while longer chains retain their structural integrity, thus imparting elasticity to the material. Representative high-functionality cross-linkers include two-dimensional nanomaterials such as clay nanosheets and graphene.[112] However, high concentrations of nanoclays and graphene can have adverse effects on cells; therefore, their incorporation into bioadhesive materials should be carefully assessed to ensure their compatibility with cellular systems.[113−115]

2.2.4. Composite Materials. Composite materials, such as the natural composites of tissues embedded with collagen fibrils, often possess superior toughness than their constituents alone.[116−119] The working principle of toughening due to fiber reinforcement is based on the dissipation of energy that results from the sliding, debonding, and fracture of fibers under mechanical loads. The incorporation of fibers can also act to reduce the swelling ratio of the composite by restricting the amount of water that can penetrate the denser structure, which can mitigate swelling-induced weakening. For example, cellulose fibers (CFs) integrated into a gelatin and alginate-based bioadhesive formulation were found to increase the cohesiveness of the matrix, significantly improving the burst strength of the bioadhesive.[120] However, caution is warranted in using CFs for internal bioadhesives due to their nonbiodegradability in humans.[121]

In general, the mechanical properties, orientation, and volume fraction of fibers or fillers in the polymer network are key parameters that influence the resulting mechanical properties, of the composite. For instance, uniformly aligned fibers can give rise to anisotropic toughness and strength, while randomly dispersed fibers result in an isotropic toughening effect. Another design parameter is the aspect ratio of the fibers. Longer fibers can provide higher toughness and crack resistance but may also lead to reduced flexibility and stretchability. For fibers that exhibit strong interfiber interactions (e.g., hydrogen bonding), the use of processing aids or coupling agents may be necessary to prevent the fibers from aggregating.[122,123]

Besides fibers and fillers, macroscale composite structures such as hydrogel-mesh composites or bilayer patches can also be employed to provide mechanical reinforcement to bioadhesive materials.[124,125] For instance, hydrogel-mesh composites combine the load-bearing capacity of a surgical mesh, such as those used for hernia repair, with a bioadhesive hydrogel,

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

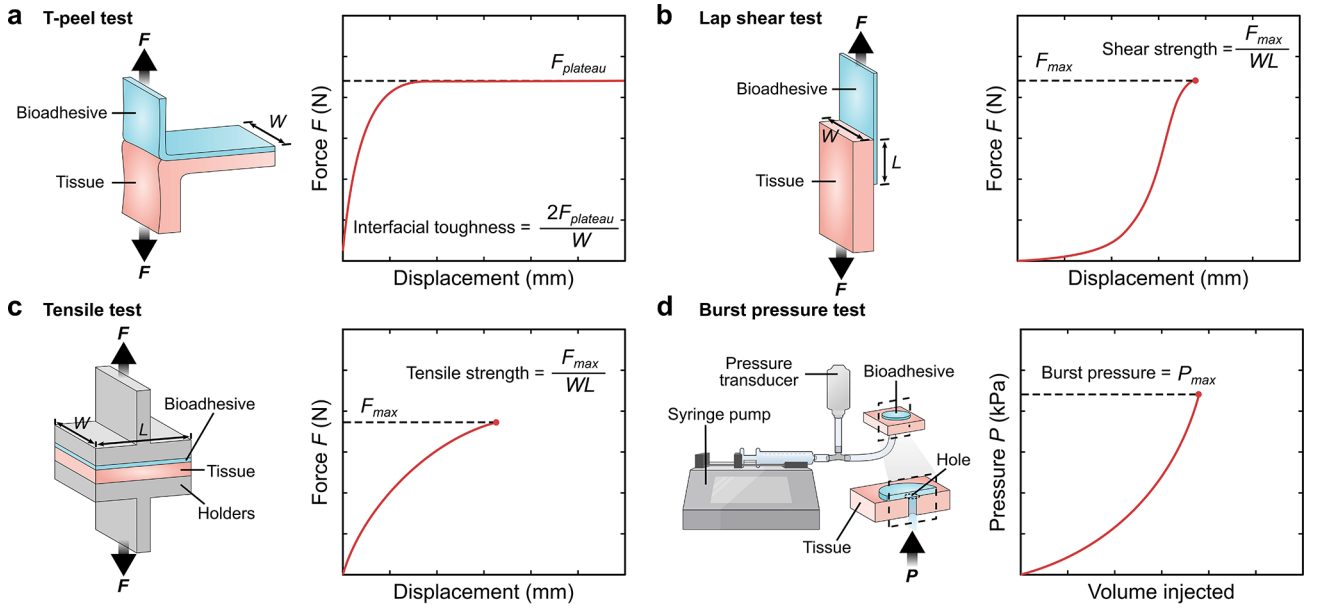


Figure 3. Experimental test setups for evaluating adhesion performance. (a) T-peel test based on ASTM F2256 for measuring interfacial toughness. (b) Lap shear test based on ASTM F2255 for measuring shear strength. (c) Tensile test based on ASTM F2258 for measuring tensile strength. (d) Burst pressure test based on ASTM F2392 for measuring burst pressure.

resulting in a structure that can maintain adhesion and cohesion under large mechanical stresses.[124] Similarly, heterogeneous bilayer patches comprising a bioadhesive layer bonded to a secondary material with favorable mechanical properties can yield improved toughness. For example, integrating a bioadhesive hydrogel with a thin backing layer of hydrophilic polyurethane has been employed to create bioadhesive patches with enhanced strain capacity and flexibility.[125] For bilayer structures, the equilibrium swelling ratios of the individual components should ideally be similar to avoid curling of the patch when hydrated, which can lead to the patch collapsing in humid environments or delaminating from tissue surfaces.

2.3. Energy Dissipation in the Tissue

As biological tissues are viscoelastic and poroelastic in nature, they too contribute to the energy dissipated under loading.[126,127] An array of biological factors gives rise to the nonlinear elastic behavior observed in tissues. Prominent among these factors are collagen, proteoglycans, elastin, and fluid content.[128] Collagen fibers, abundant in connective tissues, impart viscoelastic properties through mechanisms, such as sliding and reorientation. Proteoglycans within the extracellular matrix establish a hydration layer around collagen fibrils, facilitating load transfer and energy dissipation.[129] Elastin, a resilient structural protein, is present in large amounts in highly elastic tissues and has the ability to repetitively deform and recoil under strain.[130] Fluids residing within the extracellular matrix contribute to stress dissipation and load distribution via movement within the porous structure. The resulting fluid pressurization and viscous drag give rise to flow-dependent poroelastic properties.[131] Collectively, these factors work in concert to absorb and redistribute mechanical energy, allowing tissues to withstand dynamic loads. Notably, variations in the composition and arrangement of these components across different tissue types result in tissue-specific viscoelastic properties. Although tissues possess these energy dissipation mechanisms, in general, the relative contribution of Γ_T is low compared to the energy dissipated in the bioadhesive (Γ_A).[27] Nonetheless, the elastic and dissipative properties of the tissue influence the energy dissipation within the bioadhesive, as they can impact the size of the dissipation zone and the relative deformation of the bioadhesive. Consequently, such variations may account for the significant differences in adhesion performance of bioadhesive materials when applied to different tissue types.[27]

2.4. Adhesion Tests

The adhesion performance of bioadhesive materials is most commonly quantified using one or more of the following experimental tests based on standards established by the American Society for Testing and Materials (ASTM): the T-peel test (ASTM F2256, measuring interfacial toughness); the lap shear test (ASTM F2255, measuring shear strength); the tensile test (ASTM F2258, measuring tensile strength); and the burst test (ASTM F2392, measuring burst pressure). The experimental setups and corresponding data outputs are illustrated in Figure 3. For soft tissues and bioadhesives, a stiff backing is sometimes used to minimize elongation of the detached portion in the T-peel and lap-shear tests. Depending on the target application of a certain bioadhesive, specific adhesion tests may have a greater clinical relevance than others. For example, sealants designed to prevent air or fluid leakage should be evaluated according to their burst pressure.

The viscoelastic nature of polymeric materials and tissues, combined with the rate dependence of bond dissociation processes, introduces another aspect to consider: the rate at which peeling forces are applied affects the force required to initiate failure.[27,132] In practical terms, the rate dependence of peeling forces has implications for the durability of a bioadhesive on different tissues and its ease of removal. In general, at low peel rates, the adhesive interface experiences time to relax, resulting in a lower force required for failure. Conversely, at high peel rates, the interface is subjected to rapid stress increases, leading to a higher force for failure. When conducting experiments to measure adhesion energy, it becomes useful to account for the rate dependence behavior of peeling forces. To consistently

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

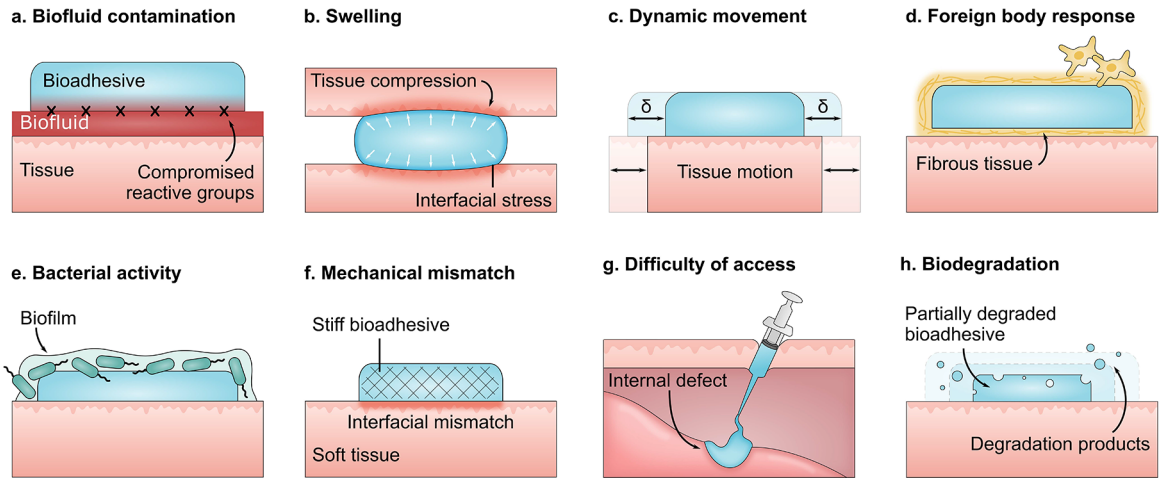


Figure 4. Key considerations related to the biological environment. (a) Premature contamination by biofluids can compromise reactive groups on the bioadhesive surface, rendering it nonadhesive. (b) Excessive swelling of the bioadhesive can give rise to interfacial stress, weakening the strength of adhesion, and adversely compress surrounding tissues. (c) Dynamic tissue movement imposes repeated deformations on the bioadhesive, which may cause it to fracture or delaminate. (d) Excessive inflammation as a result of the foreign body response can lead to fibrotic capsule formation and poor healing. (e) Bacterial activity can give rise to biofilm formation and infectious complications. (f) Mechanical mismatch between the bioadhesive and tissue can lead to interfacial stress concentrations and interfere with organ function. (g) Difficult-to-access internal defects may require specialized bioadhesive form factors or delivery methods. (h) The bioadhesive should undergo biodegradation at a suitable pace and induce minimal cytotoxicity with its degradation products.

measure a lower bound of the interfacial toughness, a sufficiently low peel rate should be applied to capture the steady state behavior.

3. BIOLOGICAL CHALLENGES

In practice, bioadhesives face a variety of complex biological challenges, which often impede their tissue bonding performance in vivo compared to in laboratory settings. These challenges highlight areas where there exists a major need for technological innovation, motivating the development of new and improved bioadhesives. This section examines the main challenges imposed by the biological environment: adhesion in a wet environment, dynamic tissue movement, the immune response, bacterial activity, mechanical mismatch, difficult-to-access application sites, and biodegradation (Figure 4).

3.1. Adhesion in a Wet Environment

Inside the body, fluids are ubiquitous. Most internal tissues are lined with a layer of interfacial water, which provides lubrication, hydration, and other functions essential for their physiology. However, biofluids also present a major obstacle for tissue adhesion, as they can physically block tissue contact, slow down diffusion, or compromise reactive groups in the bioadhesive (Figure 4a). For instance, NHS esters are susceptible to hydrolysis.[133] Achieving fast and robust adhesion with wet tissues has historically been one of the grand challenges for bioadhesive development.

A promising wet adhesion strategy is to remove the interfacial water from the tissue surface using a dry-cross-linking mechanism, in which the bioadhesive material is applied in a dry or dehydrated state to allow quick absorption of the interfacial water as the adhesive becomes hydrated.[134] This enables near-immediate consolidation with the tissue, allowing rapid formation of intermolecular bonds.[31] Although this strategy can accelerate adhesion formation compared to diffusion-limited bioadhesives (e.g., within a few seconds vs several minutes), a downside of the dry-cross-linking mechanism is its sensitivity to hydration, as the interfacial wicking effect can be compromised if the dry bioadhesive becomes prematurely hydrated before reaching the tissue surface.

An idea for circumventing premature fouling by biofluids involves coating the bioadhesive with a protective layer of liquid that is immiscible with the contaminating biofluids.[135] The implementation of this approach employs a hydrophobic liquid such as a silicone or mineral oil to serve as a dynamic physical barrier that prevents the underlying bioadhesive surface from directly contacting environmental fluids. The hydrophobic liquid can then be expelled at the tissue surface under sufficient dewetting pressure.[136] In liquid-infused systems, the solid surface typically features nano- or microscale structures that stabilize the wetting of the lubricating liquid. For example, the solid surface can take the form of a porous, sponge-like substrate, a microparticle-embedded surface, or a woven mesh.[136−138] This strategy can also be adapted to create bioadhesive pastes by suspending bioadhesive particles in a protective fluid, allowing the paste to be directly applied to actively bleeding wound sites.[139] The main advantage of these liquid-infused systems is that they allow the bioadhesive to leverage water-sensitive reactive groups without necessitating a dry, open-access surgical field, improving their practical applicability.

Another consequence of adhesion in wet environments is the swelling of hydrophilic bioadhesives, which can give rise to interfacial stresses and compress the surrounding tissues (Figure 4b). The latter concern of tissue compression is especially detrimental for applications in spaces sensitive to volume expansion, such as near nerves.[140−142] The effects of swelling can be mitigated by increasing the cross-linking degree, incorporating thermosensitive polymers, or introducing hydrophobic functional groups, although these alterations may also impact the overall adhesion performance and mechanical properties of the bioadhesive.[143,144] For preformed bioadhesive patches, stretching the bioadhesive to its equilibrium swelling ratio prior to application can cancel out the effects of swelling without altering its material composition.[125,145] However, this technique is limited by the stretchability of the bioadhesive network in its initial state.

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

3.2. Dynamic Movement

Many tissues in the body are constantly moving and stretching, which can cause bioadhesive materials undergoing tissue-induced deformations to fail (Figure 4c). Overcoming this challenge requires bioadhesives to be designed with high flexibility, extensibility, and fatigue resistance. To this end, introducing energy dissipation and self-healing mechanisms can be useful for designing tough, stretchable, and self-healing materials (e.g., the strategies discussed in Section 2). Moreover, the use of fibers/fillers or high functionality cross-linkers to introduce high-energy phases can increase the fatigue threshold of bioadhesives.[25]

The lungs are an illustrative example of a challenging dynamic application site. Lung tissues are highly elastic to accommodate large cyclic changes in volume during inspiration and expiration. Air leaks following surgical lung resection are a cause of major breathing complications, but effective methods for sealing them have remained somewhat elusive. Sutures and staples pose the risk of creating additional leak points since they puncture through tissue, while common commercial sealants lack the proper extensibility or tensile strength to support inflation and deflation. Leveraging the properties of elastin, researchers engineered a highly elastic lung sealant by cross-linking recombinant human tropoelastin (the subunit of elastin).[146,147] The resulting formulation was found to outperform commercial sealants in rat and porcine lung defect models, demonstrating the importance of bioadhesive elasticity in repairing dynamic tissues.

In addition to the mechanical properties of the bioadhesive, the time required to form adhesion is a crucial property for adhering to actively moving tissues. Tissue movement can displace or fracture a bioadhesive before it reaches full adhesive or cohesive strength, depending on the kinetics of relevant processes such as diffusion, bond formation, and gelation. Some strategies that may be incorporated to minimize the time it takes to form adhesion include employing stimuli-responsive materials (e.g., light-activated polymerization), using preformed patches to eliminate the need for in situ matrix formation, fabricating surface structures that enhance the wetting behavior and interfacial contact with the tissue, or implementing the dry-cross-linking mechanism described in Section 3.1. Still, slow adhesion formation remains a common challenge among bioadhesives.

3.3. Immune Response and Allergies

The foreign body reaction (FBR) to implanted biomaterials is a fundamental biological challenge which underlies the failure of many materials and devices (Figure 4d).[148] Adverse consequences of FBRs include fibrotic scarring and the development of postsurgical adhesions.[149] For implanted devices, fibrous tissues that form between the device and the physiological environment can also substantially interfere with biosensing, mass transport, and signal transmission. To minimize the FBR, some bioadhesive materials have been designed to incorporate molecules that inhibit protein adsorption and cell adhesion, such as zwitterionic polymers.[150−152] Bioadhesives can also serve as carriers for anti-inflammatory drugs, which can be released at the interface to modulate the local tissue response and minimize fibrotic encapsulation. However, strategies based on the release of pharmacological substances are effective only in the short term, and fibrosis can still arise after their therapeutic effects wear off. An alternative strategy to alleviate the FBR involves altering the shape or surface topography of implanted materials.[153,154] Such geometrical parameters appear to have a profound effect on the macrophage behavior and capsular contracture. It was recently reported that implants having an average surface roughness of 4 μm are associated with minimal inflammation, which may serve as a basis for the development of deliberately textured bioadhesives.[153]

Besides the FBR, the potential allergenicity of bioadhesive materials poses a substantial concern for individuals who may be sensitive to specific proteins or antigens. For example, bioadhesives containing components derived from animal sources such as collagen, gelatin, albumin, or fibrin may induce anaphylactic reactions in allergic patients.[155−157] Although synthetic polymers are generally associated with lower allergenicity, they too can elicit allergic responses.[158] In view of this risk, applying personalized medicine approaches to bioadhesive development may be a valuable strategy to tailor formulations to individual patients based on their specific medical needs.[159] In the future, screening patients for potential allergies to bioadhesive components (including specific polymers, cross-linkers, and other additives) and adjusting the formulation of a bioadhesive accordingly could be performed prior to a clinical intervention to minimize the risk of adverse reactions. To effectively carry out such an approach, establishing a library of various components of bioadhesive formulations, their alternatives, and their effects on material properties would be necessary to optimize the patient-specific safety of bioadhesives.

3.4. Bacterial Activity

The potential for biomaterials to support bacterial activity is a major concern that can pose a risk of infections and related complications (Figure 4e). To mitigate the occurrence of microorganism attachment and proliferation, bioadhesive materials can be designed to incorporate bacteria-repellent or antiadhesive properties.[160] Materials with intrinsic antibacterial properties, such as metals (e.g., copper, silver, and gold) or ceramics (e.g., zinc oxide, magnesium oxide, and titanium oxide), may be incorporated into the adhesive matrix to inhibit bacterial growth. Additionally, chitosan has been shown to produce antibacterial effects.[161] Besides bulk material strategies, tuning the surface properties of bioadhesive patches can be employed to introduce antiadhesive interfaces.[162] For example, incorporating highly hydrophilic moieties such as zwitterionic polymers can reduce bacterial attachment by increasing the energetic cost of disrupting surface-associated water molecules.[163,164] Furthermore, modifying the surface topography of implants has been shown to impact biofilm formation.[165,166] To this end, developing fabrication methods to controllably introduce optimized topographical features may be an effective strategy for hindering bacterial activity.

3.5. Mechanical Mismatch

When considering the mechanical properties of bioadhesive materials, the similarity or mismatch in properties between the bioadhesive and tissue adherend can significantly influence the performance of the adhesive bond. In the case of a substantial mechanical mismatch, stress concentrations at the interface can lead to tissue damage or premature failure (Figure 4f). For example, cyanoacrylate bioadhesives, which form rigid and brittle matrixes upon polymerization, are prone to delaminating from soft tissues due to their limited flexibility.[167] This illustrates the importance of targeting mechanical compatibility between the bioadhesive and the tissue. On the other hand, however,

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

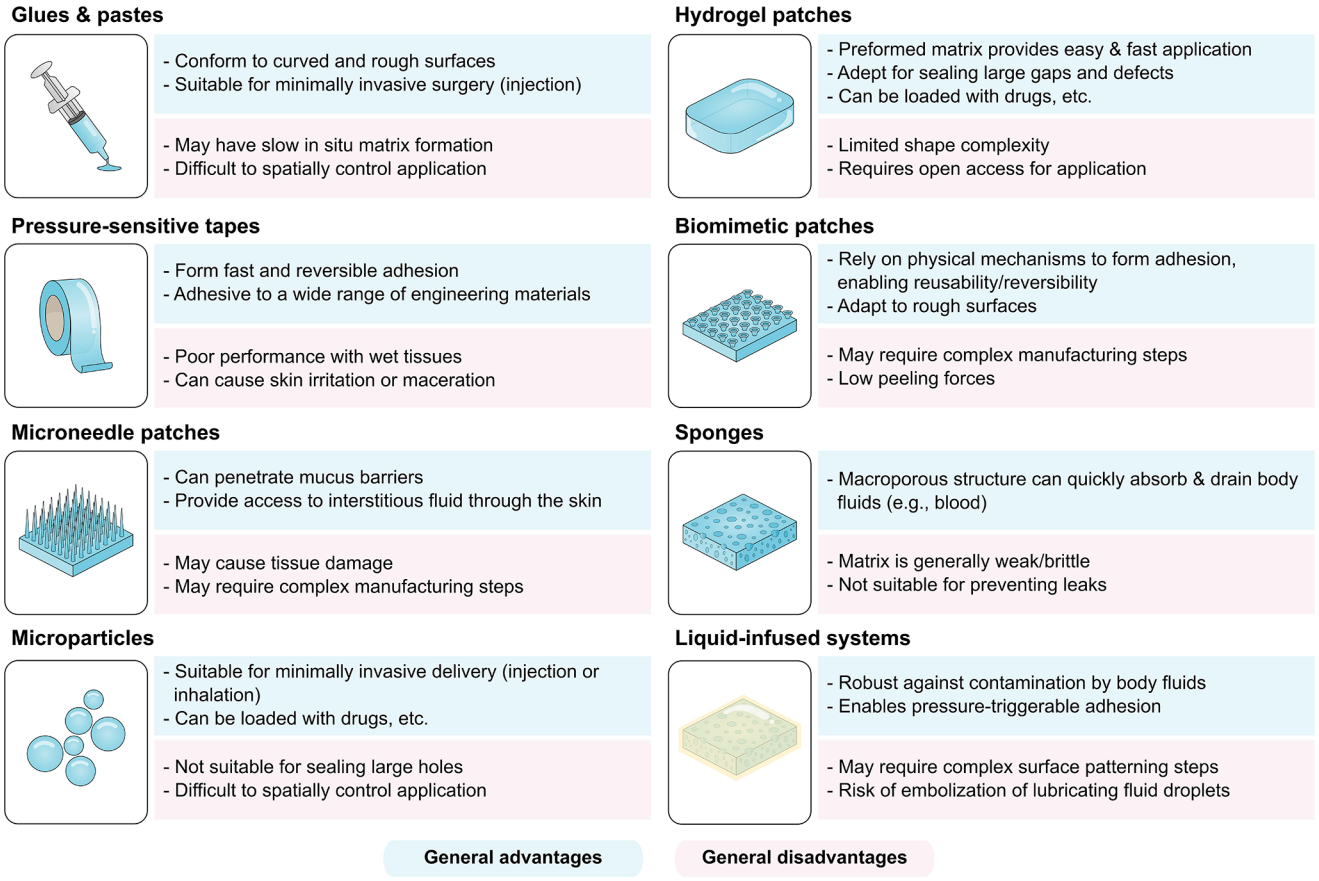


Figure 5. General advantages and disadvantages of various bioadhesive form factors, including glues and pastes, hydrogel patches, pressure-sensitive tapes, biomimetic patches (e.g., gecko-mimetic and octopus-mimetic), microneedle patches, sponges, microparticles, and liquid-infused systems. Each form factor possesses distinct pros and cons, and its suitability depends heavily on the target application and delivery method.

highly deformable bioadhesives may be ineffective at keeping wound edges together, hindering tissue repair. One strategy to reconcile these confounding material requirements for soft tissue sealing is to implement a gradient in elastic modulus along the bioadhesive, such that the tissue-material interface is mechanically well-matched (i.e., softer) while the wound-covering portion is resistant to excessive deformation (i.e., stiffer).[168]

Besides affecting adhesion performance, the mechanical properties of the bioadhesive can have profound effects on the tissue mechanics and organ function. For instance, in the context of blood vessels which experience continuous pulsatile pressures from blood flow, compliance matching between the bioadhesive and the vessel can be crucial for maintaining proper hemodynamics.[169] A compliance mismatch may disrupt blood flow or induce turbulence, potentially altering perfusion or promoting thrombus formation.[170] Furthermore, the tissues comprising blood vessels (and most tissues in general) are elastically anisotropic, which may also impact flow behavior.[171] Also worth considering is how the disease state of tissues may alter their physical (and chemical) properties, thereby influencing the performance of a bioadhesive. Certain pathologies have been linked to changes in tissue mechanics; for example, cardiomyopathy can lead to stiffening of the heart tissue.[172] Developing strategies to fabricate bioadhesives with programmable anisotropic mechanical properties, such as by electrospinning or 3D printing, may enable better tissue and patient specificity.

3.6. Difficulty of Access

The challenge of physically accessing certain tissue sites poses a distinct hurdle in the application of bioadhesives (Figure 4g). This may arise due to the nature of the procedure (e.g., minimally invasive vs open access) or the anatomical structure (e.g., within deep tissue compartments or hollow structures) and can be prohibitive to the use of common forms of bioadhesives, requiring specialized application strategies. Injectable formulations, including glues, pastes, and hydrogel microparticles, have emerged as the prevailing strategy for achieving minimally invasive delivery.[123,173−175] Injectable bioadhesives must be formulated to possess the proper rheological properties to flow through a narrow syringe, and undergo phase transitions or cross-linking processes to establish cohesive matrixes in situ.[49] While injectable bioadhesives offer notable adaptability, in situ matrix formation carries several limitations, including slow adhesion formation and low cohesive strength.

For the minimally invasive delivery of preformed bioadhesives, origami-inspired patches have been proposed, drawing inspiration from the art of paper folding.[136] These bioadhesives are designed to be collapsed or folded prior to delivery, facilitating insertion through small access ports and subsequently expanding and adhering at the target site using minimally invasive end-effectors. Designing bioadhesives that are amenable to origami techniques requires that they retain their folded shape prior to insertion and conform with the tissue upon deployment. While this strategy can achieve fast and

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

robust adhesion in difficult-to-access tissue targets, its versatility is constrained by geometric limitations.

A unique approach to deliver a bioadhesive coating to the deep branches of the airway involves the inhalation of bioadhesive microparticles.[176] These microparticles are administered using a dry powder inhaler and deposited along the airway, where they undergo swelling and cross-linking to form a hydrogel shield. The resulting bioadhesive layer can serve as a physical barrier against pathogens or can deliver drugs directly to the respiratory system.

As has become apparent throughout the discussions thus far, the choice of the bioadhesive form factor plays a central role in determining its suitability for specific applications. Bioadhesives have been developed in a wide array of shapes and forms, each of which carries distinct advantages and disadvantages, which are summarized in Figure 5. The most suitable choice depends strongly on the intended use and delivery method.

3.7. Biodegradability, Clearance, and Removability

The ultimate fate of a bioadhesive from the angles of biodegradation, clearance, and removability is a critical design consideration, especially for bioadhesives used internally.[177,178] At a high level, bioadhesives should be designed to degrade at a pace that allows them to provide the necessary support during tissue repair but eventually undergo degradation without causing a chronic immune response (Figure 4h).

The rate and process of biodegradation depend on the characteristics of the material and the physiological environment in which it resides. Biodegradation can be driven by chemical, physical, and biological mechanisms, resulting in a multitude of factors that contribute to its process. Three main mechanisms of polymer degradation in the body are oxidative, hydrolytic, and enzymatic degradation.[106,179] Oxidative degradation occurs during the inflammatory response when recruited immune cells produce reactive oxygen species, resulting in the scission of polymer chains.[180,181] Hydrolytic degradation arises when hydrolyzable bonds (e.g., esters, amides, and carbonates) are cleaved by water, breaking down the polymer into oligomers and monomers. The rate of hydrolytic degradation can be tuned by modifying the morphological and hydrophilic characteristics of the bioadhesive. Finally, enzymatic degradation occurs through the catalysis of hydrolysis by endogenous enzymes, which accelerates biodegradation.[182,183] Enzyme activity is influenced by the pH and temperature, which can vary across different anatomical sites. Overall, the design of specific chemical and surface characteristics modulates biodegradation. As these properties themselves change over the course of degradation, the interplay of biodegradation mechanisms is a dynamic process. Due to the multitude of influencing factors, it is difficult to accurately predict the timeline of in vivo biodegradation using in vitro experiments.

In certain physiological environments, biodegradation poses a substantial challenge to tissue repair. For example, the pancreas secretes a highly degradative juice containing a variety of digestive enzymes which, when leaked, can damage surrounding tissues and deteriorate suture or bioadhesive materials.[184,185] The use of synthetic bioadhesives or enzyme inhibitors may potentially hinder this aggressive degradation process; however, the design of degradation-resistant bioadhesives that can withstand pancreatic juice, as well as gastric juice and bile, remains a prominent challenge.

As a product of the biodegradation process, clearance of implanted biomaterials from the body is essential to minimize adverse effects and interference with normal physiological processes. In general, biodegradation products can be eliminated via renal or hepatic routes. Designing bioadhesives with the appropriate physicochemical properties and molecular sizes can facilitate their clearance and minimize the potential for long-term accumulation. The toxicity of biodegradation products is also a concern, exemplified by the release of cytotoxic formaldehyde from cyanoacrylate-based adhesives.[186]

Removability is another important consideration for bioadhesives intended for short-term applications. Most internal applications disfavor the requirement of secondary surgery to retrieve an implanted bioadhesive; however, for epidermal adhesion, it is often desirable to remove the bioadhesive on demand without causing damage to the underlying skin. Atraumatic detachment can be achieved through various mechanisms, such as using external triggers (e.g., heat, light, or specific chemical reactions) that weaken the adhesive interface or employing adhesion strategies that rely on nondestructive physical interactions (e.g., PSAs, gecko-mimetic adhesives, and octopus-inspired adhesives).

4. COMMON MATERIALS FOR BIOADHESIVES

A variety of natural and synthetic polymers have been explored as components of bioadhesive materials. The choice of material constituents can impact key properties, of a bioadhesive, including its biocompatibility, rheological and mechanical properties, and adhesion performance. In this section, we provide a nonexhaustive summary of commonly used components in bioadhesives to date. For more comprehensive discussions regarding the use of these materials in tissue adhesives and other biomedical applications, we suggest several detailed reviews.[9,28,177,187,188] Often, bioadhesives involve the use of multiple constituents that impart different desired properties to the resulting material system.

4.1. Natural Polymers

Natural polymers derived from plants, animals, and microorganisms have been used extensively for biomedical applications due to their inherent biocompatibility. Commonly used natural polymers include collagen, gelatin, hyaluronic acid, fibrin, alginate, chitosan, and dextran. One of the primary advantages of these materials is their tendency to share structural similarities with biological tissues, which can be beneficial for cellular growth and tissue healing. In addition, certain natural polymers possess attractive characteristics such as antimicrobial activity (e.g., chitosan) or hemostatic properties (e.g., fibrin).[189,190] Because natural polymers often provide a rich source of functional groups that are amenable to chemical modification (e.g., amino, hydroxyl, and carboxyl groups), they can be used as building blocks for tissue adhesive interactions.

Collagen and gelatin (a denatured derivative of collagen) are protein-based polymers sourced from animals and are generally regarded as having excellent biocompatibility and biodegradability. Both collagen and gelatin can be physically cross-linked to form weak hydrogels. The introduction of chemical cross-linkers, such as formaldehyde and glutaraldehyde, may be leveraged to enhance the stability of these structures; however, high concentrations of such cross-linkers can be injurious to tissues.[191−193] Both collagen and gelatin have been widely used for dressing skin wounds, as they provide a 3D microenvironment that assists with the wound healing process.[194] Collagen and gelatin both undergo degradation by enzymes such as matrix metalloproteinases.[177]

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

Fibrin is a protein involved in blood clotting that has been widely used in hemostatic bioadhesives, serving as the basis for many early bioadhesive materials (see Chapter. 5.1 for further discussion).[190,195,196] To improve the mechanical properties of weak fibrin clots, fibrin can be combined with other polymers or chemical cross-linkers. Typically, fibrin bioadhesives take the form of a two-component glue which is mixed during application to trigger cross-linking. The speed of adhesion is governed by the reaction rate constants describing the coagulation cascade, which can vary depending on the polymerization mechanism of the reactive components.[197]

Hyaluronic acid (HA), or hyaluronan, is a lubricating polysaccharide that is naturally found in joint and eye fluids.[198] Due to its propensity to form entanglements, HA can be used to tune the viscoelastic behavior of polymer networks. HA can also be covalently cross-linked to form hydrogels and chemically modified to possess a range of physical properties.[199−201] High molecular weight HA is associated with anti-inflammatory properties. However, the high hydrophilicity of HA makes it such that HA-containing hydrogels typically exhibit high swelling ratios, which may pose a risk of unwanted tissue compression.

Alginate is a polysaccharide typically derived from brown seaweed which can readily be cross-linked by means of ionic cross-linkers (i.e., divalent cations).[202] Its benign gel formation conditions make alginate a popular carrier for cells and drugs. However, native alginate is limited by low and unpredictable in vivo biodegradability. To overcome this limitation, alginate can be oxidized to enhance its biodegradation.[203] The mechanical properties, swelling behavior, and degradation profile of oxidized alginate are closely related to the degree of oxidation.

Chitosan is a cationic polysaccharide that is abundant in the shells of shrimp and other crustaceans. Because chitosan can form electrostatic interactions with negatively charged chemical groups, it exhibits intrinsic mucoadhesive properties that make it an attractive component in bioadhesives.[204] The capability of chitosan to form electrostatic interactions is also thought to contribute to its antimicrobial properties.[205] Chitosan can be physically or chemically cross-linked, with the latter providing greater mechanical stability.

Dextran is a bacterial polysaccharide that is typically modified by oxidation to generate aldehyde groups.[206] These aldehyde groups can interact with tissue amines to form adhesion. Oxidized dextran can also react with other polymers to activate gelation (for example, via Schiff base formation).[207] Dextran is commonly used in tandem with chitosan or synthetic polymers to form hydrogels.

Although natural polymers are generally well-tolerated in many biological contexts, their immunogenic potential can vary depending on factors such as their source, purity, and modification. Those derived from animal sources, such as collagen and gelatin, can induce allergic reactions or lead to immune responses if impurities or contaminants present. The use of fibrin obtained from donors can also elicit concerns regarding potential pathogens. Thus, careful sourcing, purification, and biocompatibility testing are essential to ensuring the safe use of natural polymers in bioadhesives.

4.2. Synthetic Polymers

Synthetic polymers have also played a significant role in the development of bioadhesives, offering a diverse array of materials that can be made reproducibly and tailored for specific applications.

Cyanoacrylates (CAs), famously represented by Dermabond, have been employed for decades as bioadhesives.[12] Due to their rapid curing and extremely strong bonding properties, CA-based glues are often used as adjuncts to reinforce external suture and staple lines. However, their rigidity can be restrictive to soft, moving tissues and lead to inflammation. Moreover, the exothermic polymerization process can induce tissue irritation, and the release of toxic monomers during degradation poses a biocompatibility concern.[167,186] Due to these drawbacks, cyanoacrylate bioadhesives are now largely reserved for topical use.

Polyethylene glycol (PEG) is another popular synthetic polymer for biomedical applications owing to its favorable biocompatibility and high water solubility.[6] PEG can be customized by adjusting the molecular weight and cross-linking density, allowing PEG-based materials to be tuned according to the desired application. However, the main drawback of PEG-based bioadhesives is that they typically exhibit low mechanical strength, making them vulnerable to cohesive failure. Thus, PEG-based bioadhesives typically remain reserved as adjuncts to sutures and staples as they lack the strength to function as standalone sealants. Commercial examples of PEG-based bioadhesives include CoSeal and FocalSeal.

Polyurethanes (PUs) have been used in several commercial bioadhesives, possessing favorable properties such as high flexibility and stretchability, tunable properties, and thermal stability.[208−211] In addition, PU can be used as a shape memory polymer to design stimulus-responsive structures, which has been leveraged in various bioadhesive patches to program strain or mitigate swelling.[125,145,212] Due to their robust, elastomeric character, polyurethanes are promising candidates for building durable bioadhesives.

Poly(acrylic acid) (PAA) is a hydrophilic polymer comprised of acrylic acid monomers featuring a large density of carboxyl groups. These carboxyl groups can serve a versatile number of roles, including forming hydrogen bonds with tissue surfaces, facilitating water absorption, and undergoing chemical functionalization. For example, PAA grafted with *N*-hydroxysuccinimide esters has become a widely used material in bioadhesive systems to achieve covalent bonds with tissues. PAA exhibits pH-responsive swelling behavior due to changes in the ionization state of the carboxyl groups.

Poly(vinyl alcohol) (PVA) is a hydrophilic polymer that is produced via the hydrolysis of poly(vinyl acetate). Upon undergoing freeze/thaw cycles, PVA hydrogels can be made to possess robust mechanical properties, making them useful for load-bearing applications.[213,214] The hydrophobic modification of PVA has been shown to improve its adhesive interactions with soft skin tissue.[215]

Polyesters are a family of synthetic polymers encompassing poly(-caprolactone) (PCL) and poly(lactic-*co*-glycolic acid) (PLGA), which have been widely used in biomedical applications including bioadhesives.[216] They are highly versatile polymers that can be generated to feature a range of mechanical and chemical properties, and typically have the advantage of degrading into low-toxicity degradation products. Examples of commercial polyester-based bioadhesives include TissuePatch and TissuePatchDural, which take the forms of adjunctive sealant films that prevent fluid leakage from suture and staple lines.[217,218]

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

4.3. Additional Material Selection Considerations

Thus, far, we have broadly discussed various material selection considerations from the lenses of mechanical properties, biocompatibility, and biodegradability. Worth noting that several additional considerations may impact the adhesion performance and practical application of a bioadhesive material.

A key factor that influences the effectiveness of a bioadhesive is the kinetics of matrix formation and interfacial bond formation. Many flowable bioadhesives are composed of multiple components that interact at the time of application to form a cohesive matrix. The rate at which this cross-linking occurs can significantly affect the usability of the adhesive. Rapid cross-linking is generally advantageous for adhering to dynamic tissues and preventing displacement of the bioadhesive; however, it can also be difficult to control. For example, CA-based adhesives tend to polymerize very quickly upon contact with water, which can be useful in emergency scenarios but also risks imprecise application. In contrast, slow cross-linking offers finer placement and allows for readjustments, but may be impractical in time-sensitive surgical contexts. The appropriate time window of adhesion is influenced by specific clinical application. Bioadhesives targeting the heart, lungs, or other dynamic organs should be designed to have sufficiently fast cross-linking kinetics relative to the characteristic time scale of tissue movement. Note that this time may vary depending on the surgical conditions (e.g., the level of anesthesia) and the physiology of the individual patient. In general, reaction kinetics may be controlled by tuning the type and concentration of cross-linking agent(s), the availability of cross-linking sites in the bioadhesive material system, the pH of the reactive solutions, and the intensity of external triggers such as UV light (for photochemical cross-linking).

The rheological properties of a bioadhesive also play a pivotal role in its adhesion performance as they determine its ability to flow and conform to irregular tissue surfaces and mechanically interlock with surface asperities. In this regard, the viscosity of a bioadhesive precursor should be carefully tuned: overly viscous materials may not effectively penetrate or conform to tissues, while excessively fluid materials may wash away or form insufficient adhesion. Furthermore, the shear-thinning behavior of a flowable bioadhesive is an important property for ensuring that it can be administered through the narrow tip of a syringe while maintaining sufficient structure to avoid washout from the application site.[219] The incorporation of rheology modifiers, such as pectin or nanomaterials, is one strategy that can be used to adjust shear-thinning properties.[220,221]

For preformed bioadhesives (e.g., patches and tapes), the adhesion formation time is largely determined by the time it takes for the bioadhesive material to form direct tissue contact. Employing hydrophilic materials that can undergo rapid hydration has been an effective strategy to remove interfacial biofluids and enforce fast tissue-material consolidation, enabling tissue adhesion within seconds.[31]

5. TRADITIONAL APPLICATIONS OF BIOADHESIVES

Traditionally, bioadhesives have been developed for applications mainly revolving around hemostasis, wound dressing, and tissue sealing. Hemostatic bioadhesives are employed to control bleeding by forming a seal or clot at the site of injury; wound dressings promote healing and provide a protective barrier against infection; and tissue sealants, used in the reinforcement of surgical incisions and anastomoses, aid in preventing fluid leakage. Bioadhesives can often serve more than one of these purposes, but each carries unique design considerations. In this section, we outline the main functions, design criteria, and several representative examples of bioadhesives developed for each of these applications that have laid the foundation for the development of bioadhesives with advanced properties.

5.1. Hemostatic Bioadhesives

Uncontrolled bleeding is a major cause of morbidity and mortality worldwide.[222] The urgent need for solutions to control hemorrhage has motivated the development of a host of bioadhesives for hemostasis. Besides the requirement of bonding to tissues, hemostatic bioadhesives must be designed with the primary goal of stopping bleeding as quickly as possible.[223] To this end, numerous methods for promoting blood clot formation and sealing active bleeding sites have surfaced.

Hemostatic materials typically involve the incorporation of active components that accelerate blood clotting. Fibrin glues are an illustrative example which were among the first bioadhesive agents to be widely commercialized.[190,195,196] The two main ingredients of fibrin glues, fibrinogen and thrombin, are mixed together to mimic the final phases of the coagulation cascade, resulting in the formation of a fibrin clot. In brief, this process involves the cleavage of fibrinogen by thrombin into fibrin monomers, which undergo self-assembly and cross-linking to yield a stable fibrin network. The fibrin network acts as a mechanical barrier, effectuating wound closure. Although fibrin glues have been widely used in the clinic, their applications are limited by their low mechanical strength and weak tissue adhesion, relegating them to serve mainly as adjuncts to sutures or other conventional means of tissue closure.[196] Moreover, coagulation-dependent hemostatic materials cannot be used to halt bleeding in coagulopathic patients, and certain components in fibrin glues can induce allergic reactions.[157,224,225] Thus, there is still an unmet need for innovative hemostatic materials.

Natural polymers, such as chitosan and collagen, have also been leveraged as active components in hemostatic materials due to their inherent biocompatibility, bioactivity, and biodegradability.[226−234] For instance, the positively charged amine groups of chitosan can interact with negatively charged platelets, facilitating aggregation and thrombus formation; meanwhile, collagen contains sites that support platelet adhesion and activation based on platelet receptor-specific domains. Still, most hemostatic materials that utilize these polymers exhibit slow hemostatic performance and are largely unsuitable for controlling major hemorrhaging.

Two important metrics of hemostatic performance are the time to hemostasis and the volume of blood loss until hemostasis. In efforts to minimize both parameters, several intriguing strategies have recently emerged, including the use of photoactive cross-links to enable rapid in situ UV-activated polymerization, hydrophobic bioadhesive pastes, and catechol-conjugated sponges.[139,235,224] A key feature shared by these systems is the ability to form a physical barrier at the bleeding site independent of the blood conditions. While these strategies offer notable merits, there are still open challenges. For example, the need for an external light delivery source or the potential risk of intravascular embolization of microparticles or oil droplets complicates the adoption of these approaches. Nonetheless, they represent major progress toward faster, more effective hemostatic bioadhesives, with the potential to transform the management of severe hemorrhage.

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

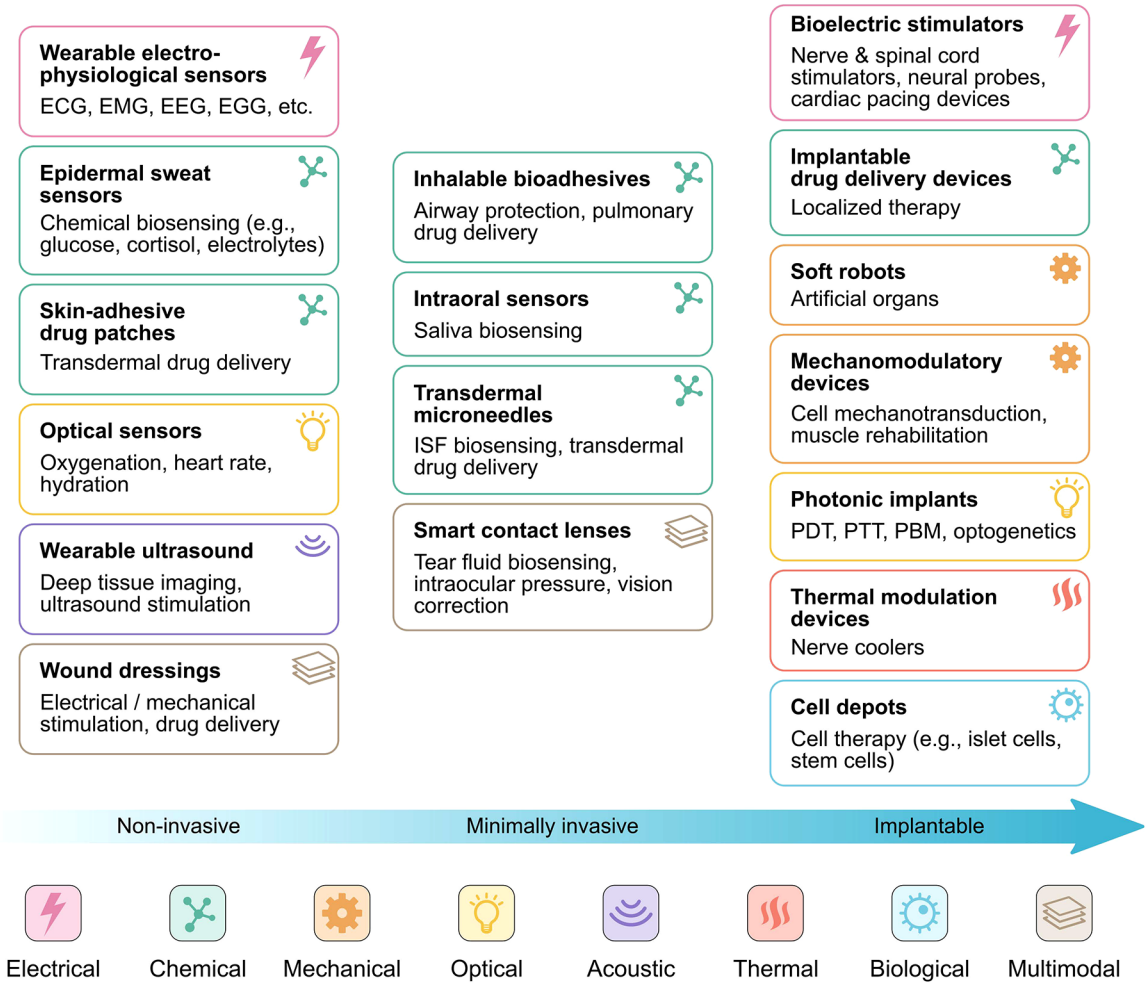


Figure 6. Landscape of emerging technologies for which bioadhesives may play a pivotal role, segmented by level of invasiveness and primary signal interaction type.

5.2. Wound Dressings

The function of a wound dressing is to provide favorable conditions for wound healing and to prevent infection or further damage. This typically entails maintaining a moist environment, allowing gas permeation and exudate drainage and discouraging microbial activity. Bioadhesive hydrogels are compelling candidates for these purposes, as they possess soft, tissue-like water contents and provide secure attachment to the skin, safeguarding the wound.[236−238] Furthermore, they can be loaded with antimicrobial or antioxidant agents, such as silver nanoparticles or lignin, to prevent bacterial infection and oxidative stress.[239−241] Recently, advanced wound dressings with electrical and mechanical modulatory functions have emerged, which are discussed in detail in Section 5.

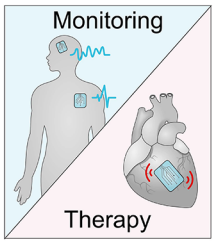
In general, a tailored approach is necessary to effectively treat different types of wounds. The design requirements of a wound dressing can depend on several factors, including the dryness of the wound, the presence of infection, and the stage of healing. Dry wounds can be hydrated with bioadhesive hydrogels, while absorbent materials, such as sponges, are suitable for wounds with heavy drainage. Meanwhile, infected wounds call for nonocclusive wound dressings with antimicrobial functionality. Advanced bioadhesive dressings may further feature multifunctional materials that can respond to various stimuli (e.g., pH, temperature, pressure, and moisture) that influence the wound healing process to monitor and adapt to the changing needs of the wound.[242] Overall, developing a diverse toolkit of wound-specific bioadhesives can be useful to ensure appropriate treatment.[243]

5.3. Tissue Sealants

Although the terms “adhesives” and “sealants” are frequently used interchangeably, here, we delineate their intended uses and functions. The primary purpose of a tissue sealant is to act as a barrier that prevents the leakage of fluids, such as blood, digestive fluids, urine, or air. For instance, tissue sealants can be used to seal defects in vessels, gastrointestinal organs, and airways.[244] Meanwhile, bioadhesives describe the general class of materials that can adhere tissues. Numerous tissue sealants have been developed over the years, with prominent commercialized examples including fibrin glues (which have also functioned as hemostatic materials, as described in Section 4.1), cyanoacrylates, and poly(ethylene glycol)-based sealants. To date, the majority of these commercial sealants suffer from limitations, such as slow and weak adhesion, poor performance in wet environments, and cytotoxicity, leaving ample room for improvement. The main design criteria for developing improved tissue sealants revolve around their adhesive properties and mechanical strength, which are crucial to withstand relevant physiological forces and ensure a leak-free seal during the time window of tissue repair.

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

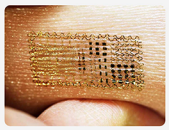
a. Bioadhesive bioelectronics

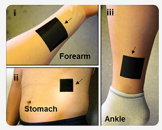


Applications
- Electrophysiological monitoring (e.g., ECG)
- Wound healing
- Electrophysiological modulation

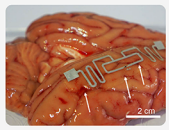
Key properties
- High electrical conductivity
- Stretchability and flexibility

Examples


Ultrathin electronics

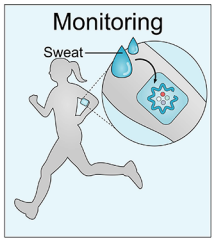


Conductive fillers


Conductive polymers

Liquid metal particles

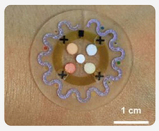
b. Bioadhesive chemical biosensors



Applications
- Monitoring biomarkers including metabolites (e.g., glucose), hormones, electrolytes, etc.

Key properties
- Biofluid-specific form factor
- Diffusivity of analytes

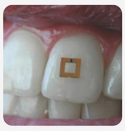
Examples



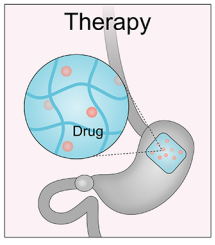
Epidermal patches (sweat, ISF)


Microneedle arrays (ISF)

Contact lenses (tear)


Tooth mounts (saliva)

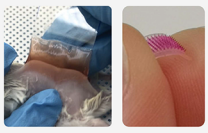
c. Bioadhesive drug delivery



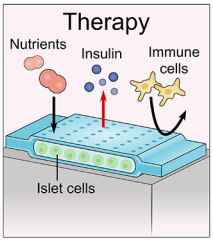
Applications
- Localized drug release

Key properties
- Desired drug kinetics
- Tight interface

Examples


Hydrogel patches & microneedles

d. Bioadhesive cell depots



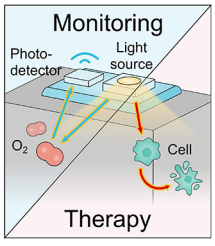
Applications
- Cell therapy (e.g., diabetes, cancer)

Key properties
- Minimal FBR
- Selective permeability

Examples


Macroencapsulation devices

e. Bioadhesive photonic devices

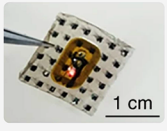


Applications
- Optical biosensors
- Photomedicine (e.g., PDT, PTT, PBM, optogenetics)

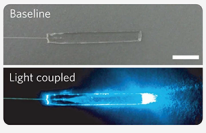
Key properties
- High optical transparency

Examples

Pressure-sensitive adhesive optical biosensors

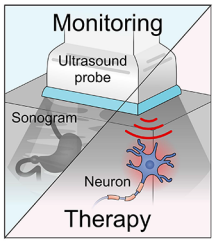


LED-embedded hydrogels



Light-guiding hydrogels

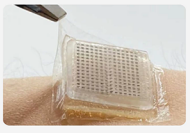
f. Bioadhesive ultrasound

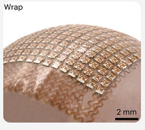


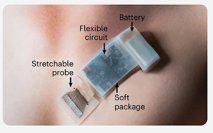
Applications
- Ultrasound-based deep tissue imaging
- Enhanced drug delivery
- Ultrasound stimulation (e.g., neuromodulation)

Key properties
- Skin-matching acoustic impedance
- Minimal air gaps

Examples

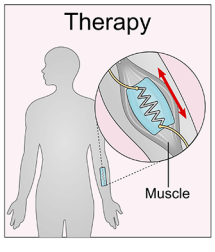

Rigid probes + bioadhesive couplant





Stretchable ultrasonic arrays

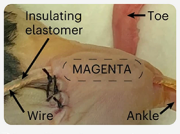
g. Bioadhesive mechanical support



Applications
- Mechanical support
- Muscle rehabilitation
- Soft robots

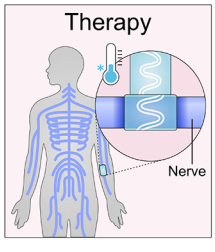
Key properties
- High force transduction

Examples



Bioadhesive-actuator composite

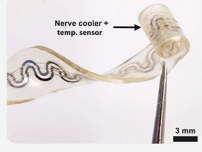
h. Bioadhesive thermal stimulators



Applications
- Nerve blocks

Key properties
- Good thermal conductivty
- Minimal swelling

Examples



Nerve cuffs

Figure 7. Emerging applications, key properties, and examples of (a) bioadhesive electronics;[250−253] (b) bioadhesive chemical sensors;[254−257] (c) bioadhesive drug delivery devices;[258,259] (d) bioadhesive cell depots;[260] (e) bioadhesive photonic devices;[261−263] (f) bioadhesive acoustic

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

Figure 7. continued

devices;[264−266] (g) bioadhesive mechanomodulation;[267] and (h) bioadhesive thermal stimulators.[268] Images reproduced with permission from ref 250 (Copyright 2011 AAAS), ref 251 (Copyright 2016 American Chemical Society), ref 252 (Copyright 2022 Elsevier), ref 253 (Copyright 2022 American Chemical Society), ref 254 (Copyright 2016 AAAS), ref 255 (Copyright 2021 Springer Nature), ref 256 (Copyright 2021 Elsevier), ref 257 (Copyright 2018 Wiley), ref 258 (Copyright 2020 Wiley), ref 259 (Copyright 2021 Wiley), ref 260 (Copyright 2014 Elsevier), ref 261 (Copyright 2013 Springer Nature), ref 262 (Copyright 2019 Springer Nature), ref 263 (licensed under CC BY 4.0), ref 264 (Copyright 2022 AAAS), ref 265 (Copyright 2023 Springer Nature), ref 266 (Copyright 2023 Springer Nature), ref 267 (Copyright 2022 Springer Nature), and ref 268 (Copyright 2022 AAAS).

6. NONTRADITIONAL APPLICATIONS OF BIOADHESIVES

Human-interfacing devices have the potential to sense biological signals, modulate physiological functions, and improve human health. In recent years, breakthroughs in flexible electronics, miniaturized sensors, and wireless communication have enabled the development of increasingly advanced and compact biomedical devices.[245−247] These come in many forms, from skin-mounted patches and smart contact lenses to ingested pills and implanted devices. Despite the diverse landscape of biointegrated devices, commercial translation of devices outside the realms of loose consumer wearables (e.g., smart watches and rings) and traditional medical implants (e.g., cardiac pacemakers and orthopedic implants) has remained relatively limited.

A crucial component underlying the capabilities of these systems is the interface they form with biological tissues.[248,249] Establishing long-term, stable biointegration is essential for achieving reliable signal readouts, effective delivery of therapeutic agents, and transmission of stimuli.[248] Bioadhesives emerge as valuable tools in this context as they can enable secure and conformal attachment of devices to external and internal tissue surfaces (Figure 6). Beyond the ability to bond with tissues, bioadhesives for these emerging applications require different functional properties depending on the modes of interaction between the tissue and the adhered device (Figure 7 and Table 1). This section explores recent advances and opportunities in the world of human-integrated devices, with a focus on the functional requirements of the bioadhesive interface as it pertains to different interaction modes. By examining diverse healthcare applications for which bioadhesives may serve as a valuable technology platform, we hope to provide motivation for new bioadhesive innovation.

6.1. Bioadhesive Bioelectronics

Many physiological systems rely on complex electrical pathways to regulate important bodily functions (Figure 7a). For example, the nervous system transmits signals throughout the body to control movement, sensation, and sleep; the cardiovascular system relies on electrical signals to coordinate cardiac contraction and relaxation; and the digestive system has extensive nerve connections which regulate gastrointestinal motility and appetite.[269−272] Electrophysiological readouts of these systems, such as electroencephalograms (EEG), electrocardiograms (ECG), and electrogastrograms (EGG), can provide valuable information about their functions and pathologies. Recently, wearable electrodes that enable ambulatory electrophysiological monitoring have attracted attention due to their implications in enabling timely detection of abnormalities, facilitating personalized treatment, and empowering individuals to actively manage their health.

On the therapeutic side of bioelectronics, electrical stimulation is an area of great interest for its potential to modulate or activate biological processes. Recognition of the therapeutic effects of electricity dates back thousands of years to ancient Egyptians, who reportedly utilized shocks from electric catfish to treat pain.[273] In the modern era, electrical stimulation has expanded to applications such as cardiac pacing, neural modulation, wound healing, and organ function enhancement. As our understanding of the human body's electrophysiology continues to deepen, so does the realm of electricity-based therapies, termed "electroceuticals", across a broad spectrum of physiological systems and their pathologies.[274−280]

The recent advent of flexible electronics has unlocked immense potential for wearable bioelectronics.[96,281−285] For example, thin film metals, organic electronic materials, conductive nanomaterial composites, and conductive polymers have emerged as strategies to fabricate electronics with flexibility and stretchability.[286−290] Still, the direct integration of these materials with biological tissues in a manner that ensures stable contact, low electrical resistance, and good biocompatibility is a challenge. Weak tissue-device integration can produce interfacial gaps and motion artifacts, diminishing the fidelity of the transmitted electrical signals. Thus, the design of bioadhesive bioelectronics may be pivotal to enabling the maximum functionality of electrophysiological monitoring and electroceuticals.

One method to produce skin-adhesive electronics is to pattern thin film metals into wavy, serpentine, or stacked geometries, enhancing their strain tolerance.[291,292] Using this strategy, ultrathin electronic films (or "e-tattoos") have emerged as a promising class of epidermal bioelectronics.[250,293−301] Due to their two-dimensional profiles, e-tattoos adhere conformally to skin by van der Waals forces alone. However, this weak physical adhesion is vulnerable to movement and delamination during daily wear. To enhance the wear resistance of conductive metals, a recent strategy emerged utilizing liquid metal particles (LMPs) functionalized with keratin-interacting polymers, yielding skin-adhesive LMPs which could form stable adhesion with skin.[253] Still, although serpentine patterns enhance the flexibility of metallic circuits, they possess limited stretchability and can crack under mild deformation.

A strategy to overcome the geometric constraints of metal circuits is to design a bioadhesive that itself is electrically conductive.[90,302] This can be achieved by incorporating conductive fillers (e.g., carbon nanotubes or graphene) or conductive polymers (e.g., polypyrrole (Pyy) or poly(3,4-ethylenedioxythiopene) polystyrenesulfonate (PEDOT)) into a bioadhesive network. For example, researchers developed a gecko-mimetic bioadhesive composite comprised of poly(dimethylsiloxane) (PDMS) filled with carbon nanotubes, simultaneously imparting adhesiveness, flexibility and stretchability, and conductivity.[251] In another example, the simultaneous polymerization of PPy and dopamine was shown to yield a functional conductive patch which remained bonded to rat hearts in vivo for up to 4 weeks.[303] Despite various promising demonstrations, conductive bioadhesives are still in their

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

Table 1. Examples of Emerging Bioadhesive Technology Platforms

Interaction mode	Type	Use case(s)	Bioadhesive technology	Key properties	refs
Electrophysiological					
Monitoring	Electrocardiography (ECG)	Arrhythmias, coronary artery disease, heart attack	Bioadhesive electrodes (epidermal)	High electrical conductivity, breathability, reversibility	453
Monitoring	Electroencephalography (EEG)	Measuring brain activity	Bioadhesive electrodes (epidermal)	High electrical conductivity, breathability. reversibility	454−457
Monitoring	Electrogastrography (EGG)	Gastric activity, gastrointestinal disorders	Bioadhesive electrodes (epidermal)	High electrical conductivity, breathability, reversibility	458−489, 460
Stimulation	Nerve stimulation	Pain relief, retinal implants, tremors	Bioadhesive nerve cuffs (invasive), epidermal electrical stimulators (noninvasive)	High electrical conductivity, low foreign body response	461
Stimulation	Functional electrical stimulation (FES)	Muscular rehabilitation, sleep apnea	Bioadhesive electrodes (epidermal)	High electrical conductivity, breathability, reversibility	462
Stimulation	Wound electrotherapy	Wound healing, diabetic foot ulcers	Electrically conductive wound dressing	High electrical conductivity, proper wound healing environment, reversibility	463
Monitoring	Bioimpedance measurement	Pulmonary function, body composition, bone growth	Bioadhesive electrodes (epidermal), orthopedic implants	High electrical conductivity, breathability, reversibility	464−466
Chemical biosensing					
Monitoring	Sweat sensors	Metabolites, hormones, electrolytes, proteins, drugs	Epidermal patches	Robustness against moisture, breathability, reversibility	319, 467, 468
Monitoring	Interstitial fluid (ISF)	Metabolites, hormones, electrolytes, proteins, neurotransmitters, drugs	Epidermal patches, microneedle arrays	Robustness against moisture, breathability, reversibility	328, 469, 470
Monitoring	Saliva	Antibodies, bacteria, metabolites	Tooth mounts, buccal adhesive devices	Robustness against saliva biofouling, swallowing forces, and mucus turnover	257, 471
Monitoring	Tear	Salts, proteins, enzymes, lipids, metabolites	Smart contact lenses	Suitable optical properties, nonobtrusive to vision, atraumatic removal	348, 350
Monitoring	Gastric fluids	Metabolites, drugs	Ingestible, gastro-retentive devices	Robustness against food, digestive fluids, and mucus turnover	472
Monitoring	Breath	Hydrogen peroxide, viruses, metabolites	Under-nose patches	Reversibility	473
Drug delivery					
Therapy	Bioadhesive patches	Miscellaneous	Drug-loaded patches and wound dressings	Porosity/mesh size, drug-matrix interactions, degradation kinetics	359, 364, 365, 372
Therapy	Microneedle arrays	Miscellaneous	Microneedles (solid, hollow, porous)	Microneedle geometry and morphology	339, 340, 375, 474, 475
Therapy	Inhalable particles	Pulmonary drug delivery	Bioadhesive microparticles	Porosity/mesh size, drug-matrix interactions, degradation kinetics	176
Mechanical					
Stimulation	Mechanical wound modulation	Wound healing, scar reduction	Mechanically active wound dressings	Proper wound healing environment	145, 433
Stimulation	Muscular mechanomodulation	Muscle rehabilitation/regeneration	Muscle-integrated force actuators	Adhesion strength, fatigue resistance, wireless actuation	267, 476
Bidirectional	Soft robots/artificial organs	Recapitulating physiological mechanics	Bioadhesive soft robots (e.g., heart sleeve, diaphragm assist)	Adhesion over large, nonplanar areas, fatigue resistance	444, 445
Optical					
Monitoring	Photoplethysmography	Heart rate, blood O_2 saturation, respiration rate	On-body optoelectronic devices	High optical transparency, reversibility	477, 478
Stimulation	Photomedicine	PTT, PDT, PBM, optogenetics, photosensitive drug activation	Skin-adhesive and implantable light sources, optical waveguides	High optical transparency, low FBR	392, 399, 479, 480

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

Table 1. continued

Interaction mode	Type	Use case(s)	Bioadhesive technology	Key properties	refs
Acoustic					
Bidirectional	Ultrasound	Deep tissue imaging, pain relief, on-demand drug delivery	Ultrasound patches	Skin-matching acoustic impedance	264, 266, 410, 412, 418
Monitoring	Audible biomarkers ("hearables")	Pneumonia, asthma, COPD, sleep apnea, vocal fatigue	Skin-interfaced acoustic sensors	Breathability, reversibility	481
Thermal					
Monitoring	Temperature sensing	Miscellaneous (e.g., hydration, disease screening)	On-body temperatures sensors	Thermal conductivity, breathability, reversibility	482
Stimulation	Nerve cooling	Pain relief	Bioadhesive nerve cuffs	Thermal conductivity, thermal resilience, minimal swelling	268
Biological					
Therapy	Cell depots	Cell therapy (e.g., type 1 diabetes, cancer)	Cell microencapsulation devices	Selective permeability, low FBR	260, 377, 378, 380

nascency, and in-depth studies of their long-term in vivo electrical conductivity, adhesion, and biocompatibility have yet to be seen.

Beyond tissue adhesion and electrical conductivity, bioadhesives for electrical applications could benefit from the incorporation of dynamic, self-healing networks to allow conductive pathways to recover after damage.[304−306] Moreover, for implanted devices, minimization of the FBR is a key requirement to avoid the buildup of insulating fibrotic tissue at the interface.

6.2. Bioadhesive Chemical Biosensors

Biological fluids such as sweat, interstitial fluid, tears, and saliva are rich in molecular analytes which can provide valuable insights into the body's physiological state, motivating a general push toward biofluid-sampling wearables for health monitoring (Figure 7b).[307,308] While this demand has produced significant advances in sensor technology, the availability of commercial products for on-body chemical biosensors remains limited.[309] A notable exception is the successful commercialization of transdermal continuous glucose monitors, exemplified by devices such as the Abbott FreeStyle Libre and Dexcom CGM, which employ semi-invasive needles to puncture the skin and measure glucose in the transcutaneous space. While these sensors have proven immensely valuable for diabetes management, their intrusive form factor and the discomfort associated with needle insertion restrict their applicability in general everyday health monitoring.

As with bioelectronics, a crucial aspect for advancing wearable chemical sensors lies in the tissue-device interface. Realizing the next generation of wearable health sensors will require tailored bioadhesive strategies for accessing various types of biofluids. Here, our focus is on four readily accessible biofluids: sweat, interstitial fluid, tears, and saliva.

6.2.1. Epidermal Biochemical Sensors. Two key biofluids that can be obtained from the epidermis are sweat and interstitial fluid (ISF). Sweat can be collected in a passive and completely noninvasive manner as it is naturally secreted onto the surface of the skin. On the other hand, sampling ISF requires strategic methods to extract it from beneath the skin.[310] ISF can be extracted to the skin using noninvasive techniques such as ultrasonic or electrical stimulation (i.e., sonophoresis and iontophoresis), or it can be directly sampled beneath the skin using microneedle arrays.[311−315] Both sweat and ISF contain a wealth of chemical biomarkers, including metabolites (e.g., glucose, lactate, and urea), electrolytes (e.g., sodium, potassium, and chloride ions), and hormones (e.g., cortisol), which provide a window into various health conditions and disorders. For example, glucose can be a useful biomarker for diabetes management; sodium and chloride ions can be indicators of cystic fibrosis; and cortisol variations can reflect stress levels.[316−318] Generally, the chemical biomarkers found in ISF exhibit closer correlations with serum composition compared to those found in sweat, making ISF a suitable target biofluid for applications requiring high-accuracy readouts.[319]

Epidermal bioadhesives can be used to interface sensors for sampling sweat and ISF.[254,319−321] To ensure the reliability and longevity of these systems, the bioadhesive must be able to withstand mechanical movement and prolonged exposure to moisture. The latter becomes particularly important when sweat or ISF is continuously secreted, as is the case with iontophoretic systems.[322] Strategies to ensure robustness against interfacial moisture include incorporating breathable pores or designing

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

fluidic relief channels to facilitate the removal of interfacial fluids.[97,254,323−326]

Microneedle bioadhesives for sampling ISF beneath the skin depend on several geometrical design considerations including the needle length, density, and morphology. Needle length and density directly determine the depth of penetration, ISF extraction, net adhesion force, and patient discomfort. Moreover, the needle morphology, whether solid, porous, or hollow, impacts the transport mechanisms involved in ISF collection.[312,327−329] Porous and hollow microneedles generally exhibit the capacity to collect larger volumes of ISF compared with solid or hydrogel microneedles by leveraging convective forces. These considerations collectively contribute to the stability and sensing capacity of microneedle sensors.

6.2.2. Intraoral Biochemical Sensors. Saliva, enriched with biomarkers from the bloodstream, offers the potential to approximate serum levels through its chemical sensing and analysis.[330−332] Early iterations of salivary sensing devices took the form of sensor-integrated mouthguards, which were limited by their bulkiness.[333−335] To improve user acceptance, less obtrusive device form factors have been proposed, including tooth-mounted or buccal-adhesive patches.[257] Teeth provide unique substrates for device integration with requirements for adhesion differing greatly from those of soft tissues. Because the outer surface of the tooth is rigid, adhesion to teeth is typically achieved using high tensile strength resins that are often paired with an acid-etch-technique to promote micromechanical interlocking with dentin.[336] While this method achieves strong adhesion, the detachment procedure requires professional handling to avoid damaging the tooth, which can be impractical for interfacing sensors with short residence times. The use of photodegradable cross-linkers can facilitate debonding by equipping the bioadhesive with UV-triggered degradation.[337] Nonetheless, the small surface area of individual teeth limits the size and number of components that can be integrated. In contrast to hard teeth, the buccal mucosa lining the inside of the cheek is composed of soft epithelial tissue coated with a dynamic layer of saliva. The buccal mucosa provides a larger surface area than teeth, but it poses challenges to adhesion including continuous shear forces caused by swallowing and mucus turnover.[338] The use of mechanical anchors, such as microneedle arrays, may be an effective strategy to achieve adhesion in this challenging environment.[339,340]

6.2.3. Ocular Biochemical Sensors. As with the previous biofluids, tear fluid biosensors offer the ability to monitor biomarkers such as glucose, proteins, salts, and pH.[256,341,342] Tear-based biosensors broadly come in two forms: those that make direct contact with the eye to access tear fluid, and noninvasive devices such as eyeglasses and undereye patches.[343,344] The main drawback of noninvasive form factors is their limited and discontinuous access to tear fluid, which limits the depth of information that they can provide.

For in situ tear sensing, an ideal ocular bioadhesive should exhibit conformal adhesion, oxygen permeability, and facile removal. Naturally, contact lenses offer an attractive form factor to meet these requirements. Contact lens adhesion is primarily governed by the wettability of the lens with the tear film, which generates a surface tension force pulling the lens toward the eye.[345] As such, the composition of soft contact lenses is typically based on high-water-content materials such as polymer or silicone-based hydrogels.[346] Additionally, the physical dimensions of the lens, including the base curve radius, diameter, and thickness, are important design parameters for ensuring a comfortable fit and sufficient oxygen transfer.[347]

One application that gained particular interest among contact lens sensors is continuous glucose monitoring for diabetes management.[348−353] In 2014, Novartis and Google formed a high-profile partnership with the aim of developing a glucose-monitoring contact lens.[354] However, the project was halted in 2017 before commercialization, with the companies citing technical challenges related to inconsistent correlations between tears and blood glucose. Nonetheless, biosensing contact lenses may be useful for applications requiring a lower bar of data accuracy, such as general health monitoring. Enhancing the functionality of contact lens sensors beyond single analyte detection, such as by embedding multiplexed microfluidic channels, may be useful to enable more holistic health insights.[355]

6.3. Bioadhesive Drug Delivery

The targeted delivery of drugs and biologics to specific tissues is an important therapeutic approach in modern medicine (Figure 7c).[356] Traditionally, pharmacological substances have been delivered through direct intravascular injection, which is limited by its nonspecific nature and the associated risks of side effects and overdose. Implantable controlled-release drug systems have emerged as promising alternatives, enabling specific and stimulus-responsive delivery to target regions.[357−361] However, poor integration with target tissues has been a challenge for achieving a high therapeutic efficacy. Standard methods of integration, such as suturing or weak physical adhesion, provide tenuous interfacial contact that can result in uncontrolled, off-target drug release. This is a particular concern for delivering drugs that harm healthy tissues if poorly localized (e.g., chemotherapy drugs).

Achieving stable, localized drug delivery requires a multifaceted material design strategy to ensure prolonged adhesion and desired drug release kinetics.[258,338,362−371] From the perspective of adhesion, the design of a tough matrix with tissue-bonding surface groups forms the basis for realizing a robust, long-term residence. From the perspective of drug delivery, the mesh size of the matrix, drug-polymer interactions, and matrix degradation kinetics are key factors for determining the drug delivery rate.[372] The mesh size of the network is dependent on factors such as the degree of cross-linking, the chemical composition, and environmental conditions (e.g., temperature, pH).[373] Leveraging the environment-sensitive properties of hydrogels can be used to impart stimulus-responsive temporal control over drug release.[358,374] In addition, tissue-penetrating structures such as microneedle arrays can increase drug efficacy by overcoming physiological barriers.[259,340,375] Besides macroscale hydrogels and patches, drug-loaded bioadhesive microparticles may also be used to minimally invasively deliver injectable or inhalable formulations.[176,376] An advantage of using microparticles is the ability to mix distinct drug-carrying microparticles, realizing multifunctional therapeutic effects.

Therapeutic cell depots have emerged as an attractive strategy for the treatment of conditions such as Type 1 diabetes and cancer (Figure 7d).[377−380] These devices are designed to provide an environment that protects transplanted cells from immune rejection, while allowing for the essential exchange of oxygen, nutrients, and desired secretions (e.g., insulin). Despite the transformative implications of cell depots, simultaneously achieving successful immune cloaking and implant cell survival

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

has proven to be a tremendous challenge. For these devices, the foreign body response is the dominating obstacle to their functionality. The formation of fibrous tissues around the device can physically block membrane pores, preventing nutrient exchange and resulting in cell death. Existing cell depots primarily rely on surgical fixation through sutures, making them vulnerable to inflammation and fibrous tissue formation along the loose interface. Bioadhesives can be promising tools to improve the tissue integration of these devices and extend their window of therapeutic efficacy. To this end, bioadhesives for cell depots must exhibit excellent biocompatibility and selective permeability to essential molecules. The porosity of the bioadhesive is a key design parameter for preventing cell migration while facilitating the efficient transport of oxygen, nutrients, and cell secretions. Furthermore, incorporation of antifouling materials may help to mitigate the occurrence of host cell adhesion and fibrosis.

6.4. Bioadhesive Photonic Devices

Light can interact with living cells and tissues in a myriad of ways to sense biometric signals, such as blood oxygen saturation, and induce therapeutic effects, such as photothermal therapy (PTT), photodynamic therapy (PDT), photobiomodulation (PBM), and optogenetic therapy (Figure 7e).[261,381−389] These therapeutic strategies leverage light to produce heat, activate photosensitive drugs, or stimulate light-regulated cellular processes, with applicability for a range of indications including cancer therapy, infection, wound healing, and neural modulation.[385,390,391] Due to the finite penetration depth of light in tissues, implantable optical devices are often required to enable deep-tissue photomedicine.[391−398] Traditional optical fibers composed of glass and plastic are nonbiodegradable and brittle, presenting an inherent mismatch between their properties and the requirements for biomedical use. A growing number of optical devices based on soft polymeric materials such as silk, agarose, and PDMS, among others, have been proposed as alternatives.[393,399−401] Despite the improved biocompatibility of these soft photonic systems, their loose integration with tissues can hinder the spatial precision of light delivery and result in inconsistent, insufficient, or excessive light illumination. Insufficient illumination can reduce the phototherapeutic effect, while excessive illumination can induce thermal tissue damage and inflammation.[402,403] In light of these challenges, bioadhesives can be used to enhance the stability and precision of deep tissue-targeting phototherapies.

Transmitting light through the bioadhesive interface requires good optical transparency to minimize the loss of light intensity delivered to the tissue. Transparency is generally achieved by amorphous polymers which have low light scattering and absorption.[404] For semicrystalline or crystalline polymers, reducing the domain size below the wavelengths of visible light can impart transparency. One method to diminish the average domain size is to disperse nanoscale fillers, such as nanocellulose and silica particles, into the polymer network.[405−407] Furthermore, the use of a thin adhesive layer can enhance transmission by reducing the distance that light needs to traverse through the interface.

Highlighting the advantages of bioadhesives in photonic devices, an implantable light source for PDT was recently designed to achieve stable, long-term illumination of internal lesions.[262] The device was composed of an LED chip sandwiched between two PDMS nanosheets, one of which was modified with polydopamine to become bioadhesive, allowing the device to achieve suture-free residence at the site of implantation for one month. The general strategy of incorporating transparent bioadhesive materials with implantable photonic devices has immense potential to enhance the efficacy of a wide range of deep-tissue phototherapies.

6.5. Bioadhesive Ultrasound

Recently, wearable ultrasound devices have attracted substantial interest for their potential to unlock continuous deep-tissue imaging and ultrasound-based stimulation (Figure 7f). The noninvasive, radiation-free characteristics of ultrasound imaging have made it a valuable tool for assessing diverse body functions, including muscular activity, cardiac function, blood flow, bone healing, and gastric activity (refs 264−266, 320, 408−412). Traditional ultrasound components are rigid and bulky, posing a challenge to their on-body integration. The emergence of flexible and stretchable ultrasonic arrays has improved wearability, but their enhanced skin conformability comes with trade-offs in image stability and resolution.[411] Regardless of their form factor, a key component to the performance of ultrasound devices is the coupling agent, whose role is to maximize signal transmission by matching acoustic impedance.[413] The most common ultrasound coupling is a wet gel, which is vulnerable to dehydration and detachment within a few hours of wear.

To concurrently address the challenges of tissue integration, image quality, and signal transmission, an ultrasound patch was recently developed consisting of a thin, rigid ultrasound probe bonded to a bioadhesive hydrogel couplant.[264] The bioadhesive couplant was composed of a hydrogel with skin-matching acoustic impedance encapsulated by a thin layer of polyurethane to prevent the hydrogel from drying out over time.[414] The polyurethane membrane was further coated with a thin bioadhesive layer containing physical tissue interaction groups and covalent-bond-forming NHS esters, imparting strong and gap-free tissue adhesion. The resulting bioadhesive ultrasound assembly was evaluated across various scenarios, including imaging of the heart, liver, and bladder, and demonstrated excellent imaging stability over several hours. This example illustrates the significance of using multifunctional design principles to rationally design a bioadhesive interface that enables efficient device-tissue coupling, allowing even rigid devices to become wearable. Still, there is room for improvement in current bioadhesive ultrasound interfaces. For example, enabling fine adjustment over the angle of sonography as opposed to imposing a fixed angle perpendicular to the skin may expand the potential utility of wearable ultrasound systems.

Beyond deep tissue imaging, wearable ultrasound systems present various potential therapeutic effects.[415] Ultrasound can increase the efficacy of drug delivery by overcoming physiological barriers and improving spatiotemporal control.[55] Low-intensity ultrasound can also be used to generate heat and increase circulation, which may provide rehabilitative effects for muscles. Additionally, the use of ultrasound for neuromodulation is an active area of research and development.[416−420]

6.6. Bioadhesive Mechanical Support

The strategy of implanting stabilizing structures to provide mechanical support to damaged tissues has been used widely in surgery. It finds applications in various procedures, such as repairing hernias and reinforcing heart tissue damaged by myocardial infarction.[421,422] The traditional use of sutures or tacks to fix mechanical support structures can lead to secondary

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

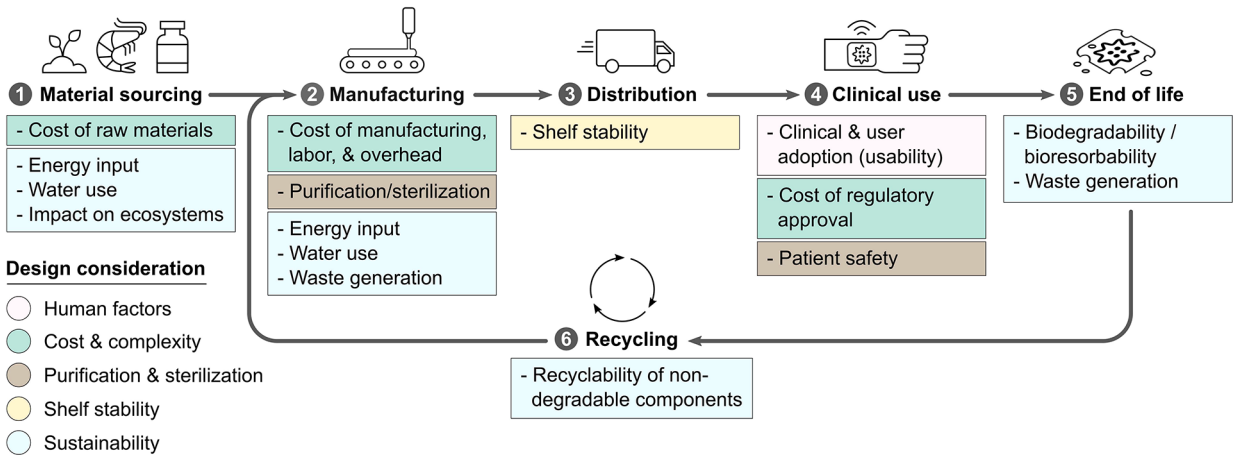


Figure 8. Multifaceted practical considerations of bioadhesives through their entire lifecycle from the categories of human factors, cost and complexity, purification and sterilization, shelf stability, and sustainability.

complications including pain, postsurgical adhesions, and dislodgement.[423−426] Bioadhesive mechanical supports are favorable alternatives. For example, self-adhesive hernia meshes can enhance the ease of attachment and mitigate postsurgical adverse effects.[427] Furthermore, bioadhesive patches can be used to provide mechanical support to infarcted heart tissue.[428] For instance, a viscoelastic bioadhesive patch based on an ionically cross-linked starch gel was developed to achieve tissue-mimetic mechanical properties, leading to superior tissue remodeling in a rat model.[428]

Another area of interest for mechanically active bioadhesives is wound healing. The phenomenon of mechanotransduction, in which physical forces are converted into biochemical signals that affect cell behavior, underlies the role that mechanical cues play in promoting wound healing and fibrosis.[429,430] By applying controlled forces to the wound microenvironment, the healing process can be modulated to promote tissue growth and minimize scar formation.[431−434] Bioadhesives which transmit contractile forces, such as thermosensitive or shape-memory polymers, can therefore be leveraged to enhance wound healing.[145,435] Based on a similar principle, dynamic mechanical actuation around an implanted device can be used to mitigate the FBR and extend the functional lifespan of the device.[436,437]

In the field of muscle rehabilitation, mechanically active devices and robotic systems have gained interest for their ability to generate forces that induce tissue regeneration (Figure 7g).[438] However, weak interfacial coupling between actuators and tissues can lead to poor force transduction, hindering the delivery of mechanical stimuli. To address this limitation, researchers developed a bioadhesive mechanical actuator to adhere directly on muscle tissue and simulate contraction.[267] The intimate mechanical coupling between the actuator and the tissue provided by the tough bioadhesive interface enabled efficient tissue stimulation, resulting in a slowdown of muscle atrophy.

On a larger scale, soft robotic technologies that recapitulate the mechanical motion of natural body parts have transformative potential as assistive devices and artificial organs.[439−444] Such implants have previously leveraged mechanical bands, sutures, or suction to fix them in place; however, these methods increase device bulkiness, inflict uneven stress localization, and can elicit significant inflammation.[445] Efficient mechanical coupling between soft robots and tissues is a crucial but challenging aspect of their performance, requiring a bioadhesive material that can achieve conformal contact over a large, nonplanar surface area.[446] Moreover, the bioadhesive must be capable of withstanding physiologically relevant shear and compressive forces over multiple cycles, demanding strength, toughness, and fatigue-resistance.

6.7. Bioadhesive Thermal Stimulators

Thermal biointegrated devices offer opportunities for temperature sensing and stimulation (Figure 7h). For example, the peripheral nervous system exhibits complex thermal sensitivity and can be modulated using variations in temperature.[447] Of particular interest is local nerve cooling, which temporarily blocks pain signals, forming the basis for potential drug-free pain relief.[448] To harness this effect, implantable nerve coolers have been developed, but these currently rely on sutures or physical wrapping around the nerve to hold them in place.[449,268] These weak integration methods limit the spatial precision of thermal cooling.[450] Poor control over cooling can pose the risk of cold nerve injury, underscoring the importance of achieving proper nerve integration.[451]

In general, bioadhesives for thermal stimulation should be designed to exhibit good thermal conductivity and resilience. Thermal conductivity can be tuned by increasing the conduction pathways in the polymer network, such as by increasing the cross-linking density or introducing filler materials with high conductivity (e.g., graphene).[452] Meanwhile, thermal resilience, referring to the robustness of the bioadhesive against changes in temperature, requires the interfacial interactions (e.g., chemical and physical bonds) and physical properties of the bioadhesive to be relatively stable within the working range of temperatures.

7. OTHER PRACTICAL CONSIDERATIONS

The previous sections have examined design considerations on the levels of the bioadhesive interface, bulk matrix, integrated device, and physiological environment. While these essentially determine the functional performance of a bioadhesive technology, they do not necessarily account for other factors essential to its commercial translation, clinical adoption, and lifecycle sustainability. Here, we identify additional practical considerations for the design, development, and translation of bioadhesive technology platforms (Figure 8).

7.1. Human Factors

In the context of bioadhesive development, human factors refer to considerations related to the usability and practicality of these

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

materials, taking into account the needs and capabilities of healthcare professionals for safe and effective application. Considering the end user (i.e., healthcare professionals and patients) is essential to ensure safe, effective application, and user acceptance of bioadhesive products. In general, providing a system that has a simple, user-friendly application process and clear instructions is required for encouraging clinical and consumer adoption. For instance, avoiding laborious preapplication steps, such as manually mixing components, can improve the usability of bioadhesives and reduce the risk of user error. Several multicomponent bioadhesives (e.g., Tisseel, Coseal, and Vitaseal) have evolved to be manufactured in dual-barrel syringes to eliminate the need for manual mixing, which has improved their clinical adoption. Ergonomic design considerations, including the size, shape, and packaging of bioadhesives and bioadhesive devices, can also enhance their user-friendliness. Furthermore, factors such as curing time and equipment requirements should be taken into account. Bioadhesives that necessitate external triggers, such as UV irradiation, may have a greater barrier to use. Overall, designing toward intuitive and accessible products with the end user in mind can facilitate the clinical adoption and success rate of bioadhesive technologies.[483]

7.2. Cost and Complexity

Cost and manufacturing complexity are chief considerations in the commercial translation of bioadhesives.[8] At the bottom line, the production cost of a bioadhesive must be sufficiently low to provide a return on investment. The calculus of cost is based on the price of raw materials, labor, manufacturing processes, and overhead and regulatory approval. Bioadhesives that require complex manufacturing steps, such as patterning intricate microstructures, may face additional challenges to achieving batch-to-batch consistency and scalability. The culmination of these costs must be balanced with the market potential of the bioadhesive, which depends on the specific clinical need(s) and the value provided by the bioadhesive material or device over existing alternatives.

7.3. Purification and Sterilization

Purification and sterilization are critical to ensure the removal of toxic monomers, cross-linkers, solvents, bacteria, and other impurities. For instance, in the case of acrylamide-based bioadhesives, the removal of residual acrylamide monomers is essential to mitigate any potential neurotoxicity.[484] Various purification techniques, such as filtration and dialysis, can be employed to eliminate these toxic components. Sterilization methods include the use of heat, γ radiation, ethylene oxide gas, and electron beams.[485] However, some sterilization techniques may be incompatible with preserving the functional performance of certain bioadhesive materials. For example, the use of moist heat or radiation may degrade reactive groups or alter the physical properties of a bioadhesive. Therefore, it is important to determine an appropriate sterilization method that balances effective pathogen elimination with the preservation of the integrity and functionality of the bioadhesive and any integrated device components.

7.4. Shelf Stability

Environmental factors, including temperature, humidity, and exposure to light, can impact the integrity of a bioadhesive material. For example, bioadhesives which contain hydrolyzable reactive groups are prone to degradation over time as they interact with water molecules in ambient air. A strategy to enhance the shelf stability of a bioadhesive without altering its material composition is to optimize its packaging, for example, by including desiccants to prolong the shelf life of moisture-sensitive materials or by using opaque containers to enclose light-sensitive materials. Such efforts to ensure long-term stability are important to minimizing waste and enabling widespread distribution.

7.5. Sustainability

The environmental sustainability of bioadhesive materials and devices is an increasingly important consideration. Researchers developing bioadhesive technologies should aim to minimize their environmental impact throughout their lifecycle, from raw material sourcing to processing to disposal.[486−489] This includes minimizing the use of environmentally hazardous reagents when possible and designing products with recyclable or biodegradable materials.[490,491] Biointegrated devices have attracted a great deal of interest, but in many cases these devices contain nondegradable electronic materials which can result in waste accumulation and cause environmental pollution. While the wear time of most bioadhesive wearables is relatively short (a day to a couple weeks), their degradation timeline and environmental consequences can be long-lasting. By factoring sustainability into their design rationale, scientists can contribute to environmentally conscious healthcare practices and align with global efforts toward a more sustainable future.

8. CONCLUDING REMARKS

Bioadhesives have emerged as a key piece of the broad landscape of biomedical technology. Just as how their ancestors, sutures, and staples transformed the evolution of surgery, the roles of bioadhesives in repairing tissues and interfacing devices position them to be one of the most important technologies for human health in the modern era. Over the past few decades, efforts to uncover and implement tissue adhesion strategies have given rise to a diverse array of bioadhesive materials, some of which have become ubiquitous tools in the clinic today.

Still, bioadhesives face numerous limitations, which call for continued innovation and improvement in the years to come. Among these, their mechanical reliability, adhesion speed with wet tissues, reversibility, and foreign body response are principal challenges. Although there is an active research community devoted to investigating new strategies to overcome these challenges, several bottlenecks stand in the way of commercial translation of new bioadhesive materials. Due to the substantial amounts of capital and time required to see a bioadhesive through the development, regulatory approval, and commercial distribution processes, researchers seeking to commercialize a bioadhesive platform should be diligent in identifying the key clinical indications and needs that can be uniquely addressed by their technology. In general, having a portfolio with multiple potential use cases stemming from one core technology can be advantageous for establishing a sizable market, though it is instructive to note that distinct indications would require their own process for clinical validation and approval.

Looking ahead, the development of personalized bioadhesives and bioadhesives with advanced functionalities beyond tissue bonding will also push the boundaries of their applications, unlocking more effective modes of healthcare monitoring and therapy by enabling efficient tissue-device integration. In this regard, a strong product/market fit is essential for successful commercial translation and adoption. At present, biointegrated devices are increasingly being developed as components of

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

patient-centric digital health management platforms to consolidate multiple biosignal streams and create a user-information feedback loop. Most emerging systems are focused on external wearables due to their lower barrier for user adoption and more forgiving biocompatibility requirements. To accelerate the capability and translation of these technologies, innovative skin bioadhesives will likely play an essential role in enhancing the human-device signal interaction. In the longer term, implantable devices will also require advancements in multifunctional internal bioadhesives to achieve effective human-machine interfacing.

Ultimately, the successful development of bioadhesive technologies hinges on many design considerations around their functional performance, biocompatibility, manufacturability, usability, and sustainability. Continued interdisciplinary research and collaboration will be essential to realizing the full potential of bioadhesive technology platforms for transformative biomedical materials and devices.

AUTHOR INFORMATION

Corresponding Authors

Sarah J. Wu − *Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States*; Email: sarahw@mit.edu

Xuanhe Zhao − *Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States; Department of Civil and Environmental Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States*; orcid.org/0000-0001-5387-6186; Email: zhaox@mit.edu

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.chemrev.3c00380

Author Contributions

CRediT: **Sarah J. Wu** visualization, writing-original draft, writing-review & editing; **Xuanhe Zhao** writing-review & editing.

Notes

The authors declare no competing financial interest.

Biographies

Sarah J. Wu is a Ph.D. candidate in the Department of Mechanical Engineering at the Massachusetts Institute of Technology in Cambridge, Massachusetts. She earned her B.S. and M.S. degrees in Mechanical Engineering, also from MIT. Her research centers on the development of bioadhesive materials, minimally invasive delivery methods, and fabrication platforms. She is an NSF Graduate Research Fellow and a recipient of various awards including the Materials Research Society Graduate Student Award, the Baxter Young Investigators Award, and the winner of the Biomedical Engineering Society Student Design Competition.

Xuanhe Zhao is a Professor of Mechanical Engineering at MIT. The mission of Zhao Lab is to advance science and technology between humans and machines to address grand societal challenges in health and sustainability. A major focus is the study and development of soft materials and systems. Dr. Zhao has won early career awards from NSF, ONR, ASME, SES, AVS, and Adhesion Society. He is a Clarivate Highly Cited Researcher. Bioadhesive ultrasound, based on Zhao Lab's work published in Science, was named one of TIME Magazine's Best Inventions of the year in 2022. SanaHeal Inc., based on Zhao Lab's work published in Nature, was awarded the 2023 Nature Spinoff Prize. Over ten patents from Zhao Lab have been licensed by companies and have contributed to FDA-approved and widely used medical devices.

ACKNOWLEDGMENTS

This work is supported by the National Institutes of Health (no. 1R01HL153857). S.J.W. acknowledges financial support from the National Science Foundation (NSF) Graduate Research Fellowship Program.

REFERENCES

(1) Mackenzie, D. The History of Sutures. *Med. Hist.* **1973**, *17*, 158−168.
(2) Muffly, T. M.; Tizzano, A. P.; Walters, M. D. The History and Evolution of Sutures in Pelvic Surgery. *J. R. Soc. Med.* **2011**, *104*, 107−112.
(3) Gaidry, A. D.; Tremblay, L.; Nakayama, D.; Ignacio, R. C. The History of Surgical Staplers: A Combination of Hungarian, Russian, and American Innovation. *Am. Surg.* **2019**, *85*, 563−566.
(4) General and Plastic Surgery Devices; Reclassification of Certain Surgical Staplers. *Federal Register*. https://www.federalregister.gov/documents/2021/10/08/2021-22041/general-and-plastic-surgery-devices-reclassification-of-certain-surgical-staplers (accessed 2023-03-02).
(5) Makanyengo, S. O.; Thiruchelvam, D. Literature Review on the Incidence of Primary Stapler Malfunction. *Surg. Innov.* **2020**, *27*, 229−234.
(6) Annabi, N.; Yue, K.; Tamayol, A.; Khademhosseini, A. Elastic Sealants for Surgical Applications. *Eur. J. Pharm. Biopharm.* **2015**, *95*, 27−39.
(7) Reece, T. B.; Maxey, T. S.; Kron, I. L. A Prospectus on Tissue Adhesives. *Am. J. Surg.* **2001**, *182*, 40S−44S.
(8) Taboada, G. M.; Yang, K.; Pereira, M. J. N.; Liu, S. S.; Hu, Y.; Karp, J. M.; Artzi, N.; Lee, Y. Overcoming the Translational Barriers of Tissue Adhesives. *Nat. Rev. Mater.* **2020**, *5*, 310−329.
(9) Nam, S.; Mooney, D. Polymeric Tissue Adhesives. *Chem. Rev.* **2021**, *121*, 11336−11384.
(10) Borst, H. G.; Haverich, A.; Walterbusch, G.; Maatz, W.; Messmer, B. Fibrin Adhesive: An Important Hemostatic Adjunct in Cardiovascular Operations. *J. Thorac. Cardiovasc. Surg.* **1982**, *84*, 548−553.
(11) Kulkarni, M. R.; Thomas, B. S.; Varghese, J. M.; Bhat, G. S. Platelet-Rich Fibrin as an Adjunct to Palatal Wound Healing after Harvesting a Free Gingival Graft: A Case Series. *J. Indian Soc. Periodontol.* **2014**, *18*, 399−402.
(12) Kerber, C. W.; Cromwell, L. D.; Sheptak, P. E. Intraarterial Cyanoacrylate: An Adjunct in the Treatment of Spinal/Paraspinal Arteriovenous Malformations. *AJR Am. J. Roentgenol.* **1978**, *130*, 99−103.
(13) Chen, X.; Yuk, H.; Wu, J.; Nabzdyk, C. S.; Zhao, X. Instant Tough Bioadhesive with Triggerable Benign Detachment. *Proc. Natl. Acad. Sci. U. S. A.* **2020**, *117*, 15497−15503.
(14) Chen, H.; Cheng, J.; Ran, L.; Yu, K.; Lu, B.; Lan, G.; Dai, F.; Lu, F. An Injectable Self-Healing Hydrogel with Adhesive and Antibacterial Properties Effectively Promotes Wound Healing. *Carbohydr. Polym.* **2018**, *201*, 522−531.
(15) Du, X.; Wu, L.; Yan, H.; Qu, L.; Wang, L.; Wang, X.; Ren, S.; Kong, D.; Wang, L. Multifunctional Hydrogel Patch with Toughness, Tissue Adhesiveness, and Antibacterial Activity for Sutureless Wound Closure. *ACS Biomater. Sci. Eng.* **2019**, *5*, 2610−2620.
(16) Deng, J.; Yuk, H.; Wu, J.; Varela, C. E.; Chen, X.; Roche, E. T.; Guo, C. F.; Zhao, X. Electrical Bioadhesive Interface for Bioelectronics. *Nat. Mater.* **2021**, *20*, 229−236.
(17) Mehdizadeh, M.; Yang, J. Design Strategies and Applications of Tissue Bioadhesives. *Macromol. Biosci.* **2013**, *13*, 271−288.
(18) Bhagat, V.; Becker, M. L. Degradable Adhesives for Surgery and Tissue Engineering. *Biomacromolecules* **2017**, *18*, 3009−3039.

(19) Yang, J.; Bai, R.; Chen, B.; Suo, Z. Hydrogel Adhesion: A Supramolecular Synergy of Chemistry, Topology, and Mechanics. *Adv. Funct. Mater.* **2020**, *30*, 1901693.
(20) Bovone, G.; Dudaryeva, O. Y.; Marco-Dufort, B.; Tibbitt, M. W. Engineering Hydrogel Adhesion for Biomedical Applications via Chemical Design of the Junction. *ACS Biomater. Sci. Eng.* **2021**, *7*, 4048−4076.
(21) Cui, C.; Liu, W. Recent Advances in Wet Adhesives: Adhesion Mechanism, Design Principle and Applications. *Prog. Polym. Sci.* **2021**, *116*, 101388.
(22) Ma, Z.; Bao, G.; Li, J. Multifaceted Design and Emerging Applications of Tissue Adhesives. *Adv. Mater.* **2021**, *33*, 2007663.
(23) Zhu, J.; Zhou, H.; Gerhard, E. M.; Zhang, S.; Parra Rodríguez, F. I.; Pan, T.; Yang, H.; Lin, Y.; Yang, J.; Cheng, H. Smart Bioadhesives for Wound Healing and Closure. *Bioact. Mater.* **2023**, *19*, 360−375.
(24) Creton, C.; Ciccotti, M. Fracture and Adhesion of Soft Materials: A Review. *Rep. Prog. Phys.* **2016**, *79*, 046601.
(25) Zhao, X.; Chen, X.; Yuk, H.; Lin, S.; Liu, X.; Parada, G. Soft Materials by Design: Unconventional Polymer Networks Give Extreme Properties. *Chem. Rev.* **2021**, *121*, 4309−4372.
(26) Yuk, H.; Zhang, T.; Lin, S.; Parada, G. A.; Zhao, X. Tough Bonding of Hydrogels to Diverse Non-Porous Surfaces. *Nat. Mater.* **2016**, *15*, 190−196.
(27) Yang, Z.; Ma, Z.; Liu, S.; Li, J. Tissue Adhesion with Tough Hydrogels: Experiments and Modeling. *Mech. Mater.* **2021**, *157*, 103800.
(28) Bouten, P. J. M.; Zonjee, M.; Bender, J.; Yauw, S. T. K.; van Goor, H.; van Hest, J. C. M.; Hoogenboom, R. The Chemistry of Tissue Adhesive Materials. *Prog. Polym. Sci.* **2014**, *39*, 1375−1405.
(29) Tighe, B. J.; Mann, A. 11 - Adhesives and Interfacial Phenomena in Wound Healing. In *Advanced Wound Repair Therapies*; Farrar, D., Ed.; Woodhead Publishing Series in Biomaterials; Woodhead Publishing, 2011; pp 247−283.
(30) Wallace, D. G.; Cruise, G. M.; Rhee, W. M.; Schroeder, J. A.; Prior, J. J.; Ju, J.; Maroney, M.; Duronio, J.; Ngo, M. H.; Estridge, T.; Coker, G. C. A Tissue Sealant Based on Reactive Multifunctional Polyethylene Glycol. *J. Biomed. Mater. Res.* **2001**, *58*, 545−555.
(31) Yuk, H.; Varela, C. E.; Nabzdyk, C. S.; Mao, X.; Padera, R. F.; Roche, E. T.; Zhao, X. Dry Double-Sided Tape for Adhesion of Wet Tissues and Devices. *Nature* **2019**, *575*, 169−174.
(32) Zhang, Y.; Li, X.; Wei, W.; Liu, X. A Strong Dual-Component Bioadhesive Based on Solventless Thiol-Isocyanate Click Chemistry. *ACS Biomater. Sci. Eng.* **2021**, *7*, 3389−3398.
(33) Li, J.; Celiz, A. D.; Yang, J.; Yang, Q.; Wamala, I.; Whyte, W.; Seo, B. R.; Vasilyev, N. V.; Vlassak, J. J.; Suo, Z.; Mooney, D. J. Tough Adhesives for Diverse Wet Surfaces. *Science* **2017**, *357*, 378−381.
(34) Quan, W.-Y.; Hu, Z.; Liu, H.-Z.; Ouyang, Q.-Q.; Zhang, D.-Y.; Li, S.-D.; Li, P.-W.; Yang, Z.-M. Mussel-Inspired Catechol-Functionalized Hydrogels and Their Medical Applications. *Molecules* **2019**, *24*, 2586.
(35) Saiz-Poseu, J.; Mancebo-Aracil, J.; Nador, F.; Busqué, F.; Ruiz-Molina, D. The Chemistry behind Catechol-Based Adhesion. *Angew. Chem., Int. Ed.* **2019**, *58*, 696−714.
(36) Zhang, Y.; Qi, Y.; Ulrich, S.; Barboiu, M.; Ramström, O. Dynamic Covalent Polymers for Biomedical Applications. *Mater. Chem. Front.* **2020**, *4*, 489−506.
(37) Hua, Y.; Gan, Y.; Li, P.; Song, L.; Shi, C.; Bao, C.; Yang, Y.; Zhou, Q.; Lin, Q.; Zhu, L. Moldable and Removable Wound Dressing Based on Dynamic Covalent Cross-Linking of Thiol-Aldehyde Addition. *ACS Biomater. Sci. Eng.* **2019**, *5*, 4048−4053.
(38) Yang, S.; Bai, J.; Sun, X.; Zhang, J. Robust and Healable Poly(Disulfides) Supramolecular Adhesives Enabled by Dynamic Covalent Adaptable Networks and Noncovalent Hydrogen-Bonding Interactions. *Chem. Eng. J.* **2023**, *461*, 142066.
(39) Chen, M.; Wu, Y.; Chen, B.; Tucker, A. M.; Jagota, A.; Yang, S. Fast, Strong, and Reversible Adhesives with Dynamic Covalent Bonds for Potential Use in Wound Dressing. *Proc. Natl. Acad. Sci. U. S. A.* **2022**, *119*, No. e2203074119.
(40) Belowich, M. E.; Stoddart, J. F. Dynamic Imine Chemistry. *Chem. Soc. Rev.* **2012**, *41*, 2003−2024.
(41) Hofman, A. H.; van Hees, I. A.; Yang, J.; Kamperman, M. Bioinspired Underwater Adhesives by Using the Supramolecular Toolbox. *Adv. Mater.* **2018**, *30*, 1704640.
(42) Chen, S.; Zhang, K.; Li, Z.; Wu, Y.; Zhu, B.; Zhu, J. Hydrogen-Bonded Supramolecular Adhesives: Synthesis, Responsiveness, and Application. *Supramol. Mater.* **2023**, *2*, 100032.
(43) Fan, H.; Gong, J. P. Bioinspired Underwater Adhesives. *Adv. Mater.* **2021**, *33*, 2102983.
(44) Ahn, B. K. Perspectives on Mussel-Inspired Wet Adhesion. *J. Am. Chem. Soc.* **2017**, *139*, 10166−10171.
(45) Lee, B. P.; Messersmith, P. B.; Israelachvili, J. N.; Waite, J. H. Mussel-Inspired Adhesives and Coatings. *Annu. Rev. Mater. Res.* **2011**, *41*, 99−132.
(46) Kord Forooshani, P.; Lee, B. P. Recent Approaches in Designing Bioadhesive Materials Inspired by Mussel Adhesive Protein. *J. Polym. Sci. Part Polym. Chem.* **2017**, *55*, 9−33.
(47) Waite, J. H. Mussel Adhesion - Essential Footwork. *J. Exp. Biol.* **2017**, *220*, 517−530.
(48) Guo, Q.; Chen, J.; Wang, J.; Zeng, H.; Yu, J. Recent Progress in Synthesis and Application of Mussel-Inspired Adhesives. *Nanoscale* **2020**, *12*, 1307−1324.
(49) Guo, Z.; Xia, J.; Mi, S.; Sun, W. Mussel-Inspired Naturally Derived Double-Network Hydrogels and Their Application in 3D Printing: From Soft, Injectable Bioadhesives to Mechanically Strong Hydrogels. *ACS Biomater. Sci. Eng.* **2020**, *6*, 1798−1808.
(50) Montazerian, H.; Mitra, S.; Hassani Najafabadi, A.; Seyedmahmoud, R.; Zheng, Y.; Dokmeci, M. R.; Annabi, N.; Khademhosseini, A.; Weiss, P. S. Catechol Conjugation for Bioadhesion in Photo-Cross-Linkable Biomaterials. *ACS Mater. Lett.* **2023**, *5*, 1672−1683.
(51) Yang, J.; Bai, R.; Suo, Z. Topological Adhesion of Wet Materials. *Adv. Mater.* **2018**, *30*, 1800671.
(52) Gao, Y.; Chen, J.; Han, X.; Pan, Y.; Wang, P.; Wang, T.; Lu, T. A Universal Strategy for Tough Adhesion of Wet Soft Material. *Adv. Funct. Mater.* **2020**, *30*, 2003207.
(53) Roma-Luciow, R.; Sarraf, L.; Morcellet, M. Complexes of Poly(Acrylic Acid) with Some Divalent, Trivalent and Tetravalent Metal Ions. *Eur. Polym. J.* **2001**, *37*, 1741−1745.
(54) Gao, Y.; Wu, K.; Suo, Z. Photodetachable Adhesion. *Adv. Mater.* **2019**, *31*, 1806948.
(55) Delaney, L. J.; Isguven, S.; Eisenbrey, J. R.; Hickok, N. J.; Forsberg, F. Making Waves: How Ultrasound-Targeted Drug Delivery Is Changing Pharmaceutical Approaches. *Mater. Adv.* **2022**, *3*, 3023−3040.
(56) Ma, Z.; Bourquard, C.; Gao, Q.; Jiang, S.; De Iure-Grimmel, T.; Huo, R.; Li, X.; He, Z.; Yang, Z.; Yang, G.; Wang, Y.; Lam, E.; Gao, Z.; Supponen, O.; Li, J. Controlled Tough Bioadhesion Mediated by Ultrasound. *Science* **2022**, *377*, 751−755.
(57) Kim, W.-S.; Yun, I.-H.; Lee, J.-J.; Jung, H.-T. Evaluation of Mechanical Interlock Effect on Adhesion Strength of Polymer-Metal Interfaces Using Micro-Patterned Surface Topography. *Int. J. Adhes. Adhes.* **2010**, *30*, 408−417.
(58) Webster, I. Recent Developments in Pressure-Sensitive Adhesives for Medical Applications. *Int. J. Adhes. Adhes.* **1997**, *17*, 69−73.
(59) *DuPont™ Liveo™ Medical Grade Pressure Sensitive Adhesives (PSAs)*. https://www.dupont.com/products/LiveoMedicalGradeMGPressureSensitiveAdhesives.html (accessed 2023-05-11).
(60) Dressing and Device Securement. *3M Medical*; 3M United States. https://www.3m.com/3M/en_US/medical-us/dressing-and-device-securement/ (accessed 2023-05-11).
(61) Soft skin adhesives | Silicones | Products. *Elkem*. https://www.elkem.com/products/silicones/medical-grade-silicones/soft-skin-adhesives/ (accessed 2023-05-11).
(62) Pushing boundaries in health tech: 3M launches new medical adhesive offering premium wear time, up to 28 days. *3M News Center*. https://news.3m.com/2023-02-06-Pushing-boundaries-in-health-

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

tech-3M-launches-new-medical-adhesive-offering-premium-wear-time,-up-to-28-days (accessed 2023-05-11).
(63) Fitzgerald, D. M.; Colson, Y. L.; Grinstaff, M. W. Advancing Pressure-Sensitive Adhesives for Internal Wound Closure. *Nat. Rev. Mater.* **2023**, *8*, 3−5.
(64) Zhu, M.; Zhang, F.; Chen, X. Bioinspired Mechanically Interlocking Structures. *Small Struct.* **2020**, *1*, 2000045.
(65) Kochhar, J. S.; Quek, T. C.; Soon, W. J.; Choi, J.; Zou, S.; Kang, L. Effect of Microneedle Geometry and Supporting Substrate on Microneedle Array Penetration into Skin. *J. Pharm. Sci.* **2013**, *102*, 4100−4108.
(66) Yang, S. Y.; O'Cearbhaill, E. D.; Sisk, G. C.; Park, K. M.; Cho, W. K.; Villiger, M.; Bouma, B. E.; Pomahac, B.; Karp, J. M. A Bio-Inspired Swellable Microneedle Adhesive for Mechanical Interlocking with Tissue. *Nat. Commun.* **2013**, *4*, 1702.
(67) Han, D.; Morde, R. S.; Mariani, S.; La Mattina, A. A.; Vignali, E.; Yang, C.; Barillaro, G.; Lee, H. 4D Printing of a Bioinspired Microneedle Array with Backward-Facing Barbs for Enhanced Tissue Adhesion. *Adv. Funct. Mater.* **2020**, *30*, 1909197.
(68) Seong, K.-Y.; Seo, M.-S.; Hwang, D. Y.; O'Cearbhaill, E. D.; Sreenan, S.; Karp, J. M.; Yang, S. Y. A Self-Adherent, Bullet-Shaped Microneedle Patch for Controlled Transdermal Delivery of Insulin. *J. Controlled Release* **2017**, *265*, 48−56.
(69) Writer, L. M. H. S. Harvard entrepreneurs weave silk with science. *Harvard Gazette*. https://news.harvard.edu/gazette/story/2012/06/harvard-entrepreneurs-weave-silk-with-science/ (accessed 2023-05-22).
(70) Micron Biomedical, Inc. *Micron Biomedical Initiates First-Ever Microneedle Vaccine Clinical Trial in Children*. https://www.prnewswire.com/news-releases/micron-biomedical-initiates-first-ever-microneedle-vaccine-clinical-trial-in-children-301331844.html (accessed 2023-05−22).
(71) *Sofusa™ | Medication Delivery Platform Enabling A Distinct Therapeutic Advantage Through Nanotechnology | Technology*. http://www.sofusa.com/technology/ (accessed 2023-05-22).
(72) Stinson, J. A.; Boopathy, A. V.; Cieslewicz, B. M.; Zhang, Y.; Hartman, N. W.; Miller, D. P.; Dirckx, M.; Hurst, B. L.; Tarbet, E. B.; Kluge, J. A.; Kosuda, K. M. Enhancing Influenza Vaccine Immunogenicity and Efficacy through Infection Mimicry Using Silk Microneedles. *Vaccine* **2021**, *39*, 5410−5421.
(73) Stinson, J. A.; Palmer, C. R.; Miller, D. P.; Li, A. B.; Lightner, K.; Jost, H.; Weldon, W. C.; Oberste, M. S.; Kluge, J. A.; Kosuda, K. M. Thin Silk Fibroin Films as a Dried Format for Temperature Stabilization of Inactivated Polio Vaccine. *Vaccine* **2020**, *38*, 1652−1660.
(74) Makvandi, P.; Kirkby, M.; Hutton, A. R. J.; Shabani, M.; Yiu, C. K. Y.; Baghbantaraghdari, Z.; Jamaledin, R.; Carlotti, M.; Mazzolai, B.; Mattoli, V.; Donnelly, R. F. Engineering Microneedle Patches for Improved Penetration: Analysis, Skin Models and Factors Affecting Needle Insertion. *Nano-Micro Lett.* **2021**, *13*, 93.
(75) Chimutengwende-Gordon, M.; Dowling, R.; Pendegrass, C.; Blunn, G. Determining the Porous Structure for Optimal Soft-Tissue Ingrowth: An in Vivo Histological Study. *PLoS One* **2018**, *13*, No. e0206228.
(76) Matos, G. R. M. Surface Roughness of Dental Implant and Osseointegration. *J. Maxillofac. Oral Surg.* **2021**, *20*, 1−4.
(77) Yabe, A.; Okada, M.; Hara, E. S.; Torii, Y.; Matsumoto, T. Self-Adhering Implantable Device of Titanium: Enhanced Soft-Tissue Adhesion by Sandblast Pretreatment. *Colloids Surf. B Biointerfaces* **2022**, *211*, 112283.
(78) Ban, S.; Iwaya, Y.; Kono, H.; Sato, H. Surface Modification of Titanium by Etching in Concentrated Sulfuric Acid. *Dent. Mater.* **2006**, *22*, 1115−1120.
(79) Syam, S.; Wu, C.-J.; Lan, W.-C.; Ou, K.-L.; Huang, B.-H.; Lin, Y.-Y.; Saito, T.; Tsai, H.-Y.; Chuo, Y.-C.; Yen, M.-L.; Liu, C.-M.; Hou, P.-J. The Potential of a Surface-Modified Titanium Implant with Tetrapeptide for Osseointegration Enhancement. *Appl. Sci.* **2021**, *11*, 2616.
(80) Carpenter, R. D.; Klosterhoff, B. S.; Torstrick, F. B.; Foley, K. T.; Burkus, J. K.; Lee, C. S. D.; Gall, K.; Guldberg, R. E.; Safranski, D. L. Effect of Porous Orthopaedic Implant Material and Structure on Load Sharing with Simulated Bone Ingrowth: A Finite Element Analysis Comparing Titanium and PEEK. *J. Mech. Behav. Biomed. Mater.* **2018**, *80*, 68−76.
(81) Wang, W.; Liu, Y.; Xie, Z. Gecko-Like Dry Adhesive Surfaces and Their Applications: A Review. *J. Bionic Eng.* **2021**, *18*, 1011−1044.
(82) Mahdavi, A.; Ferreira, L.; Sundback, C.; Nichol, J. W.; Chan, E. P.; Carter, D. J. D.; Bettinger, C. J.; Patanavanich, S.; Chignozha, L.; Ben-Joseph, E.; Galakatos, A.; Pryor, H.; Pomerantseva, I.; Masiakos, P. T.; Faquin, W.; Zumbuehl, A.; Hong, S.; Borenstein, J.; Vacanti, J.; Langer, R.; Karp, J. M. A Biodegradable and Biocompatible Gecko-Inspired Tissue Adhesive. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 2307−2312.
(83) Autumn, K.; Liang, Y. A.; Hsieh, S. T.; Zesch, W.; Chan, W. P.; Kenny, T. W.; Fearing, R.; Full, R. J. Adhesive Force of a Single Gecko Foot-Hair. *Nature* **2000**, *405*, 681−685.
(84) Pennisi, E. Geckos Climb by the Hairs of Their Toes. *Science* **2000**, *288*, 1717−1718.
(85) Autumn, K.; Sitti, M.; Liang, Y. A.; Peattie, A. M.; Hansen, W. R.; Sponberg, S.; Kenny, T. W.; Fearing, R.; Israelachvili, J. N.; Full, R. J. Evidence for van Der Waals Adhesion in Gecko Setae. *Proc. Natl. Acad. Sci. U. S. A.* **2002**, *99*, 12252−12256.
(86) Kim, J.-K.; Varenberg, M. Contact Splitting in Dry Adhesion and Friction: Reducing the Influence of Roughness. *Beilstein J. Nanotechnol.* **2019**, *10*, 1−8.
(87) Arzt, E.; Gorb, S.; Spolenak, R. From Micro to Nano Contacts in Biological Attachment Devices. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*, 10603−10606.
(88) Johnson, K. L.; Kendall, K.; Roberts, A. D. Surface Energy and the Contact of Elastic Solids. *Proc. R. Soc. London A* **1971**, *324*, 301−313.
(89) Zeng, H.; Pesika, N.; Tian, Y.; Zhao, B.; Chen, Y.; Tirrell, M.; Turner, K. L.; Israelachvili, J. N. Frictional Adhesion of Patterned Surfaces and Implications for Gecko and Biomimetic Systems. *Langmuir* **2009**, *25*, 7486−7495.
(90) Drotlef, D.-M.; Amjadi, M.; Yunusa, M.; Sitti, M. Bioinspired Composite Microfibers for Skin Adhesion and Signal Amplification of Wearable Sensors. *Adv. Mater.* **2017**, *29*, 1701353.
(91) Bae, W. G.; Kim, D.; Kwak, M. K.; Ha, L.; Kang, S. M.; Suh, K. Y. Enhanced Skin Adhesive Patch with Modulus-Tunable Composite Micropillars. *Adv. Healthc. Mater.* **2013**, *2*, 109−113.
(92) Kerst, C. F. Gecko Inspired Adhesives: Permanent Practical Manufacturing, New Materials, and Applications. Ph.D. Dissertation, Stanford University, Stanford, California, 2020. https://www.proquest.com/docview/2509703362/abstract/9B16EAA90FB4407CPQ/1 (accessed 2023-05-24).
(93) Tramacere, F.; Pugno, N. M.; Kuba, M. J.; Mazzolai, B. Unveiling the Morphology of the Acetabulum in Octopus Suckers and Its Role in Attachment. *Interface Focus* **2015**, *5*, 20140050.
(94) Baik, S.; Kim, D. W.; Park, Y.; Lee, T.-J.; Ho Bhang, S.; Pang, C. A Wet-Tolerant Adhesive Patch Inspired by Protuberances in Suction Cups of Octopi. *Nature* **2017**, *546*, 396−400.
(95) Baik, S.; Kim, J.; Lee, H. J.; Lee, T. H.; Pang, C. Highly Adaptable and Biocompatible Octopus-Like Adhesive Patches with Meniscus-Controlled Unfoldable 3D Microtips for Underwater Surface and Hairy Skin. *Adv. Sci.* **2018**, *5*, 1800100.
(96) Chun, S.; Son, W.; Kim, D. W.; Lee, J.; Min, H.; Jung, H.; Kwon, D.; Kim, A.-H.; Kim, Y.-J.; Lim, S. K.; Pang, C.; Choi, C. Water-Resistant and Skin-Adhesive Wearable Electronics Using Graphene Fabric Sensor with Octopus-Inspired Microsuckers. *ACS Appl. Mater. Interfaces* **2019**, *11*, 16951−16957.
(97) Kim, D. W.; Baik, S.; Min, H.; Chun, S.; Lee, H. J.; Kim, K. H.; Lee, J. Y.; Pang, C. Highly Permeable Skin Patch with Conductive Hierarchical Architectures Inspired by Amphibians and Octopi for Omnidirectionally Enhanced Wet Adhesion. *Adv. Funct. Mater.* **2019**, *29*, 1807614.

(98) Huang, R.; Zhang, X.; Li, W.; Shang, L.; Wang, H.; Zhao, Y. Suction Cups-Inspired Adhesive Patch with Tailorable Patterns for Versatile Wound Healing. *Adv. Sci.* **2021**, *8*, 2100201.
(99) Lee, Y.-W.; Chun, S.; Son, D.; Hu, X.; Schneider, M.; Sitti, M. A Tissue Adhesion-Controllable and Biocompatible Small-Scale Hydrogel Adhesive Robot. *Adv. Mater.* **2022**, *34*, 2109325.
(100) Wang, H.; Su, X.; Chai, Z.; Tian, Z.; Xie, W.; Wang, Y.; Wan, Z.; Deng, M.; Yuan, Z.; Huang, J. A Hydra Tentacle-Inspired Hydrogel with Underwater Ultra-Stretchability for Adhering Adipose Surfaces. *Chem. Eng. J.* **2022**, *428*, 131049.
(101) Smith, A. M. Cephalopod Sucker Design and the Physical Limits to Negative Pressure. *J. Exp. Biol.* **1996**, *199*, 949−958.
(102) Baik, S.; Lee, H. J.; Kim, D. W.; Min, H.; Pang, C. Capillarity-Enhanced Organ-Attachable Adhesive with Highly Drainable Wrinkled Octopus-Inspired Architectures. *ACS Appl. Mater. Interfaces* **2019**, *11*, 25674−25681.
(103) Zhao, X. Multi-Scale Multi-Mechanism Design of Tough Hydrogels: Building Dissipation into Stretchy Networks. *Soft Matter* **2014**, *10*, 672−687.
(104) Fuchs, S.; Shariati, K.; Ma, M. Specialty Tough Hydrogels and Their Biomedical Applications. *Adv. Healthc. Mater.* **2020**, *9*, No. e1901396.
(105) Gong, J. p.; Katsuyama, Y.; Kurokawa, T.; Osada, Y. Double-Network Hydrogels with Extremely High Mechanical Strength. *Adv. Mater.* **2003**, *15*, 1155−1158.
(106) Azuma, C.; Yasuda, K.; Tanabe, Y.; Taniguro, H.; Kanaya, F.; Nakayama, A.; Chen, Y. M.; Gong, J. P.; Osada, Y. Biodegradation of High-Toughness Double Network Hydrogels as Potential Materials for Artificial Cartilage. *J. Biomed. Mater. Res., Part A* **2007**, *81A*, 373−380.
(107) Liu, J.; Wang, S.; Shen, Q.; Kong, L.; Huang, G.; Wu, J. Tough Underwater Super-Tape Composed of Semi-Interpenetrating Polymer Networks with a Water-Repelling Liquid Surface. *ACS Appl. Mater. Interfaces* **2021**, *13*, 1535−1544.
(108) Wu, J.; Yuk, H.; Sarrafian, T. L.; Guo, C. F.; Griffiths, L. G.; Nabzdyk, C. S.; Zhao, X. An Off-the-Shelf Bioadhesive Patch for Sutureless Repair of Gastrointestinal Defects. *Sci. Transl. Med.* **2022**, *14*, No. eabh2857.
(109) Karami, P.; Wyss, C. S.; Khoushabi, A.; Schmocker, A.; Broome, M.; Moser, C.; Bourban, P.-E.; Pioletti, D. P. Composite Double-Network Hydrogels To Improve Adhesion on Biological Surfaces. *ACS Appl. Mater. Interfaces* **2018**, *10*, 38692−38699.
(110) Rahman, M. A.; Bowland, C.; Ge, S.; Acharya, S. R.; Kim, S.; Cooper, V. R.; Chen, X. C.; Irle, S.; Sokolov, A. P.; Savara, A.; Saito, T. Design of Tough Adhesive from Commodity Thermoplastics through Dynamic Crosslinking. *Sci. Adv.* **2021**, *7*, No. eabk2451.
(111) Xie, C.; Wang, X.; He, H.; Ding, Y.; Lu, X. Mussel-Inspired Hydrogels for Self-Adhesive Bioelectronics. *Adv. Funct. Mater.* **2020**, *30*, 1909954.
(112) Han, L.; Lu, X.; Liu, K.; Wang, K.; Fang, L.; Weng, L.-T.; Zhang, H.; Tang, Y.; Ren, F.; Zhao, C.; Sun, G.; Liang, R.; Li, Z. Mussel-Inspired Adhesive and Tough Hydrogel Based on Nanoclay Confined Dopamine Polymerization. *ACS Nano* **2017**, *11*, 2561−2574.
(113) Verma, N.; Moore, E.; Blau, W.; Volkov, Y.; Babu, R. Cytotoxicity Evaluation of Nanoclays in Human Epithelial Cell Line A549 Using High Content Screening and Real-Time Impedance Analysis. *J. Nanoparticle Res.* **2012**, *14*, 1137.
(114) Ou, L.; Song, B.; Liang, H.; Liu, J.; Feng, X.; Deng, B.; Sun, T.; Shao, L. Toxicity of Graphene-Family Nanoparticles: A General Review of the Origins and Mechanisms. *Part. Fibre Toxicol.* **2016**, *13*, 57.
(115) Liao, C.; Li, Y.; Tjong, S. C. Graphene Nanomaterials: Synthesis, Biocompatibility, and Cytotoxicity. *Int. J. Mol. Sci.* **2018**, *19*, 3564.
(116) Wegst, U. G. K.; Bai, H.; Saiz, E.; Tomsia, A. P.; Ritchie, R. O. Bioinspired Structural Materials. *Nat. Mater.* **2015**, *14*, 23−36.
(117) Ni, J.; Lin, S.; Qin, Z.; Veysset, D.; Liu, X.; Sun, Y.; Hsieh, A. J.; Radovitzky, R.; Nelson, K. A.; Zhao, X. Strong Fatigue-Resistant Nanofibrous Hydrogels Inspired by Lobster Underbelly. *Matter* **2021**, *4*, 1919−1934.
(118) Mo, C.; Long, H.; Raney, J. R. Tough, Aorta-Inspired Soft Composites. *Proc. Natl. Acad. Sci. U. S. A.* **2022**, *119*, No. e2123497119.
(119) Zhao, X. Designing Toughness and Strength for Soft Materials. *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114*, 8138−8140.
(120) Pinkas, O.; Haneman, O.; Chemke, O.; Zilberman, M. Fiber-Reinforced Composite Hydrogels for Bioadhesive and Sealant Applications. *Polym. Adv. Technol.* **2017**, *28*, 1162−1169.
(121) Béguin, P.; Aubert, J. P. The Biological Degradation of Cellulose. *FEMS Microbiol. Rev.* **1994**, *13*, 25−58.
(122) Saheb, D. N.; Jog, J. P. Natural Fiber Polymer Composites: A Review. *Adv. Polym. Technol.* **1999**, *18*, 351−363.
(123) Nishiguchi, A.; Taguchi, T. Engineering an Injectable Tough Tissue Adhesive through Nanocellulose Reinforcement. *ACS Appl. Bio Mater.* **2020**, *3*, 9093−9100.
(124) Gao, Y.; Han, X.; Chen, J.; Pan, Y.; Yang, M.; Lu, L.; Yang, J.; Suo, Z.; Lu, T. Hydrogel-Mesh Composite for Wound Closure. *Proc. Natl. Acad. Sci. U. S. A.* **2021**, *118*, e2103457118.
(125) Wu, J.; Yuk, H.; Sarrafian, T. L.; Guo, C. F.; Griffiths, L. G.; Nabzdyk, C. S.; Zhao, X. An Off-the-Shelf Bioadhesive Patch for Sutureless Repair of Gastrointestinal Defects. *Sci. Transl. Med.* **2022**, *14*, No. eabh2857.
(126) Fung, Y. C. Elasticity of Soft Tissues in Simple Elongation. *Am. J. Physiol.* **1967**, *213*, 1532−1544.
(127) Purslow, P. P.; Wess, T. J.; Hukins, D. W. Collagen Orientation and Molecular Spacing during Creep and Stress-Relaxation in Soft Connective Tissues. *J. Exp. Biol.* **1998**, *201*, 135−142.
(128) Screen, H. R. C. Investigating Load Relaxation Mechanics in Tendon. *J. Mech. Behav. Biomed. Mater.* **2008**, *1*, 51−58.
(129) Silver, F. H.; Kelkar, N.; Deshmukh, T. Molecular Basis for Mechanical Properties of ECMs: Proposed Role of Fibrillar Collagen and Proteoglycans in Tissue Biomechanics. *Biomolecules* **2021**, *11*, 1018.
(130) Trębacz, H.; Barzycka, A. Mechanical Properties and Functions of Elastin: An Overview. *Biomolecules* **2023**, *13*, 574.
(131) Nia, H. T.; Han, L.; Li, Y.; Ortiz, C.; Grodzinsky, A. Poroelasticity of Cartilage at the Nanoscale. *Biophys. J.* **2011**, *101*, 2304−2313.
(132) Kovalchick, C.; Molinari, A.; Ravichandran, G. Rate Dependent Adhesion Energy and Nonsteady Peeling of Inextensible Tapes. *J. Appl. Mech.* **2014**, *81*, 041016.
(133) Lim, C. Y.; Owens, N. A.; Wampler, R. D.; Ying, Y.; Granger, J. H.; Porter, M. D.; Takahashi, M.; Shimazu, K. Succinimidyl Ester Surface Chemistry: Implications of the Competition between Aminolysis and Hydrolysis on Covalent Protein Immobilization. *Langmuir* **2014**, *30*, 12868−12878.
(134) Mao, X.; Yuk, H.; Zhao, X. Hydration and Swelling of Dry Polymers for Wet Adhesion. *J. Mech. Phys. Solids* **2020**, *137*, 103863.
(135) Epstein, A. K.; Wong, T.-S.; Belisle, R. A.; Boggs, E. M.; Aizenberg, J. Liquid-Infused Structured Surfaces with Exceptional Anti-Biofouling Performance. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 13182−13187.
(136) Wu, S. J.; Yuk, H.; Wu, J.; Nabzdyk, C. S.; Zhao, X. A Multifunctional Origami Patch for Minimally Invasive Tissue Sealing. *Adv. Mater.* **2021**, *33*, 2007667.
(137) Bao, G.; Gao, Q.; Cau, M.; Ali-Mohamad, N.; Strong, M.; Jiang, S.; Yang, Z.; Valiei, A.; Ma, Z.; Amabili, M.; Gao, Z.-H.; Mongeau, L.; Kastrup, C.; Li, J. Liquid-Infused Microstructured Bioadhesives Halt Non-Compressible Hemorrhage. *Nat. Commun.* **2022**, *13*, 1−14.
(138) Geraldi, N. R.; Guan, J. H.; Dodd, L. E.; Maiello, P.; Xu, B. B.; Wood, D.; Newton, M. I.; Wells, G. G.; McHale, G. Double-Sided Slippery Liquid-Infused Porous Materials Using Conformable Mesh. *Sci. Rep.* **2019**, *9*, 13280.
(139) Yuk, H.; Wu, J.; Sarrafian, T. L.; Mao, X.; Varela, C. E.; Roche, E. T.; Griffiths, L. G.; Nabzdyk, C. S.; Zhao, X. Rapid and Coagulation-Independent Haemostatic Sealing by a Paste Inspired by Barnacle Glue. *Nat. Biomed. Eng.* **2021**, *5*, 1131−1142.
(140) Thavarajah, D.; De Lacy, P.; Hussain, R.; Redfern, R. M. Postoperative Cervical Cord Compression Induced by Hydrogel (DuraSeal): A Possible Complication. *Spine* **2010**, *35*, No. E25.

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

(141) Blackburn, S. L.; Smyth, M. D. Hydrogel-Induced Cervicomedullary Compression after Posterior Fossa Decompression for Chiari Malformation. Case Report. *J. Neurosurg.* **2007**, *106*, 302−304.
(142) Mulder, M.; Crosier, J.; Dunn, R. Cauda Equina Compression by Hydrogel Dural Sealant after a Laminotomy and Discectomy: Case Report. *Spine* **2009**, *34*, E144−148.
(143) Barrett, D. G.; Bushnell, G. G.; Messersmith, P. B. Mechanically Robust, Negative-Swelling, Mussel-Inspired Tissue Adhesives. *Adv. Healthc. Mater.* **2013**, *2*, 745−755.
(144) Tian, G.; Yang, D.; Liang, C.; Liu, Y.; Chen, J.; Zhao, Q.; Tang, S.; Huang, J.; Xu, P.; Liu, Z.; Qi, D. A Nonswelling Hydrogel with Regenerable High Wet Tissue Adhesion for Bioelectronics. *Adv. Mater.* **2023**, *35*, 2212302.
(145) Theocharidis, G.; Yuk, H.; Roh, H.; Wang, L.; Mezghani, I.; Wu, J.; Kafanas, A.; Contreras, M.; Sumpio, B.; Li, Z.; Wang, E.; Chen, L.; Guo, C. F.; Jayaswal, N.; Katopodi, X.-L.; Kalavros, N.; Nabzdyk, C. S.; Vlachos, I. S.; Veves, A.; Zhao, X. A Strain-Programmed Patch for the Healing of Diabetic Wounds. *Nat. Biomed. Eng.* **2022**, *6*, 1118−1133.
(146) Annabi, N.; Zhang, Y.-N.; Assmann, A.; Sani, E. S.; Cheng, G.; Lassaletta, A. D.; Vegh, A.; Dehghani, B.; Ruiz-Esparza, G. U.; Wang, X.; Gangadharan, S.; Weiss, A. S.; Khademhosseini, A. Engineering a Highly Elastic Human Protein-Based Sealant for Surgical Applications. *Sci. Transl. Med.* **2017**, *9*, eaai7466.
(147) Annabi, N.; Mithieux, S. M.; Zorlutuna, P.; Camci-Unal, G.; Weiss, A. S.; Khademhosseini, A. Engineered Cell-Laden Human Protein-Based Elastomer. *Biomaterials* **2013**, *34*, 5496−5505.
(148) Anderson, J. M.; Rodriguez, A.; Chang, D. T. Foreign Body Reaction to Biomaterials. *Semin. Immunol.* **2008**, *20*, 86−100.
(149) Fatehi Hassanabad, A.; Zarzycki, A. N.; Jeon, K.; Dundas, J. A.; Vasanthan, V.; Deniset, J. F.; Fedak, P. W. M. Prevention of Post-Operative Adhesions: A Comprehensive Review of Present and Emerging Strategies. *Biomolecules* **2021**, *11*, 1027.
(150) Klopfleisch, R.; Jung, F. The Pathology of the Foreign Body Reaction against Biomaterials. *J. Biomed. Mater. Res., Part A* **2017**, *105*, 927−940.
(151) Zhang, L.; Cao, Z.; Bai, T.; Carr, L.; Ella-Menye, J.-R.; Irvin, C.; Ratner, B. D.; Jiang, S. Zwitterionic Hydrogels Implanted in Mice Resist the Foreign-Body Reaction. *Nat. Biotechnol.* **2013**, *31*, 553−556.
(152) Jansen, L. E.; Amer, L. D.; Chen, E. Y.-T.; Nguyen, T. V.; Saleh, L. S.; Emrick, T.; Liu, W. F.; Bryant, S. J.; Peyton, S. R. Zwitterionic PEG-PC Hydrogels Modulate the Foreign Body Response in a Modulus-Dependent Manner. *Biomacromolecules* **2018**, *19*, 2880−2888.
(153) Doloff, J. C.; Veiseh, O.; de Mezerville, R.; Sforza, M.; Perry, T. A.; Haupt, J.; Jamiel, M.; Chambers, C.; Nash, A.; Aghlara-Fotovat, S.; Stelzel, J. L.; Bauer, S. J.; Neshat, S. Y.; Hancock, J.; Romero, N. A.; Hidalgo, Y. E.; Leiva, I. M.; Munhoz, A. M.; Bayat, A.; Kinney, B. M.; Hodges, H. C.; Miranda, R. N.; Clemens, M. W.; Langer, R. The Surface Topography of Silicone Breast Implants Mediates the Foreign Body Response in Mice, Rabbits and Humans. *Nat. Biomed. Eng.* **2021**, *5*, 1115−1130.
(154) Veiseh, O.; Doloff, J. C.; Ma, M.; Vegas, A. J.; Tam, H. H.; Bader, A. R.; Li, J.; Langan, E.; Wyckoff, J.; Loo, W. S.; Jhunjhunwala, S.; Chiu, A.; Siebert, S.; Tang, K.; Hollister-Lock, J.; Aresta-Dasilva, S.; Bochenek, M.; Mendoza-Elias, J.; Wang, Y.; Qi, M.; Lavin, D. M.; Chen, M.; Dholakia, N.; Thakrar, R.; Lacík, I.; Weir, G. C.; Oberholzer, J.; Greiner, D. L.; Langer, R.; Anderson, D. G. Size- and Shape-Dependent Foreign Body Immune Response to Materials Implanted in Rodents and Non-Human Primates. *Nat. Mater.* **2015**, *14*, 643−651.
(155) Hilger, C.; Clark, E.; Swiontek, K.; Chiriac, A. M.; Caimmi, D. P.; Demoly, P.; Bourrain, J. L. Anaphylaxis to Bovine Serum Albumin Tissue Adhesive in a Non-Meat-Allergic Patient. *J. Investig. Allergol. Clin. Immunol.* **2020**, *30*, 369−371.
(156) Mitsuhata, H.; Horiguchi, Y.; Saitoh, J.; Saitoh, K.; Fukuda, H.; Hirabayasi, Y.; Togashi, H.; Shimizu, R. An Anaphylactic Reaction to Topical Fibrin Glue. *Anesthesiology* **1994**, *81*, 1074−1077.
(157) Saffarzadeh, M.; Mulpuri, A.; Arneja, J. S. Recalcitrant Anaphylaxis Associated with Fibrin Sealant: Treatment with "TISSEEL-Ectomy. *Plast. Reconstr. Surg. Glob. Open* **2021**, *9*, No. e3382.
(158) Shupak, R. P.; Blackmore, S.; Kim, R. Y. Skin Hypersensitivity Following Application of Tissue Adhesive (2-Octyl Cyanoacrylate). *Bayl. Univ. Med. Cent. Proc.* **2021**, *34*, 736−738.
(159) Aguado, B. A.; Grim, J. C.; Rosales, A. M.; Watson-Capps, J. J.; Anseth, K. S. Engineering Precision Biomaterials for Personalized Medicine. *Sci. Transl. Med.* **2018**, *10*, No. eaam8645.
(160) Pahlevanzadeh, F.; Setayeshmehr, M.; Bakhsheshi-Rad, H. R.; Emadi, R.; Kharaziha, M.; Poursamar, S. A.; Ismail, A. F.; Sharif, S.; Chen, X.; Berto, F. A Review on Antibacterial Biomaterials in Biomedical Applications: From Materials Perspective to Bioinks Design. *Polymers* **2022**, *14*, 2238.
(161) Sarasam, A. R.; Krishnaswamy, R. K.; Madihally, S. V. Blending Chitosan with Polycaprolactone: Effects on Physicochemical and Antibacterial Properties. *Biomacromolecules* **2006**, *7*, 1131−1138.
(162) Li, W.; Thian, E. S.; Wang, M.; Wang, Z.; Ren, L. Surface Design for Antibacterial Materials: From Fundamentals to Advanced Strategies. *Adv. Sci.* **2021**, *8*, 2100368.
(163) Wang, F.; Wang, S.; Nan, L.; Lu, J.; Zhu, Z.; Yang, J.; Zhang, D.; Liu, J.; Zhao, X.; Wu, D. Conductive Adhesive and Antibacterial Zwitterionic Hydrogel Dressing for Therapy of Full-Thickness Skin Wounds. *Front. Bioeng. Biotechnol.* **2022**, *10*, 833887.
(164) Zheng, L.; Sundaram, H. S.; Wei, Z.; Li, C.; Yuan, Z. Applications of Zwitterionic Polymers. *React. Funct. Polym.* **2017**, *118*, 51−61.
(165) Drago, L.; Bortolin, M.; De Vecchi, E.; Agrappi, S.; Weinstein, R. L.; Mattina, R.; Francetti, L. Antibiofilm Activity of Sandblasted and Laser-Modified Titanium against Microorganisms Isolated from Peri-Implantitis Lesions. *J. Chemother.* **2016**, *28*, 383−389.
(166) Kargar, M.; Chang, Y.-R.; Khalili Hoseinabad, H.; Pruden, A.; Ducker, W. A. Colloidal Crystals Delay Formation of Early Stage Bacterial Biofilms. *ACS Biomater. Sci. Eng.* **2016**, *2*, 1039−1048.
(167) Pascual, G.; Sotomayor, S.; Rodríguez, M.; Pérez-Köhler, B.; Kühnhardt, A.; Fernández-Gutiérrez, M.; San Román, J.; Bellón, J. M. Cytotoxicity of Cyanoacrylate-Based Tissue Adhesives and Short-Term Preclinical In Vivo Biocompatibility in Abdominal Hernia Repair. *PLoS One* **2016**, *11*, No. e0157920.
(168) Li, Y.; Li, G.; Chen, Y.; Zhao, X.; Wang, Y.; Liu, J.; Li, Z. Gradient Modulus Tissue Adhesive Composite for Dynamic Wound Closure. *Adv. Funct. Mater.* **2022**, *32*, 2207306.
(169) Kelly, B. A.; Chowienczyk, P. Vascular Compliance. In *An Introduction to Vascular Biology: From Basic Science to Clinical Practice*; Halliday, A. W., Hunt, B. J., Poston, L., Schachter, M., Eds.; Cambridge University Press: Cambridge, 2002; pp 33−48.
(170) Abbott, W. M.; Megerman, J.; Hasson, J. E.; L'Italien, G.; Warnock, D. F. Effect of Compliance Mismatch on Vascular Graft Patency. *J. Vasc. Surg.* **1987**, *5*, 376−382.
(171) Zhou, J.; Fung, Y. C. The Degree of Nonlinearity and Anisotropy of Blood Vessel Elasticity. *Proc. Natl. Acad. Sci. U. S. A.* **1997**, *94*, 14255−14260.
(172) Bhupathi, S. S.; Chalasani, S.; Rokey, R. Stiff Heart Syndrome. *Clin. Med. Res.* **2011**, *9*, 92−99.
(173) Lang, N.; Pereira, M. J.; Lee, Y.; Friehs, I.; Vasilyev, N. V.; Feins, E. N.; Ablasser, K.; O'Cearbhaill, E. D.; Xu, C.; Fabozzo, A.; Padera, R.; Wasserman, S.; Freudenthal, F.; Ferreira, L. S.; Langer, R.; Karp, J. M.; del Nido, P. J. A Blood-Resistant Surgical Glue for Minimally Invasive Repair of Vessels and Heart Defects. *Sci. Transl. Med.* **2014**, *6*, 218ra6.
(174) Kurzawski, J.; Janion-Sadowska, A.; Sadowski, M. A Novel Minimally Invasive Method of Successful Tissue Glue Injection in Patients with Iatrogenic Pseudoaneurysm. *Br. J. Radiol.* **2018**, *91*, 20170538.
(175) Zhou, F.; Yang, Y.; Zhang, W.; Liu, S.; Shaikh, A. B.; Yang, L.; Lai, Y.; Ouyang, H.; Zhu, W. Bioinspired, Injectable, Tissue-Adhesive and Antibacterial Hydrogel for Multiple Tissue Regeneration by Minimally Invasive Therapy. *Appl. Mater. Today* **2022**, *26*, 101290.
(176) Mei, X.; Li, J.; Wang, Z.; Zhu, D.; Huang, K.; Hu, S.; Popowski, K. D.; Cheng, K. An Inhaled Bioadhesive Hydrogel to Shield Non-

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

Human Primates from SARS-CoV-2 Infection. *Nat. Mater.* **2023**, *22*, 903.
(177) Song, R.; Murphy, M.; Li, C.; Ting, K.; Soo, C.; Zheng, Z. Current Development of Biodegradable Polymeric Materials for Biomedical Applications. *Drug Des. Devel. Ther.* **2018**, *12*, 3117−3145.
(178) Tamariz, E.; Rios-Ramírez, A.; Tamariz, E.; Rios-Ramírez, A. Biodegradation of Medical Purpose Polymeric Materials and Their Impact on Biocompatibility. In *Biodegradation - Life of Science*; IntechOpen, 2013.
(179) Brugmans, M. C. P.; Söntjens, S. H. M.; Cox, M. A. J.; Nandakumar, A.; Bosman, A. W.; Mes, T.; Janssen, H. M.; Bouten, C. V. C.; Baaijens, F. P. T.; Driessen-Mol, A. Hydrolytic and Oxidative Degradation of Electrospun Supramolecular Biomaterials: In Vitro Degradation Pathways. *Acta Biomater.* **2015**, *27*, 21−31.
(180) Williams, D. F.; Zhong, S. P. Biodeterioration/Biodegradation of Polymeric Medical Devices in Situ. *Int. Biodeterior. Biodegrad.* **1994**, *34*, 95−130.
(181) Santerre, J. P.; Woodhouse, K.; Laroche, G.; Labow, R. S. Understanding the Biodegradation of Polyurethanes: From Classical Implants to Tissue Engineering Materials. *Biomaterials* **2005**, *26*, 7457−7470.
(182) Azevedo, H. S.; Reis, R. L. Enzymatic Degradation of Biodegradable Polymers and Strategies to Control Their Degradation Rate. *Biodegrad. Syst. Tissue Eng. Regen. Med.* **2004**, 177−200.
(183) Santerre, J. P.; Labow, R. S.; Duguay, D. G.; Erfle, D.; Adams, G. A. Biodegradation Evaluation of Polyether and Polyester-Urethanes with Oxidative and Hydrolytic Enzymes. *J. Biomed. Mater. Res.* **1994**, *28*, 1187−1199.
(184) Crippa, S.; Salvia, R.; Falconi, M.; Butturini, G.; Landoni, L.; Bassi, C. Anastomotic Leakage in Pancreatic Surgery. *HPB* **2007**, *9*, 8−15.
(185) Tian, F.; Appert, H. E.; Howard, J. M. The Disintegration of Absorbable Suture Materials on Exposure to Human Digestive Juices: An Update. *Am. Surg.* **1994**, *60*, 287−291.
(186) Leggat, P. A.; Smith, D. R.; Kedjarune, U. Surgical Applications of Cyanoacrylate Adhesives: A Review of Toxicity. *ANZ. J. Surg.* **2007**, *77*, 209−213.
(187) Peppas, N. A.; Hilt, J. Z.; Khademhosseini, A.; Langer, R. Hydrogels in Biology and Medicine: From Molecular Principles to Bionanotechnology. *Adv. Mater.* **2006**, *18*, 1345−1360.
(188) Hoffman, A. S. Hydrogels for Biomedical Applications. *Adv. Drug Delivery Rev.* **2012**, *64*, 18−23.
(189) Sahariah, P.; Másson, M. Antimicrobial Chitosan and Chitosan Derivatives: A Review of the Structure-Activity Relationship. *Biomacromolecules* **2017**, *18*, 3846−3868.
(190) Jackson, M. R. Fibrin Sealants in Surgical Practice: An Overview. *Am. J. Surg.* **2001**, *182*, S1−S7.
(191) Nomori, H.; Horio, H.; Morinaga, S.; Suemasu, K. Gelatin-Resorcinol-Formaldehyde-Glutaraldehyde Glue for Sealing Pulmonary Air Leaks during Thoracoscopic Operation. *Ann. Thorac. Surg.* **1999**, *67*, 212−216.
(192) Liu, Y.; Cheong NG, S.; Yu, J.; Tsai, W.-B. Modification and Crosslinking of Gelatin-Based Biomaterials as Tissue Adhesives. *Colloids Surf. B Biointerfaces* **2019**, *174*, 316−323.
(193) Braunwald, N. S.; Gay, W.; Tatooles, C. J. Evaluation of Crosslinked Gelatin as a Tissue Adhesive and Hemostatic Agent: An Experimental Study. *Surgery* **1966**, *59*, 1024−1030.
(194) Naomi, R.; Bahari, H.; Ridzuan, P. M.; Othman, F. Natural-Based Biomaterial for Skin Wound Healing (Gelatin vs. Collagen): Expert Review. *Polymers* **2021**, *13*, 2319.
(195) Radosevich, M.; Goubran, H. A.; Burnouf, T. Fibrin Sealant: Scientific Rationale, Production Methods, Properties, and Current Clinical Use. *Vox Sang.* **1997**, *72*, 133−143.
(196) Spotnitz, W. D. Fibrin Sealant: The Only Approved Hemostat, Sealant, and Adhesive—a Laboratory and Clinical Perspective. *Int. Sch. Res. Not.* **2014**, *2014*, No. e203943.
(197) Kjaergard, H. K.; Velada, J. L.; Pedersen, J. H.; Fleron, H.; Hollingsbee, D. A. Comparative Kinetics of Polymerisation of Three Fibrin Sealants and Influence on Timing of Tissue Adhesion. *Thromb. Res.* **2000**, *98*, 221−228.
(198) Laurent, T. C.; Laurent, U. B.; Fraser, J. R. E. The Structure and Function of Hyaluronan: An Overview. *Immunol. Cell Biol.* **1996**, *74*, a1−a7.
(199) Hintze, V.; Schnabelrauch, M.; Rother, S. Chemical Modification of Hyaluronan and Their Biomedical Applications. *Front. Chem.* **2022**, *10*, 830671.
(200) Zhou, D.; Li, S.; Pei, M.; Yang, H.; Gu, S.; Tao, Y.; Ye, D.; Zhou, Y.; Xu, W.; Xiao, P. Dopamine-Modified Hyaluronic Acid Hydrogel Adhesives with Fast-Forming and High Tissue Adhesion. *ACS Appl. Mater. Interfaces* **2020**, *12*, 18225−18234.
(201) Li, M.; Shi, X.; Yang, B.; Qin, J.; Han, X.; Peng, W.; He, Y.; Mao, H.; Kong, D.; Gu, Z. Single-Component Hyaluronic Acid Hydrogel Adhesive Based on Phenylboronic Ester Bonds for Hemostasis and Wound Closure. *Carbohydr. Polym.* **2022**, *296*, 119953.
(202) Lee, K. Y.; Mooney, D. J. Alginate: Properties and Biomedical Applications. *Prog. Polym. Sci.* **2012**, *37*, 106−126.
(203) Reakasame, S.; Boccaccini, A. R. Oxidized Alginate-Based Hydrogels for Tissue Engineering Applications: A Review. *Biomacromolecules* **2018**, *19*, 3−21.
(204) M. Ways, T. M.; Lau, W. M.; Khutoryanskiy, V. V. Chitosan and Its Derivatives for Application in Mucoadhesive Drug Delivery Systems. *Polymers* **2018**, *10*, 267.
(205) Yilmaz Atay, H. Antibacterial Activity of Chitosan-Based Systems. *Funct. Chitosan* **2019**, 457−489.
(206) Maia, J.; Evangelista, M. B.; Gil, H.; Ferreira, L. Dextran-Based Materials for Biomedical Applications. In *Carbohydrates Applications in Medicine*; Gil, M. H., Ed.; Research Signpost, 2014; pp 31−53.
(207) Balakrishnan, B.; Soman, D.; Payanam, U.; Laurent, A.; Labarre, D.; Jayakrishnan, A. A Novel Injectable Tissue Adhesive Based on Oxidized Dextran and Chitosan. *Acta Biomater.* **2017**, *53*, 343−354.
(208) Agnol, L. D.; Dias, F. T. G.; Nicoletti, N. F.; Marinowic, D.; Moura E Silva, S.; Marcos-Fernandez, A.; Falavigna, A.; Bianchi, O. Polyurethane Tissue Adhesives for Annulus Fibrosus Repair: Mechanical Restoration and Cytotoxicity. *J. Biomater. Appl.* **2019**, *34*, 673−686.
(209) Wendels, S.; Balahura, R.; Dinescu, S.; Costache, M.; Avérous, L. Synthesis and Properties of Biobased Polyurethane Tissue Adhesives from Bacterial Polyester. *Sustain. Mater. Technol.* **2022**, *34*, No. e00515.
(210) Balcioğlu, S.; Parlakpınar, H.; Vardi, N.; Denkbas, E.; Karaaslan, M.; Gulgen, S.; Taslidere, E.; Köytepe, S.; Ates, B. Design of Xylose-Based Semisynthetic Polyurethane Tissue Adhesives with Enhanced Bioactivity Properties. *ACS Appl. Mater. Interfaces* **2016**, *8*, 4456.
(211) Zdrahala, R. J.; Zdrahala, I. J. Biomedical Applications of Polyurethanes: A Review of Past Promises, Present Realities, and a Vibrant Future. *J. Biomater. Appl.* **1999**, *14*, 67−90.
(212) Thakur, S.; Hu, J.; Thakur, S.; Hu, J. Polyurethane: A Shape Memory Polymer (SMP). In *Aspects of Polyurethanes*; IntechOpen, 2017.
(213) Hassan, C. M.; Peppas, N. A. Structure and Morphology of Freeze/Thawed PVA Hydrogels. *Macromolecules* **2000**, *33*, 2472−2479.
(214) Stammen, J. A.; Williams, S.; Ku, D. N.; Guldberg, R. E. Mechanical Properties of a Novel PVA Hydrogel in Shear and Unconfined Compression. *Biomaterials* **2001**, *22*, 799.
(215) Chen, X.; Taguchi, T. Enhanced Skin Adhesive Property of Hydrophobically Modified Poly(Vinyl Alcohol) Films. *ACS Omega* **2020**, *5*, 1519−1527.
(216) Daristotle, J. L.; Erdi, M.; Lau, L. W.; Zaki, S. T.; Srinivasan, P.; Balabhadrapatruni, M.; Ayyub, O. B.; Sandler, A. D.; Kofinas, P. Biodegradable, Tissue Adhesive Polyester Blends for Safe, Complete Wound Healing. *ACS Biomater. Sci. Eng.* **2021**, *7*, 3908−3916.
(217) Zhang, R.; Bures, M.; Höffler, H.-K.; Zinne, N.; Länger, F.; Bisdas, T.; Haverich, A.; Krüger, M. TissuePatch™ as a Novel Synthetic Sealant for Repair of Superficial Lung Defect: In Vitro Tests Results. *Ann. Surg. Innov. Res.* **2012**, *6*, 12.

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

(218) Shea, L. Comparison of TissuePatch3 with Other Commonly Used Surgical Sealants. *Adhesive Sealant Biomaterials Technical Bulletin*; 2009.
(219) Chen, M. H.; Wang, L. L.; Chung, J. J.; Kim, Y.-H.; Atluri, P.; Burdick, J. A. Methods To Assess Shear-Thinning Hydrogels for Application As Injectable Biomaterials. *ACS Biomater. Sci. Eng.* **2017**, *3*, 3146−3160.
(220) Lapomarda, A.; Pulidori, E.; Cerqueni, G.; Chiesa, I.; De Blasi, M.; Geven, M. A.; Montemurro, F.; Duce, C.; Mattioli-Belmonte, M.; Tiné, M. R.; Vozzi, G.; De Maria, C. Pectin as Rheology Modifier of a Gelatin-Based Biomaterial Ink. *Materials* **2021**, *14*, 3109.
(221) Pang, Y.; Liu, J.; Moussa, Z. L.; Collins, J. E.; McDonnell, S.; Hayward, A. M.; Jajoo, K.; Langer, R.; Traverso, G. Endoscopically Injectable Shear-Thinning Hydrogels Facilitating Polyp Removal. *Adv. Sci.* **2019**, *6*, 1901041.
(222) El Sayad, M.; Noureddine, H. Recent Advances of Hemorrhage Management in Severe Trauma. *Emerg. Med. Int.* **2014**, *2014*, No. e638956.
(223) Guo, B.; Dong, R.; Liang, Y.; Li, M. Haemostatic Materials for Wound Healing Applications. *Nat. Rev. Chem.* **2021**, *5*, 773−791.
(224) Kim, K.; Ryu, J. H.; Koh, M.-Y.; Yun, S. P.; Kim, S.; Park, J. P.; Jung, C.-W.; Lee, M. S.; Seo, H.-I.; Kim, J. H.; Lee, H. Coagulopathy-Independent, Bioinspired Hemostatic Materials: A Full Research Story from Preclinical Models to a Human Clinical Trial. *Sci. Adv.* **2021**, *7*, No. eabc9992.
(225) Kanazawa, R.; Sato, S.; Iwamoto, N.; Teramoto, A. Allergic Reaction Following Arachnoid Plasty with a Fibrin Sealant. *Neurol. Med. Chir. (Tokyo)* **2010**, *50*, 608−610.
(226) Radwan-Pragłowska, J.; Piątkowski, M.; Deineka, V.; Janus, Ł.; Korniienko, V.; Husak, E.; Holubnycha, V.; Liubchak, I.; Zhurba, V.; Sierakowska, A.; Pogorielov, M.; Bogdał, D. Chitosan-Based Bioactive Hemostatic Agents with Antibacterial Properties—Synthesis and Characterization. *Molecules* **2019**, *24*, 2629.
(227) Leonhardt, E. E.; Kang, N.; Hamad, M. A.; Wooley, K. L.; Elsabahy, M. Absorbable Hemostatic Hydrogels Comprising Composites of Sacrificial Templates and Honeycomb-like Nanofibrous Mats of Chitosan. *Nat. Commun.* **2019**, *10*, 2307.
(228) Lan, G.; Lu, B.; Wang, T.; Wang, L.; Chen, J.; Yu, K.; Liu, J.; Dai, F.; Wu, D. Chitosan/Gelatin Composite Sponge Is an Absorbable Surgical Hemostatic Agent. *Colloids Surf. B Biointerfaces* **2015**, *136*, 1026−1034.
(229) Ibne Mahbub, M. S.; Sultana, T.; Gwon, J.-G.; Lee, B.-T. Fabrication of Thrombin Loaded TEMPO-Oxidized Cellulose Nanofiber-Gelatin Sponges and Their Hemostatic Behavior in Rat Liver Hemorrhage Model. *J. Biomater. Sci. Polym. Ed.* **2022**, *33*, 499−516.
(230) Zhou, Y.; Ma, X.; Li, Z.; Wang, B. Efficacy, Safety, and Physicochemical Properties of a Flowable Hemostatic Agent Made from Absorbable Gelatin Sponge via Vacuum Pressure Steam Sterilization. *J. Biomater. Appl.* **2021**, *35*, 776−789.
(231) Chen, J.; Ai, J.; Chen, S.; Xu, Z.; Lin, J.; Liu, H.; Chen, Q. Synergistic Enhancement of Hemostatic Performance of Mesoporous Silica by Hydrocaffeic Acid and Chitosan. *Int. J. Biol. Macromol.* **2019**, *139*, 1203−1211.
(232) Lu, D.; Wang, H.; Wang, X.; Li, Y.; Guo, H.; Sun, S.; Zhao, X.; Yang, Z.; Lei, Z. Biomimetic Chitosan-Graft-Polypeptides for Improved Adhesion in Tissue and Metal. *Carbohydr. Polym.* **2019**, *215*, 20−28.
(233) Wu, Z.; Zhou, W.; Deng, W.; Xu, C.; Cai, Y.; Wang, X. Antibacterial and Hemostatic Thiol-Modified Chitosan-Immobilized AgNPs Composite Sponges. *ACS Appl. Mater. Interfaces* **2020**, *12*, 20307−20320.
(234) Farndale, R. W.; Sixma, J. J.; Barnes, M. J.; De Groot, P. G. The Role of Collagen in Thrombosis and Hemostasis. *J. Thromb. Haemost.* **2004**, *2*, 561−573.
(235) Shin, M.; Park, S.-G.; Oh, B.-C.; Kim, K.; Jo, S.; Lee, M. S.; Oh, S. S.; Hong, S.-H.; Shin, E.-C.; Kim, K.-S.; Kang, S.-W.; Lee, H. Complete Prevention of Blood Loss with Self-Sealing Haemostatic Needles. *Nat. Mater.* **2017**, *16*, 147−152.
(236) Ghobril, C.; Grinstaff, M. W. The Chemistry and Engineering of Polymeric Hydrogel Adhesives for Wound Closure: A Tutorial. *Chem. Soc. Rev.* **2015**, *44*, 1820−1835.
(237) Kamoun, E. A.; Kenawy, E.-R. S.; Chen, X. A Review on Polymeric Hydrogel Membranes for Wound Dressing Applications: PVA-Based Hydrogel Dressings. *J. Adv. Res.* **2017**, *8*, 217−233.
(238) George, B.; Bhatia, N.; Kumar, A.; A., G.; R., T.; S. K., S.; Vadakkadath Meethal, K.; T. M., S.; T. V., S. Bioinspired Gelatin Based Sticky Hydrogel for Diverse Surfaces in Burn Wound Care. *Sci. Rep.* **2022**, *12*, 13735.
(239) Dong, Y.; Li, Y.; Fan, B.; Peng, W.; Qian, W.; Ji, X.; Gan, D.; Liu, P. Long-Term Antibacterial, Antioxidative, and Bioadhesive Hydrogel Wound Dressing for Infected Wound Healing Applications. *Biomater. Sci.* **2023**, *11*, 2080−2090.
(240) Pham, T.-N.; Jiang, Y.-S.; Su, C.-F.; Jan, J.-S. In Situ Formation of Silver Nanoparticles-Contained Gelatin-PEG-Dopamine Hydrogels via Enzymatic Cross-Linking Reaction for Improved Antibacterial Activities. *Int. J. Biol. Macromol.* **2020**, *146*, 1050−1059.
(241) Ke, X.; Dong, Z.; Tang, S.; Chu, W.; Zheng, X.; Zhen, L.; Chen, X.; Ding, C.; Luo, J.; Li, J. A Natural Polymer Based Bioadhesive with Self-Healing Behavior and Improved Antibacterial Properties. *Biomater. Sci.* **2020**, *8*, 4346−4357.
(242) Hwang, I.; Kim, H. N.; Seong, M.; Lee, S.-H.; Kang, M.; Yi, H.; Bae, W. G.; Kwak, M. K.; Jeong, H. E. Multifunctional Smart Skin Adhesive Patches for Advanced Health Care. *Adv. Healthc. Mater.* **2018**, *7*, 1800275.
(243) Britto, E. J.; Nezwek, T. A.; Popowicz, P.; Robins, M. Wound Dressings. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, 2023.
(244) Sanders, L.; Nagatomi, J. Clinical Applications of Surgical Adhesives and Sealants. *Crit. Rev. Biomed. Eng.* **2014**, *42*, 271−292.
(245) Chen, X.; Rogers, J. A.; Lacour, S. P.; Hu, W.; Kim, D.-H. Materials Chemistry in Flexible Electronics. *Chem. Soc. Rev.* **2019**, *48*, 1431−1433.
(246) Huang, S.; Liu, Y.; Zhao, Y.; Ren, Z.; Guo, C. F. Flexible Electronics: Stretchable Electrodes and Their Future. *Adv. Funct. Mater.* **2019**, *29*, 1805924.
(247) Gao, W.; Ota, H.; Kiriya, D.; Takei, K.; Javey, A. Flexible Electronics toward Wearable Sensing. *Acc. Chem. Res.* **2019**, *52*, 523−533.
(248) Ray, T. R.; Choi, J.; Bandodkar, A. J.; Krishnan, S.; Gutruf, P.; Tian, L.; Ghaffari, R.; Rogers, J. A. Bio-Integrated Wearable Systems: A Comprehensive Review. *Chem. Rev.* **2019**, *119*, 5461−5533.
(249) Yuk, H.; Wu, J.; Zhao, X. Hydrogel Interfaces for Merging Humans and Machines. *Nat. Rev. Mater.* **2022**, *7*, 935−952.
(250) Kim, D.-H.; Lu, N.; Ma, R.; Kim, Y.-S.; Kim, R.-H.; Wang, S.; Wu, J.; Won, S. M.; Tao, H.; Islam, A.; Yu, K. J.; Kim, T.; Chowdhury, R.; Ying, M.; Xu, L.; Li, M.; Chung, H.-J.; Keum, H.; McCormick, M.; Liu, P.; Zhang, Y.-W.; Omenetto, F. G.; Huang, Y.; Coleman, T.; Rogers, J. A. Epidermal Electronics. *Science* **2011**, *333*, 838−843.
(251) Kim, T.; Park, J.; Sohn, J.; Cho, D.; Jeon, S. Bioinspired, Highly Stretchable, and Conductive Dry Adhesives Based on 1D-2D Hybrid Carbon Nanocomposites for All-in-One ECG Electrodes. *ACS Nano* **2016**, *10*, 4770−4778.
(252) Wang, X.; Sun, X.; Gan, D.; Soubrier, M.; Chiang, H.-Y.; Yan, L.; Li, Y.; Li, J.; Yu, S.; Xia, Y.; Wang, K.; Qin, Q.; Jiang, X.; Han, L.; Pan, T.; Xie, C.; Lu, X. Bioadhesive and Conductive Hydrogel-Integrated Brain-Machine Interfaces for Conformal and Immune-Evasive Contact with Brain Tissue. *Matter* **2022**, *5*, 1204−1223.
(253) Ding, L.; Hang, C.; Yang, S.; Qi, J.; Dong, R.; Zhang, Y.; Sun, H.; Jiang, X. In Situ Deposition of Skin-Adhesive Liquid Metal Particles with Robust Wear Resistance for Epidermal Electronics. *Nano Lett.* **2022**, *22*, 4482−4490.
(254) Koh, A.; Kang, D.; Xue, Y.; Lee, S.; Pielak, R. M.; Kim, J.; Hwang, T.; Min, S.; Banks, A.; Bastien, P.; et al. A Soft, Wearable Microfluidic Device for the Capture, Storage, and Colorimetric Sensing of Sweat. *Sci. Transl. Med.* **2016**, *8*, 366ra165−366ra165.
(255) Wang, Z.; Luan, J.; Seth, A.; Liu, L.; You, M.; Gupta, P.; Rathi, P.; Wang, Y.; Cao, S.; Jiang, Q.; Zhang, X.; Gupta, R.; Zhou, Q.;

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

Morrissey, J. J.; Scheller, E. L.; Rudra, J. S.; Singamaneni, S. Microneedle Patch for the Ultrasensitive Quantification of Protein Biomarkers in Interstitial Fluid. *Nat. Biomed. Eng.* **2021**, *5*, 64−76.
(256) Thomas, N.; Lähdesmäki, I.; Parviz, B. A. A Contact Lens with an Integrated Lactate Sensor. *Sens. Actuators B Chem.* **2012**, *162*, 128−134.
(257) Tseng, P.; Napier, B.; Garbarini, L.; Kaplan, D. L.; Omenetto, F. G. Functional, RF-Trilayer Sensors for Tooth-Mounted, Wireless Monitoring of the Oral Cavity and Food Consumption. *Adv. Mater.* **2018**, *30*, 1703257.
(258) Jung, H.; Kim, M. K.; Lee, J. Y.; Choi, S. W.; Kim, J. Adhesive Hydrogel Patch with Enhanced Strength and Adhesiveness to Skin for Transdermal Drug Delivery. *Adv. Funct. Mater.* **2020**, *30*, 2004407.
(259) Ziesmer, J.; Tajpara, P.; Hempel, N.-J.; Ehrström, M.; Melican, K.; Eidsmo, L.; Sotiriou, G. A. Vancomycin-Loaded Microneedle Arrays against Methicillin-Resistant Staphylococcus Aureus Skin Infections. *Adv. Mater. Technol.* **2021**, *6*, 2001307.
(260) Lathuilière, A.; Cosson, S.; Lutolf, M. P.; Schneider, B. L.; Aebischer, P. A High-Capacity Cell Macroencapsulation System Supporting the Long-Term Survival of Genetically Engineered Allogeneic Cells. *Biomaterials* **2014**, *35*, 779−791.
(261) Choi, M.; Choi, J. W.; Kim, S.; Nizamoglu, S.; Hahn, S. K.; Yun, S. H. Light-Guiding Hydrogels for Cell-Based Sensing and Optogenetic Synthesis in Vivo. *Nat. Photonics* **2013**, *7*, 987−994.
(262) Yamagishi, K.; Kirino, I.; Takahashi, I.; Amano, H.; Takeoka, S.; Morimoto, Y.; Fujie, T. Tissue-Adhesive Wirelessly Powered Optoelectronic Device for Metronomic Photodynamic Cancer Therapy. *Nat. Biomed. Eng.* **2019**, *3*, 27−36.
(263) Barrios, C. A. Pressure Sensitive Adhesive Tape: A Versatile Material Platform for Optical Sensors. *Sensors* **2020**, *20*, 5303.
(264) Wang, C.; Chen, X.; Wang, L.; Makihata, M.; Liu, H.-C.; Zhou, T.; Zhao, X. Bioadhesive Ultrasound for Long-Term Continuous Imaging of Diverse Organs. *Science* **2022**, *377*, 517−523.
(265) Hu, H.; Ma, Y.; Gao, X.; Song, D.; Li, M.; Huang, H.; Qian, X.; Wu, R.; Shi, K.; Ding, H.; et al. Stretchable Ultrasonic Arrays for the Three-Dimensional Mapping of the Modulus of Deep Tissue. *Nat. Biomed. Eng.* **2023**, *7*, 1321.
(266) Lin, M.; Zhang, Z.; Gao, X.; Bian, Y.; Wu, R. S.; Park, G.; Lou, Z.; Zhang, Z.; Xu, X.; Chen, X.; et al. A Fully Integrated Wearable Ultrasound System to Monitor Deep Tissues in Moving Subjects. *Nat. Biotechnol.* **2023**, 1−10.
(267) Nam, S.; Seo, B. R.; Najibi, A. J.; McNamara, S. L.; Mooney, D. J. Active Tissue Adhesive Activates Mechanosensors and Prevents Muscle Atrophy. *Nat. Mater.* **2023**, *22*, 249.
(268) Reeder, J. T.; Xie, Z.; Yang, Q.; Seo, M.-H.; Yan, Y.; Deng, Y.; Jinkins, K. R.; Krishnan, S. R.; Liu, C.; McKay, S.; et al. Soft, Bioresorbable Coolers for Reversible Conduction Block of Peripheral Nerves. *Science* **2022**, *377*, 109−115.
(269) Schwartz, A. R.; Bennett, M. L.; Smith, P. L.; De Backer, W.; Hedner, J.; Boudewyns, A.; Van de Heyning, P.; Ejnell, H.; Hochban, W.; Knaack, L. P.; et al. Therapeutic Electrical Stimulation of the Hypoglossal Nerve in Obstructive Sleep Apnea. *Arch. Otolaryngol. Neck Surg.* **2001**, *127*, 1216−1223.
(270) Rutten, W. L. C. Selective Electrical Interfaces with the Nervous System. *Annu. Rev. Biomed. Eng.* **2002**, *4*, 407−452.
(271) Trohman, R. G.; Kim, M. H.; Pinski, S. L. Cardiac Pacing: The State of the Art. *Lancet* **2004**, *364*, 1701−1719.
(272) Chen, J. D. Z.; Yin, J.; Wei, W. Electrical Therapies for Gastrointestinal Motility Disorders. *Expert Rev. Gastroenterol. Hepatol.* **2017**, *11*, 407−418.
(273) Kellaway, P. The Part Played by Electric Fish in the Early History of Bioelectricity and Electrotherapy. *Bull. Hist. Med.* **1946**, *20*, 112−137.
(274) Jünger, M.; Arnold, A.; Zuder, D.; Stahl, H.-W.; Heising, S. Local Therapy and Treatment Costs of Chronic, Venous Leg Ulcers with Electrical Stimulation (Dermapulse): A Prospective, Placebo Controlled, Double Blind Trial. *Wound Repair Regen. Off. Publ. Wound Heal. Soc. Eur. Tissue Repair Soc.* **2008**, *16*, 480−487.
(275) Li, Z.; Feng, H.; Zheng, Q.; Li, H.; Zhao, C.; Ouyang, H.; Noreen, S.; Yu, M.; Su, F.; Liu, R.; Li, L.; Wang, Z. L.; Li, Z. Photothermally Tunable Biodegradation of Implantable Triboelectric Nanogenerators for Tissue Repairing. *Nano Energy* **2018**, *54*, 390−399.
(276) Nazari-Vanani, R.; Vafaiee, M.; Asadian, E.; Mohammadpour, R.; Rafii-Tabar, H.; Sasanpour, P. Enhanced Proliferation and Migration of Fibroblast Cells by Skin-Attachable and Self-Cleaning Triboelectric Nanogenerator. *Biomater. Adv.* **2023**, *149*, 213364.
(277) Reilly, J. P. *Applied Bioelectricity: From Electrical Stimulation to Electropathology*; Springer Science & Business Media, 2012.
(278) Reilly, J. P.; Antoni, H. *Electrical Stimulation and Electropathology*; Cambridge University Press, 1992.
(279) Meng, X.; Xiao, X.; Jeon, S.; Kim, D.; Park, B.-J.; Kim, Y.-J.; Rubab, N.; Kim, S.; Kim, S.-W. An Ultrasound-Driven Bioadhesive Triboelectric Nanogenerator for Instant Wound Sealing and Electrically Accelerated Healing in Emergencies. *Adv. Mater.* **2023**, *35*, 2209054.
(280) Wang, C.; Jiang, X.; Kim, H.-J.; Zhang, S.; Zhou, X.; Chen, Y.; Ling, H.; Xue, Y.; Chen, Z.; Qu, M. A.; et al. Flexible Patch with Printable and Antibacterial Conductive Hydrogel Electrodes for Accelerated Wound Healing. *Biomaterials* **2022**, *285*, 121479.
(281) Wang, C.; Wang, C.; Huang, Z.; Xu, S. Materials and Structures toward Soft Electronics. *Adv. Mater.* **2018**, *30*, 1801368.
(282) Zhang, Y.; Tao, T. H. Skin-Friendly Electronics for Acquiring Human Physiological Signatures. *Adv. Mater.* **2019**, *31*, 1905767.
(283) Ma, Y.; Zhang, Y.; Cai, S.; Han, Z.; Liu, X.; Wang, F.; Cao, Y.; Wang, Z.; Li, H.; Chen, Y.; Feng, X. Flexible Hybrid Electronics for Digital Healthcare. *Adv. Mater.* **2020**, *32*, 1902062.
(284) Wang, C.; He, K.; Li, J.; Chen, X. Conformal Electrodes for On-Skin Digitalization. *SmartMat* **2021**, *2*, 252−262.
(285) Keplinger, C.; Sun, J.-Y.; Foo, C. C.; Rothemund, P.; Whitesides, G. M.; Suo, Z. Stretchable, Transparent, Ionic Conductors. *Science* **2013**, *341*, 984−987.
(286) Pitsalidis, C.; Pappa, A.-M.; Boys, A. J.; Fu, Y.; Moysidou, C.-M.; van Niekerk, D.; Saez, J.; Savva, A.; Iandolo, D.; Owens, R. M. Organic Bioelectronics for In Vitro Systems. *Chem. Rev.* **2022**, *122*, 4700−4790.
(287) Xu, F.; Zhu, Y. Highly Conductive and Stretchable Silver Nanowire Conductors. *Adv. Mater.* **2012**, *24*, 5117−5122.
(288) Kramer, R. K.; Majidi, C.; Wood, R. J. Masked Deposition of Gallium-Indium Alloys for Liquid-Embedded Elastomer Conductors. *Adv. Funct. Mater.* **2013**, *23*, 5292−5296.
(289) Wang, Y.; Zhu, C.; Pfattner, R.; Yan, H.; Jin, L.; Chen, S.; Molina-Lopez, F.; Lissel, F.; Liu, J.; Rabiah, N. I.; Chen, Z.; Chung, J. W.; Linder, C.; Toney, M. F.; Murmann, B.; Bao, Z. A Highly Stretchable, Transparent, and Conductive Polymer. *Sci. Adv.* **2017**, *3*, No. e1602076.
(290) Choi, G. M.; Lim, S.-M.; Lee, Y.-Y.; Yi, S.-M.; Lee, Y.-J.; Sun, J.-Y.; Joo, Y.-C. PEDOT:PSS/Polyacrylamide Nanoweb: Highly Reliable Soft Conductors with Swelling Resistance. *ACS Appl. Mater. Interfaces* **2019**, *11*, 10099−10107.
(291) Choi, C.; Lee, Y.; Cho, K. W.; Koo, J. H.; Kim, D.-H. Wearable and Implantable Soft Bioelectronics Using Two-Dimensional Materials. *Acc. Chem. Res.* **2019**, *52*, 73−81.
(292) Xue, Z.; Song, H.; Rogers, J. A.; Zhang, Y.; Huang, Y. Mechanically-Guided Structural Designs in Stretchable Inorganic Electronics. *Adv. Mater.* **2020**, *32*, 1902254.
(293) Wang, S.; Li, M.; Wu, J.; Kim, D.-H.; Lu, N.; Su, Y.; Kang, Z.; Huang, Y.; Rogers, J. A. Mechanics of Epidermal Electronics. *J. Appl. Mech.* **2012**, *79*, 031022.
(294) Yeo, W.-H.; Kim, Y.-S.; Lee, J.; Ameen, A.; Shi, L.; Li, M.; Wang, S.; Ma, R.; Jin, S. H.; Kang, Z.; Huang, Y.; Rogers, J. A. Multifunctional Epidermal Electronics Printed Directly Onto the Skin. *Adv. Mater.* **2013**, *25*, 2773−2778.
(295) Wang, L.; Lu, N. Conformability of a Thin Elastic Membrane Laminated on a Soft Substrate With Slightly Wavy Surface. *J. Appl. Mech.* **2016**, *83*, 041007.
(296) Xu, B.; Akhtar, A.; Liu, Y.; Chen, H.; Yeo, W.-H.; Park, S. I.; Boyce, B.; Kim, H.; Yu, J.; Lai, H.-Y.; Jung, S.; Zhou, Y.; Kim, J.; Cho, S.; Huang, Y.; Bretl, T.; Rogers, J. A. An Epidermal Stimulation and

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

Sensing Platform for Sensorimotor Prosthetic Control, Management of Lower Back Exertion, and Electrical Muscle Activation. *Adv. Mater.* **2016**, *28*, 4462−4471.
(297) Kabiri Ameri, S.; Ho, R.; Jang, H.; Tao, L.; Wang, Y.; Wang, L.; Schnyer, D. M.; Akinwande, D.; Lu, N. Graphene Electronic Tattoo Sensors. *ACS Nano* **2017**, *11*, 7634−7641.
(298) Wang, Y.; Qiu, Y.; Ameri, S. K.; Jang, H.; Dai, Z.; Huang, Y.; Lu, N. Low-Cost, Mm-Thick, Tape-Free Electronic Tattoo Sensors with Minimized Motion and Sweat Artifacts. *Npj Flex. Electron.* **2018**, *2*, 1−7.
(299) Gong, S.; Yap, L. W.; Zhu, B.; Zhai, Q.; Liu, Y.; Lyu, Q.; Wang, K.; Yang, M.; Ling, Y.; Lai, D. T. H.; Marzbanrad, F.; Cheng, W. Local Crack-Programmed Gold Nanowire Electronic Skin Tattoos for In-Plane Multisensor Integration. *Adv. Mater.* **2019**, *31*, 1903789.
(300) Alberto, J.; Leal, C.; Fernandes, C.; Lopes, P. A.; Paisana, H.; de Almeida, A. T.; Tavakoli, M. Fully Untethered Battery-Free Biomonitoring Electronic Tattoo with Wireless Energy Harvesting. *Sci. Rep.* **2020**, *10*, 5539.
(301) Gogurla, N.; Kim, Y.; Cho, S.; Kim, J.; Kim, S. Multifunctional and Ultrathin Electronic Tattoo for On-Skin Diagnostic and Therapeutic Applications. *Adv. Mater.* **2021**, *33*, 2008308.
(302) Gan, D.; Huang, Z.; Wang, X.; Jiang, L.; Wang, C.; Zhu, M.; Ren, F.; Fang, L.; Wang, K.; Xie, C.; Lu, X. Graphene Oxide-Templated Conductive and Redox-Active Nanosheets Incorporated Hydrogels for Adhesive Bioelectronics. *Adv. Funct. Mater.* **2020**, *30*, 1907678.
(303) Liang, S.; Zhang, Y.; Wang, H.; Xu, Z.; Chen, J.; Bao, R.; Tan, B.; Cui, Y.; Fan, G.; Wang, W.; Wang, W.; Liu, W. Paintable and Rapidly Bondable Conductive Hydrogels as Therapeutic Cardiac Patches. *Adv. Mater.* **2018**, *30*, 1704235.
(304) Deng, Z.; Wang, H.; Ma, P. X.; Guo, B. Self-Healing Conductive Hydrogels: Preparation, Properties and Applications. *Nanoscale* **2020**, *12*, 1224−1246.
(305) Lu, Y.; Liu, Z.; Yan, H.; Peng, Q.; Wang, R.; Barkey, M. E.; Jeon, J.-W.; Wujcik, E. K. Ultrastretchable Conductive Polymer Complex as a Strain Sensor with a Repeatable Autonomous Self-Healing Ability. *ACS Appl. Mater. Interfaces* **2019**, *11*, 20453−20464.
(306) Han, L.; Yan, L.; Wang, K.; Fang, L.; Zhang, H.; Tang, Y.; Ding, Y.; Weng, L.-T.; Xu, J.; Weng, J.; Liu, Y.; Ren, F.; Lu, X. Tough, Self-Healable and Tissue-Adhesive Hydrogel with Tunable Multifunctionality. *NPG Asia Mater.* **2017**, *9*, No. e372.
(307) Bandodkar, A. J.; Wang, J. Non-Invasive Wearable Electrochemical Sensors: A Review. *Trends Biotechnol.* **2014**, *32*, 363−371.
(308) Bariya, M.; Nyein, H. Y. Y.; Javey, A. Wearable Sweat Sensors. *Nat. Electron.* **2018**, *1*, 160−171.
(309) Luo, Y.; Abidian, M. R.; Ahn, J.-H.; Akinwande, D.; Andrews, A. M.; Antonietti, M.; Bao, Z.; Berggren, M.; Berkey, C. A.; Bettinger, C. J.; et al. Technology Roadmap for Flexible Sensors. *ACS Nano* **2023**, *17*, 5211−5295.
(310) Zhao, J.; Guo, H.; Li, J.; Bandodkar, A. J.; Rogers, J. A. Body-Interfaced Chemical Sensors for Noninvasive Monitoring and Analysis of Biofluids. *Trends Chem.* **2019**, *1*, 559−571.
(311) Miller, P. R.; Skoog, S. A.; Edwards, T. L.; Wheeler, D. R.; Xiao, X.; Brozik, S. M.; Polsky, R.; Narayan, R. J. Hollow Microneedle-Based Sensor for Multiplexed Transdermal Electrochemical Sensing. *J. Vis. Exp. JoVE* **2012**, No. 64, 4067.
(312) Samant, P. P.; Prausnitz, M. R. Mechanisms of Sampling Interstitial Fluid from Skin Using a Microneedle Patch. *Proc. Natl. Acad. Sci. U. S. A.* **2018**, *115*, 4583−4588.
(313) Bollella, P.; Sharma, S.; Cass, A. E. G.; Antiochia, R. Microneedle-Based Biosensor for Minimally-Invasive Lactate Detection. *Biosens. Bioelectron.* **2019**, *123*, 152−159.
(314) Li, J.; Lu, H.; Wang, Y.; Yang, S.; Zhang, Y.; Wei, W.; Qiao, Y.; Dai, W.; Ge, R.; Dong, H. Interstitial Fluid Biomarkers' Minimally Invasive Monitoring Using Microneedle Sensor Arrays. *Anal. Chem.* **2022**, *94*, 968−974.
(315) Mitragotri, S.; Coleman, M.; Kost, J.; Langer, R. Analysis of Ultrasonically Extracted Interstitial Fluid as a Predictor of Blood Glucose Levels. *J. Appl. Physiol.* **2000**, *89*, 961−966.
(316) Lee, H.; Choi, T. K.; Lee, Y. B.; Cho, H. R.; Ghaffari, R.; Wang, L.; Choi, H. J.; Chung, T. D.; Lu, N.; Hyeon, T.; Choi, S. H.; Kim, D.-H. A Graphene-Based Electrochemical Device with Thermoresponsive Microneedles for Diabetes Monitoring and Therapy. *Nat. Nanotechnol.* **2016**, *11*, 566−572.
(317) Green, A.; Dodds, P.; Pennock, C. A Study of Sweat Sodium and Chloride; Criteria for the Diagnosis of Cystic Fibrosis. *Ann. Clin. Biochem.* **1985**, *22*, 171−174.
(318) Torrente-Rodríguez, R. M.; Tu, J.; Yang, Y.; Min, J.; Wang, M.; Song, Y.; Yu, Y.; Xu, C.; Ye, C.; IsHak, W. W.; Gao, W. Investigation of Cortisol Dynamics in Human Sweat Using a Graphene-Based Wireless mHealth System. *Matter* **2020**, *2*, 921−937.
(319) Kim, J.; Sempionatto, J. R.; Imani, S.; Hartel, M. C.; Barfidokht, A.; Tang, G.; Campbell, A. S.; Mercier, P. P.; Wang, J. Simultaneous Monitoring of Sweat and Interstitial Fluid Using a Single Wearable Biosensor Platform. *Adv. Sci.* **2018**, *5*, 1800880.
(320) Gao, W.; Emaminejad, S.; Nyein, H. Y. Y.; Challa, S.; Chen, K.; Peck, A.; Fahad, H. M.; Ota, H.; Shiraki, H.; Kiriya, D.; Lien, D.-H.; Brooks, G. A.; Davis, R. W.; Javey, A. Fully Integrated Wearable Sensor Arrays for Multiplexed in Situ Perspiration Analysis. *Nature* **2016**, *529*, 509−514.
(321) Rose, D. P.; Ratterman, M. E.; Griffin, D. K.; Hou, L.; Kelley-Loughnane, N.; Naik, R. R.; Hagen, J. A.; Papautsky, I.; Heikenfeld, J. C. Adhesive RFID Sensor Patch for Monitoring of Sweat Electrolytes. *IEEE Trans. Biomed. Eng.* **2015**, *62*, 1457−1465.
(322) Hansen, D.; Zajforoushan Moghaddam, S.; Eiler, J.; Hansen, K.; Thormann, E. Performance of Polymeric Skin Adhesives during Perspiration. *ACS Appl. Polym. Mater.* **2020**, *2*, 1535−1542.
(323) Nyein, H. Y. Y.; Tai, L.-C.; Ngo, Q. P.; Chao, M.; Zhang, G. B.; Gao, W.; Bariya, M.; Bullock, J.; Kim, H.; Fahad, H. M.; Javey, A. A Wearable Microfluidic Sensing Patch for Dynamic Sweat Secretion Analysis. *ACS Sens.* **2018**, *3*, 944−952.
(324) Miyamoto, A.; Lee, S.; Cooray, N. F.; Lee, S.; Mori, M.; Matsuhisa, N.; Jin, H.; Yoda, L.; Yokota, T.; Itoh, A.; Sekino, M.; Kawasaki, H.; Ebihara, T.; Amagai, M.; Someya, T. Inflammation-Free, Gas-Permeable, Lightweight, Stretchable on-Skin Electronics with Nanomeshes. *Nat. Nanotechnol.* **2017**, *12*, 907−913.
(325) Yang, X.; Li, L.; Wang, S.; Lu, Q.; Bai, Y.; Sun, F.; Li, T.; Li, Y.; Wang, Z.; Zhao, Y.; Shi, Y.; Zhang, T. Ultrathin, Stretchable, and Breathable Epidermal Electronics Based on a Facile Bubble Blowing Method. *Adv. Electron. Mater.* **2020**, *6*, 2000306.
(326) Min, H.; Baik, S.; Kim, J.; Lee, J.; Bok, B.-G.; Song, J. H.; Kim, M.-S.; Pang, C. Tough Carbon Nanotube-Implanted Bioinspired Three-Dimensional Electrical Adhesive for Isotropically Stretchable Water-Repellent Bioelectronics. *Adv. Funct. Mater.* **2022**, *32*, 2107285.
(327) Bollella, P.; Sharma, S.; Cass, A. E. G.; Tasca, F.; Antiochia, R. Minimally Invasive Glucose Monitoring Using a Highly Porous Gold Microneedles-Based Biosensor: Characterization and Application in Artificial Interstitial Fluid. *Catalysts* **2019**, *9*, 580.
(328) Madden, J.; O'Mahony, C.; Thompson, M.; O'Riordan, A.; Galvin, P. Biosensing in Dermal Interstitial Fluid Using Microneedle Based Electrochemical Devices. *Sens. Bio-Sens. Res.* **2020**, *29*, 100348.
(329) Yi, K.; Wang, Y.; Shi, K.; Chi, J.; Lyu, J.; Zhao, Y. Aptamer-Decorated Porous Microneedles Arrays for Extraction and Detection of Skin Interstitial Fluid Biomarkers. *Biosens. Bioelectron.* **2021**, *190*, 113404.
(330) Kaufman, E.; Lamster, I. B. Analysis of Saliva for Periodontal Diagnosis. *J. Clin. Periodontol.* **2000**, *27*, 453−465.
(331) Pfaffe, T.; Cooper-White, J.; Beyerlein, P.; Kostner, K.; Punyadeera, C. Diagnostic Potential of Saliva: Current State and Future Applications. *Clin. Chem.* **2011**, *57*, 675−687.
(332) Lee, Y.-H.; Wong, D. T. Saliva: An Emerging Biofluid for Early Detection of Diseases. *Am. J. Dent.* **2009**, *22*, 241−248.
(333) Kim, J.; Valdés-Ramírez, G.; Bandodkar, A. J.; Jia, W.; Martinez, A. G.; Ramírez, J.; Mercier, P.; Wang, J. Non-Invasive Mouthguard Biosensor for Continuous Salivary Monitoring of Metabolites. *Analyst* **2014**, *139*, 1632−1636.
(334) Kim, J.; Imani, S.; de Araujo, W. R.; Warchall, J.; Valdés-Ramírez, G.; Paixão, T. R. L. C.; Mercier, P. P.; Wang, J. Wearable Salivary Uric Acid Mouthguard Biosensor with Integrated Wireless Electronics. *Biosens. Bioelectron.* **2015**, *74*, 1061−1068.

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

(335) Arakawa, T.; Kuroki, Y.; Nitta, H.; Chouhan, P.; Toma, K.; Sawada, S.; Takeuchi, S.; Sekita, T.; Akiyoshi, K.; Minakuchi, S.; Mitsubayashi, K. Mouthguard Biosensor with Telemetry System for Monitoring of Saliva Glucose: A Novel Cavitas Sensor. *Biosens. Bioelectron.* **2016**, *84*, 106−111.
(336) Perdigão, J.; Frankenberger, R.; Rosa, B. T.; Breschi, L. New Trends in Dentin/Enamel Adhesion. *Am. J. Dent.* **2000**, *13*, 25D−30D.
(337) Matsunaga, S.; Tamura, A.; Fushimi, M.; Santa, H.; Arisaka, Y.; Nikaido, T.; Tagami, J.; Yui, N. Light-Embrittled Dental Resin Cements Containing Photodegradable Polyrotaxane Cross-Linkers for Attenuating Debonding Strength. *ACS Appl. Polym. Mater.* **2020**, *2*, 5756−5766.
(338) Hu, S.; Pei, X.; Duan, L.; Zhu, Z.; Liu, Y.; Chen, J.; Chen, T.; Ji, P.; Wan, Q.; Wang, J. A Mussel-Inspired Film for Adhesion to Wet Buccal Tissue and Efficient Buccal Drug Delivery. *Nat. Commun.* **2021**, *12*, 1689.
(339) Zhu, T.; Yu, X.; Yi, X.; Guo, X.; Li, L.; Hao, Y.; Wang, W. Lidocaine-Loaded Hyaluronic Acid Adhesive Microneedle Patch for Oral Mucosal Topical Anesthesia. *Pharmaceutics* **2022**, *14*, 686.
(340) Caffarel-Salvador, E.; Kim, S.; Soares, V.; Tian, R. Y.; Stern, S. R.; Minahan, D.; Yona, R.; Lu, X.; Zakaria, F. R.; Collins, J.; Wainer, J.; Wong, J.; McManus, R.; Tamang, S.; McDonnell, S.; Ishida, K.; Hayward, A.; Liu, X.; Hubálek, F.; Fels, J.; Vegge, A.; Frederiksen, M. R.; Rahbek, U.; Yoshitake, T.; Fujimoto, J.; Roxhed, N.; Langer, R.; Traverso, G. A Microneedle Platform for Buccal Macromolecule Delivery. *Sci. Adv.* **2021**, *7*, No. eabe2620.
(341) Hagan, S.; Martin, E.; Enríquez-de-Salamanca, A. Tear Fluid Biomarkers in Ocular and Systemic Disease: Potential Use for Predictive, Preventive and Personalised Medicine. *EPMA J.* **2016**, *7*, 15.
(342) Yu, L.; Yang, Z.; An, M. Lab on the Eye: A Review of Tear-Based Wearable Devices for Medical Use and Health Management. *Biosci. Trends* **2019**, *13*, 308−313.
(343) Sempionatto, J. R.; Brazaca, L. C.; García-Carmona, L.; Bolat, G.; Campbell, A. S.; Martin, A.; Tang, G.; Shah, R.; Mishra, R. K.; Kim, J.; Zucolotto, V.; Escarpa, A.; Wang, J. Eyeglasses-Based Tear Biosensing System: Non-Invasive Detection of Alcohol, Vitamins and Glucose. *Biosens. Bioelectron.* **2019**, *137*, 161−170.
(344) Xu, J.; Tao, X.; Liu, X.; Yang, L. Wearable Eye Patch Biosensor for Noninvasive and Simultaneous Detection of Multiple Biomarkers in Human Tears. *Anal. Chem.* **2022**, *94*, 8659−8667.
(345) Hayashi, T. T.; Fatt, I. Forces Retaining a Contact Lens on the Eye between Blinks. *Am. J. Optom. Physiol. Opt.* **1980**, *57*, 485−507.
(346) Musgrave, C. S. A.; Fang, F. Contact Lens Materials: A Materials Science Perspective. *Materials* **2019**, *12*, 261.
(347) Farandos, N. M.; Yetisen, A. K.; Monteiro, M. J.; Lowe, C. R.; Yun, S. H. Contact Lens Sensors in Ocular Diagnostics. *Adv. Healthc. Mater.* **2015**, *4*, 792−810.
(348) Yao, H.; Shum, A. J.; Cowan, M.; Lähdesmäki, I.; Parviz, B. A. A Contact Lens with Embedded Sensor for Monitoring Tear Glucose Level. *Biosens. Bioelectron.* **2011**, *26*, 3290−3296.
(349) Ascaso, F. J.; Huerva, V. Noninvasive Continuous Monitoring of Tear Glucose Using Glucose-Sensing Contact Lenses. *Optom. Vis. Sci.* **2016**, *93*, 426.
(350) Yao, H.; Liao, Y.; Lingley, A. R.; Afanasiev, A.; Lähdesmäki, I.; Otis, B. P.; Parviz, B. A. A Contact Lens with Integrated Telecommunication Circuit and Sensors for Wireless and Continuous Tear Glucose Monitoring. *J. Micromechanics Microengineering* **2012**, *22*, 075007.
(351) Kim, J.; Kim, M.; Lee, M.-S.; Kim, K.; Ji, S.; Kim, Y.-T.; Park, J.; Na, K.; Bae, K.-H.; Kyun Kim, H.; Bien, F.; Young Lee, C.; Park, J.-U. Wearable Smart Sensor Systems Integrated on Soft Contact Lenses for Wireless Ocular Diagnostics. *Nat. Commun.* **2017**, *8*, 14997.
(352) Park, J.; Kim, J.; Kim, S.-Y.; Cheong, W. H.; Jang, J.; Park, Y.-G.; Na, K.; Kim, Y.-T.; Heo, J. H.; Lee, C. Y.; Lee, J. H.; Bien, F.; Park, J.-U. Soft, Smart Contact Lenses with Integrations of Wireless Circuits, Glucose Sensors, and Displays. *Sci. Adv.* **2018**, *4*, No. eaap9841.
(353) Xie, M.; Yao, G.; Zhang, T.; Wang, Q.; Mo, X.; Dong, Q.; Lou, W.; Lu, F.; Pan, T.; Gao, M.; Jiang, D.; Zhao, K.; Lin, Y. Multifunctional Flexible Contact Lens for Eye Health Monitoring Using Inorganic Magnetic Oxide Nanosheets. *J. Nanobiotechnology* **2022**, *20*, 202.
(354) Senior, M. Novartis Signs up for Google Smart Lens. *Nat. Biotechnol.* **2014**, *32*, 856−856.
(355) Yang, X.; Yao, H.; Zhao, G.; Ameer, G. A.; Sun, W.; Yang, J.; Mi, S. Flexible, Wearable Microfluidic Contact Lens with Capillary Networks for Tear Diagnostics. *J. Mater. Sci.* **2020**, *55*, 9551−9561.
(356) Langer, R. Drug Delivery and Targeting. *Nature* **1998**, *392*, 5−10.
(357) Graham, N. B.; McNeill, M. E. Hydrogels for Controlled Drug Delivery. *Biomaterials* **1984**, *5*, 27−36.
(358) Qiu, Y.; Park, K. Environment-Sensitive Hydrogels for Drug Delivery. *Adv. Drug Delivery Rev.* **2001**, *53*, 321−339.
(359) Bhattarai, N.; Gunn, J.; Zhang, M. Chitosan-Based Hydrogels for Controlled, Localized Drug Delivery. *Adv. Drug Delivery Rev.* **2010**, *62*, 83−99.
(360) Xu, J.; Strandman, S.; Zhu, J. X. X.; Barralet, J.; Cerruti, M. Genipin-Crosslinked Catechol-Chitosan Mucoadhesive Hydrogels for Buccal Drug Delivery. *Biomaterials* **2015**, *37*, 395−404.
(361) das Neves, J.; Bahia, M. F. Gels as Vaginal Drug Delivery Systems. *Int. J. Pharm.* **2006**, *318*, 1−14.
(362) Mirani, B.; Pagan, E.; Currie, B.; Siddiqui, M. A.; Hosseinzadeh, R.; Mostafalu, P.; Zhang, Y. S.; Ghahary, A.; Akbari, M. An Advanced Multifunctional Hydrogel-Based Dressing for Wound Monitoring and Drug Delivery. *Adv. Healthc. Mater.* **2017**, *6*, 1700718.
(363) Livnat, M.; Beyar, R.; Seliktar, D. Endoluminal Hydrogel Films Made of Alginate and Polyethylene Glycol: Physical Characteristics and Drug-Eluting Properties. *J. Biomed. Mater. Res., Part A* **2005**, *75A*, 710−722.
(364) Alvarez-Lorenzo, C.; Anguiano-Igea, S.; Varela-García, A.; Vivero-Lopez, M.; Concheiro, A. Bioinspired Hydrogels for Drug-Eluting Contact Lenses. *Acta Biomater.* **2019**, *84*, 49−62.
(365) Kim, Y. E.; Jung, H. Y.; Park, N.; Kim, J. Adhesive Composite Hydrogel Patch for Sustained Transdermal Drug Delivery To Treat Atopic Dermatitis. *Chem. Mater.* **2023**, *35*, 1209−1217.
(366) Chen, J.; Wang, D.; Wang, L.-H.; Liu, W.; Chiu, A.; Shariati, K.; Liu, Q.; Wang, X.; Zhong, Z.; Webb, J.; Schwartz, R. E.; Bouklas, N.; Ma, M. An Adhesive Hydrogel with "Load-Sharing" Effect as Tissue Bandages for Drug and Cell Delivery. *Adv. Mater.* **2020**, *32*, 2001628.
(367) Wright, Z. M.; Holt, B. D.; Sydlik, S. A. Covalently-Controlled Drug Delivery via Therapeutic Methacrylic Tissue Adhesives. *J. Mater. Chem. B* **2017**, *5*, 7743−7755.
(368) Kakinoki, S.; Taguchi, T. Antitumor Effect of an Injectable In-Situ Forming Drug Delivery System Composed of a Novel Tissue Adhesive Containing Doxorubicin Hydrochloride. *Eur. J. Pharm. Biopharm.* **2007**, *67*, 676−681.
(369) Lurtz, C.; Voss, K.; Hahn, V.; Schauer, F.; Wegmann, J.; Odermatt, E. K.; Schmitz, K.-P.; Sternberg, K. In Vitro Degradation and Drug Release of a Biodegradable Tissue Adhesive Based on Functionalized 1,2-Ethylene Glycol Bis(Dilactic Acid) and Chitosan. *J. Mater. Sci. Mater. Med.* **2013**, *24*, 667−678.
(370) Zhang, M.; An, H.; Gu, Z.; Huang, Z.; Zhang, F.; Wen, Y.; Zhang, P. Mimosa-Inspired Stimuli-Responsive Curling Bioadhesive Tape Promotes Peripheral Nerve Regeneration. *Adv. Mater.* **2023**, *35*, 2212015.
(371) Freedman, B. R.; Kuttler, A.; Beckmann, N.; Nam, S.; Kent, D.; Schuleit, M.; Ramazani, F.; Accart, N.; Rock, A.; Li, J.; Kurz, M.; Fisch, A.; Ullrich, T.; Hast, M. W.; Tinguely, Y.; Weber, E.; Mooney, D. J. Enhanced Tendon Healing by a Tough Hydrogel with an Adhesive Side and High Drug-Loading Capacity. *Nat. Biomed. Eng.* **2022**, *6*, 1167−1179.
(372) Li, J.; Mooney, D. J. Designing Hydrogels for Controlled Drug Delivery. *Nat. Rev. Mater.* **2016**, *1*, 1−17.
(373) Lin, C.-C.; Metters, A. T. Hydrogels in Controlled Release Formulations: Network Design and Mathematical Modeling. *Adv. Drug Delivery Rev.* **2006**, *58*, 1379−1408.
(374) Bagherifard, S.; Tamayol, A.; Mostafalu, P.; Akbari, M.; Comotto, M.; Annabi, N.; Ghaderi, M.; Sonkusale, S.; Dokmeci, M. R.; Khademhosseini, A. Dermal Patch with Integrated Flexible Heater for on Demand Drug Delivery. *Adv. Healthc. Mater.* **2016**, *5*, 175−184.

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118

(375) Lee, J. W.; Park, J.-H.; Prausnitz, M. R. Dissolving Microneedles for Transdermal Drug Delivery. *Biomaterials* **2008**, *29*, 2113−2124.
(376) Daly, A. C.; Riley, L.; Segura, T.; Burdick, J. A. Hydrogel Microparticles for Biomedical Applications. *Nat. Rev. Mater.* **2020**, *5*, 20−43.
(377) Liu, W.; Wang, Y.; Wang, J.; Lanier, O. L.; Wechsler, M. E.; Peppas, N. A.; Gu, Z. Macroencapsulation Devices for Cell Therapy. *Engineering* **2022**, *13*, 53−70.
(378) Orive, G.; Santos, E.; Poncelet, D.; Hernández, R. M.; Pedraz, J. L.; Wahlberg, L. U.; De Vos, P.; Emerich, D. Cell Encapsulation: Technical and Clinical Advances. *Trends Pharmacol. Sci.* **2015**, *36*, 537−546.
(379) Song, S.; Roy, S. Progress and Challenges in Macroencapsulation Approaches for Type 1 Diabetes (T1D) Treatment: Cells, Biomaterials, and Devices. *Biotechnol. Bioeng.* **2016**, *113*, 1381−1402.
(380) Wang, L.-H.; Ernst, A. U.; An, D.; Datta, A. K.; Epel, B.; Kotecha, M.; Ma, M. A Bioinspired Scaffold for Rapid Oxygenation of Cell Encapsulation Systems. *Nat. Commun.* **2021**, *12*, 5846.
(381) Yun, S. H.; Kwok, S. J. J. Light in Diagnosis, Therapy and Surgery. *Nat. Biomed. Eng.* **2017**, *1*, 0008.
(382) Lee, G.-H.; Moon, H.; Kim, H.; Lee, G. H.; Kwon, W.; Yoo, S.; Myung, D.; Yun, S. H.; Bao, Z.; Hahn, S. K. Multifunctional Materials for Implantable and Wearable Photonic Healthcare Devices. *Nat. Rev. Mater.* **2020**, *5*, 149−165.
(383) Zhi, D.; Yang, T.; O'Hagan, J.; Zhang, S.; Donnelly, R. F. Photothermal Therapy. *J. Controlled Release* **2020**, *325*, 52−71.
(384) Huang, X.; Jain, P. K.; El-Sayed, I. H.; El-Sayed, M. A. Plasmonic Photothermal Therapy (PPTT) Using Gold Nanoparticles. *Lasers Med. Sci.* **2008**, *23*, 217−228.
(385) Dolmans, D. E. J. G. J.; Fukumura, D.; Jain, R. K. Photodynamic Therapy for Cancer. *Nat. Rev. Cancer* **2003**, *3*, 380−387.
(386) Ong, F. L. L.; Loh, C. H.; Oh, C. C. Wearable Devices for Photodynamic Therapy - A Systematic Review. *JAAD Int.* **2023**, *11*, 59−62.
(387) Hamblin, M. R. Mechanisms and Applications of the Anti-Inflammatory Effects of Photobiomodulation. *AIMS Biophys.* **2017**, *4*, 337−361.
(388) Williams, J. C.; Denison, T. From Optogenetic Technologies to Neuromodulation Therapies. *Sci. Transl. Med.* **2013**, *5*, 177ps6−177ps6.
(389) Pan, J.; Zhang, Z.; Jiang, C.; Zhang, L.; Tong, L. A Multifunctional Skin-like Wearable Optical Sensor Based on an Optical Micro-/Nanofibre. *Nanoscale* **2020**, *12*, 17538−17544.
(390) Tariq, R.; Khalid, U. A.; Kanwal, S.; Adnan, F.; Qasim, M. Photodynamic Therapy: A Rational Approach Toward COVID-19 Management. *J. Explor. Res. Pharmacol.* **2021**, *6*, 44−52.
(391) Park, S. I.; Brenner, D. S.; Shin, G.; Morgan, C. D.; Copits, B. A.; Chung, H. U.; Pullen, M. Y.; Noh, K. N.; Davidson, S.; Oh, S. J.; et al. Soft, Stretchable, Fully Implantable Miniaturized Optoelectronic Systems for Wireless Optogenetics. *Nat. Biotechnol.* **2015**, *33*, 1280−1286.
(392) Nizamoglu, S.; Gather, M. C.; Humar, M.; Choi, M.; Kim, S.; Kim, K. S.; Hahn, S. K.; Scarcelli, G.; Randolph, M.; Redmond, R. W.; Yun, S. H. Bioabsorbable Polymer Optical Waveguides for Deep-Tissue Photomedicine. *Nat. Commun.* **2016**, *7*, 10374.
(393) Parker, S. T.; Domachuk, P.; Amsden, J.; Bressner, J.; Lewis, J. A.; Kaplan, D. L.; Omenetto, F. G. Biocompatible Silk Printed Optical Waveguides. *Adv. Mater.* **2009**, *21*, 2411−2415.
(394) Shan, D.; Zhang, C.; Kalaba, S.; Mehta, N.; Kim, G. B.; Liu, Z.; Yang, J. Flexible Biodegradable Citrate-Based Polymeric Step-Index Optical Fiber. *Biomaterials* **2017**, *143*, 142−148.
(395) Dupuis, A.; Guo, N.; Gao, Y.; Godbout, N.; Lacroix, S.; Dubois, C.; Skorobogatiy, M. Prospective for Biodegradable Microstructured Optical Fibers. *Opt. Lett.* **2007**, *32*, 109−111.
(396) Feng, J.; Zheng, Y.; Bhusari, S.; Villiou, M.; Pearson, S.; del Campo, A. Printed Degradable Optical Waveguides for Guiding Light into Tissue. *Adv. Funct. Mater.* **2020**, *30*, 2004327.
(397) Chen, G.; Hou, K.; Yu, N.; Wei, P.; Chen, T.; Zhang, C.; Wang, S.; Liu, H.; Cao, R.; Zhu, L.; Hsiao, B. S.; Zhu, M. Temperature-Adaptive Hydrogel Optical Waveguide with Soft Tissue-Affinity for Thermal Regulated Interventional Photomedicine. *Nat. Commun.* **2022**, *13*, 7789.
(398) Jeong, S.-H.; Lee, M.-G.; Kim, C.-C.; Park, J.; Baek, Y.; Park, B. I.; Doh, J.; Sun, J.-Y. An Implantable Ionic Therapeutic Platform for Photodynamic Therapy with Wireless Capacitive Power Transfer. *Mater. Horiz.* **2023**, *10*, 2215.
(399) Jain, A.; Yang, A. H. J.; Erickson, D. Gel-Based Optical Waveguides with Live Cell Encapsulation and Integrated Microfluidics. *Opt. Lett.* **2012**, *37*, 1472−1474.
(400) Missinne, J.; Kalathimekkad, S.; Van Hoe, B.; Bosman, E.; Vanfleteren, J.; Van Steenberge, G. Stretchable Optical Waveguides. *Opt. Express* **2014**, *22*, 4168−4179.
(401) Sykes, E. A.; Albanese, A.; Chan, W. C. W. Implantable Waveguides. *Nat. Photonics* **2013**, *7*, 940−941.
(402) Kinsey, J. H.; Cortese, D. A.; Neel, H. B. Thermal Considerations in Murine Tumor Killing Using Hematoporphyrin Derivative Phototherapy. *Cancer Res.* **1983**, *43*, 1562−1567.
(403) Horimatsu, T.; Muto, M.; Yoda, Y.; Yano, T.; Ezoe, Y.; Miyamoto, S.; Chiba, T. Tissue Damage in the Canine Normal Esophagus by Photoactivation with Talaporfin Sodium (Laserphyrin): A Preclinical Study. *PLoS One* **2012**, *7*, No. e38308.
(404) Lin, Y.; Bilotti, E.; Bastiaansen, C. W. M.; Peijs, T. Transparent Semi-Crystalline Polymeric Materials and Their Nanocomposites: A Review. *Polym. Eng. Sci.* **2020**, *60*, 2351−2376.
(405) Althues, H.; Henle, J.; Kaskel, S. Functional Inorganic Nanofillers for Transparent Polymers. *Chem. Soc. Rev.* **2007**, *36*, 1454.
(406) Tummala, G. K.; Rojas, R.; Mihranyan, A. Poly(Vinyl Alcohol) Hydrogels Reinforced with Nanocellulose for Ophthalmic Applications: General Characteristics and Optical Properties. *J. Phys. Chem. B* **2016**, *120*, 13094−13101.
(407) Takeoka, Y.; Asai, F.; Gao, G.; He, J.; Liu, S. Transparent and Mechanically High-Performance Soft Materials Consisting of Colloidal Building Blocks. *Acc. Mater. Res.* **2022**, *3*, 799−811.
(408) Protopappas, V. C.; Baga, D. A.; Fotiadis, D. I.; Likas, A. C.; Papachristos, A. A.; Malizos, K. N. An Ultrasound Wearable System for the Monitoring and Acceleration of Fracture Healing in Long Bones. *IEEE Trans. Biomed. Eng.* **2005**, *52*, 1597−1608.
(409) Yang, X.; Chen, Z.; Hettiarachchi, N.; Yan, J.; Liu, H. A Wearable Ultrasound System for Sensing Muscular Morphological Deformations. *IEEE Trans. Syst. Man Cybern. Syst.* **2021**, *51*, 3370−3379.
(410) Kenny, J.-É. S. Functional Hemodynamic Monitoring With a Wireless Ultrasound Patch. *J. Cardiothorac. Vasc. Anesth.* **2021**, *35*, 1509−1515.
(411) Wang, C.; Qi, B.; Lin, M.; Zhang, Z.; Makihata, M.; Liu, B.; Zhou, S.; Huang, Y.; Hu, H.; Gu, Y.; Chen, Y.; Lei, Y.; Lee, T.; Chien, S.; Jang, K.-I.; Kistler, E. B.; Xu, S. Continuous Monitoring of Deep-Tissue Haemodynamics with Stretchable Ultrasonic Phased Arrays. *Nat. Biomed. Eng.* **2021**, *5*, 749−758.
(412) Hu, H.; Huang, H.; Li, M.; Gao, X.; Yin, L.; Qi, R.; Wu, R. S.; Chen, X.; Ma, Y.; Shi, K.; et al. A Wearable Cardiac Ultrasound Imager. *Nature* **2023**, *613*, 667−675.
(413) Ginzel, E.; MacNEIL, R.; Ginzel, R.; Zuber, M.; Sinclar, A. N. Acoustic Properties of the Elastomeric Materials Aqualene™ and ACE™. *NDT E Int.* **2015**, 1.
(414) Yu, Y.; Yuk, H.; Parada, G. A.; Wu, Y.; Liu, X.; Nabzdyk, C. S.; Youcef-Toumi, K.; Zang, J.; Zhao, X. Multifunctional "Hydrogel Skins" on Diverse Polymers with Arbitrary Shapes. *Adv. Mater.* **2019**, *31*, 1807101.
(415) Mitragotri, S. Healing Sound: The Use of Ultrasound in Drug Delivery and Other Therapeutic Applications. *Nat. Rev. Drug Discovery* **2005**, *4*, 255−260.
(416) Miller, D.; Smith, N.; Bailey, M.; Czarnota, G.; Hynynen, K.; Makin, I. Overview of Therapeutic Ultrasound Applications and Safety Considerations. *J. Ultrasound Med. Off. J. Am. Inst. Ultrasound Med.* **2012**, *31*, 623−634.

(417) Winkler, S. L.; Urbisci, A. E.; Best, T. M. Sustained Acoustic Medicine for the Treatment of Musculoskeletal Injuries: A Systematic Review and Meta-Analysis. *BMC Sports Sci. Med. Rehabil.* **2021**, *13*, 159.
(418) Uddin, S. M. Z.; Komatsu, D. E.; Motyka, T.; Petterson, S. Low-Intensity Continuous Ultrasound Therapies—A Systematic Review of Current State-of-the-Art and Future Perspectives. *J. Clin. Med.* **2021**, *10*, 2698.
(419) Jarit, P.; Klyve, D.; Walters, R. Long Duration Sonophoresis of Diclofenac to Augment Rehabilitation of Common Musculoskeletal Injuries. *Glob. J. Orthop. Res.* **2023**, *4*, 584.
(420) Yang, Y.; Yuan, J.; Field, R. L.; Ye, D.; Hu, Z.; Xu, K.; Xu, L.; Gong, Y.; Yue, Y.; Kravitz, A. V.; Bruchas, M. R.; Cui, J.; Brestoff, J. R.; Chen, H. Induction of a Torpor-like Hypothermic and Hypometabolic State in Rodents by Ultrasound. *Nat. Metab.* **2023**, *5*, 789.
(421) Wang See, C.; Kim, T.; Zhu, D. Hernia Mesh and Hernia Repair: A Review. *Eng. Regen.* **2020**, *1*, 19−33.
(422) Nguyen-Truong, M.; Li, Y. V.; Wang, Z. Mechanical Considerations of Electrospun Scaffolds for Myocardial Tissue and Regenerative Engineering. *Bioengineering* **2020**, *7*, 122.
(423) Beldi, G.; Wagner, M.; Bruegger, L. E.; Kurmann, A.; Candinas, D. Mesh Shrinkage and Pain in Laparoscopic Ventral Hernia Repair: A Randomized Clinical Trial Comparing Suture versus Tack Mesh Fixation. *Surg. Endosc.* **2011**, *25*, 749−755.
(424) Karahasanoglu, T.; Onur, E.; Baca, B.; Hamzaoglu, I.; Pekmezci, S.; Boler, D. E.; Kilic, N.; Altug, T. Spiral Tacks May Contribute to Intra-Abdominal Adhesion Formation. *Surg. Today* **2004**, *34*, 860−864.
(425) Gungor, B.; Malazgirt, Z.; Topgül, K.; Gök, A.; Bilgin, M.; Yürüker, S. Comparative Evaluation of Adhesions to Intraperitoneally Placed Fixation Materials: A Laparoscopic Study in Rats. *Indian J. Surg.* **2010**, *72*, 475−480.
(426) Peach, G.; Tan, L. C. Small Bowel Obstruction and Perforation Due to a Displaced Spiral Tacker: A Rare Complication of Laparoscopic Inguinal Hernia Repair. *Hernia* **2008**, *12*, 303−305.
(427) Ben Yehuda, A.; Nyska, A.; Szold, A. Mesh Fixation Using Novel Bio-Adhesive Coating Compared to Tack Fixation for IPOM Hernia Repair: In Vivo Evaluation in a Porcine Model. *Surg. Endosc.* **2019**, *33*, 2364−2375.
(428) Lin, X.; Liu, Y.; Bai, A.; Cai, H.; Bai, Y.; Jiang, W.; Yang, H.; Wang, X.; Yang, L.; Sun, N.; Gao, H. A Viscoelastic Adhesive Epicardial Patch for Treating Myocardial Infarction. *Nat. Biomed. Eng.* **2019**, *3*, 632−643.
(429) Kuehlmann, B.; Bonham, C. A.; Zucal, I.; Prantl, L.; Gurtner, G. C. Mechanotransduction in Wound Healing and Fibrosis. *J. Clin. Med.* **2020**, *9*, 1423.
(430) Barnes, L. A.; Marshall, C. D.; Leavitt, T.; Hu, M. S.; Moore, A. L.; Gonzalez, J. G.; Longaker, M. T.; Gurtner, G. C. Mechanical Forces in Cutaneous Wound Healing: Emerging Therapies to Minimize Scar Formation. *Adv. Wound Care* **2018**, *7*, 47−56.
(431) Thompson, J. T.; Marks, M. W. Negative Pressure Wound Therapy. *Clin. Plast. Surg.* **2007**, *34*, 673−684.
(432) Gurtner, G. C.; Werner, S.; Barrandon, Y.; Longaker, M. T. Wound Repair and Regeneration. *Nature* **2008**, *453*, 314−321.
(433) Wong, V. W.; Beasley, B.; Zepeda, J.; Dauskardt, R. H.; Yock, P. G.; Longaker, M. T.; Gurtner, G. C. A Mechanomodulatory Device to Minimize Incisional Scar Formation. *Adv. Wound Care* **2013**, *2*, 185−194.
(434) Harn, H. I.-C.; Ogawa, R.; Hsu, C.-K.; Hughes, M. W.; Tang, M.-J.; Chuong, C.-M. The Tension Biology of Wound Healing. *Exp. Dermatol.* **2019**, *28*, 464−471.
(435) Blacklow, S. O.; Li, J.; Freedman, B. R.; Zeidi, M.; Chen, C.; Mooney, D. J. Bioinspired Mechanically Active Adhesive Dressings to Accelerate Wound Closure. *Sci. Adv.* **2019**, *5*, No. eaaw3963.
(436) Dolan, E. B.; Varela, C. E.; Mendez, K.; Whyte, W.; Levey, R. E.; Robinson, S. T.; Maye, E.; O'Dwyer, J.; Beatty, R.; Rothman, A.; et al. An Actuatable Soft Reservoir Modulates Host Foreign Body Response. *Sci. Robot.* **2019**, *4*, No. eaax7043.
(437) Whyte, W.; Goswami, D.; Wang, S. X.; Fan, Y.; Ward, N. A.; Levey, R. E.; Beatty, R.; Robinson, S. T.; Sheppard, D.; O'Connor, R.; et al. Dynamic Actuation Enhances Transport and Extends Therapeutic Lifespan in an Implantable Drug Delivery Platform. *Nat. Commun.* **2022**, *13*, 4496.
(438) Seo, B. R.; Payne, C. J.; McNamara, S. L.; Freedman, B. R.; Kwee, B. J.; Nam, S.; de Lázaro, I.; Darnell, M.; Alvarez, J. T.; Dellacherie, M. O.; Vandenburgh, H. H.; Walsh, C. J.; Mooney, D. J. Skeletal Muscle Regeneration with Robotic Actuation-Mediated Clearance of Neutrophils. *Sci. Transl. Med.* **2021**, *13*, No. eabe8868.
(439) Kung, R. T. V.; Rosenberg, M. Heart Booster: A Pericardial Support Device. *Ann. Thorac. Surg.* **1999**, *68*, 764−767.
(440) Kwon, M. H.; Cevasco, M.; Schmitto, J. D.; Chen, F. Y. Ventricular Restraint Therapy for Heart Failure: A Review, Summary of State of the Art, and Future Directions. *J. Thorac. Cardiovasc. Surg.* **2012**, *144*, 771−777.e1.
(441) Payne, C. J.; Wamala, I.; Bautista-Salinas, D.; Saeed, M.; Van Story, D.; Thalhofer, T.; Horvath, M. A.; Abah, C.; del Nido, P. J.; Walsh, C. J.; Vasilyev, N. V. Soft Robotic Ventricular Assist Device with Septal Bracing for Therapy of Heart Failure. *Sci. Robot.* **2017**, *2*, No. eaan6736.
(442) Zrinscak, D.; Lorenzon, L.; Maselli, M.; Cianchetti, M. Soft Robotics for Physical Simulators, Artificial Organs and Implantable Assistive Devices. *Prog. Biomed. Eng.* **2023**, *5*, 012002.
(443) Yang, X.; An, C.; Liu, S.; Cheng, T.; Bunpetch, V.; Liu, Y.; Dong, S.; Li, S.; Zou, X.; Li, T.; Ouyang, H.; Wu, Z.; Yang, W. Soft Artificial Bladder Detrusor. *Adv. Healthc. Mater.* **2018**, *7*, 1701014.
(444) Hu, L.; Bonnemain, J.; Saeed, M. Y.; Singh, M.; Quevedo Moreno, D.; Vasilyev, N. V.; Roche, E. T. An Implantable Soft Robotic Ventilator Augments Inspiration in a Pig Model of Respiratory Insufficiency. *Nat. Biomed. Eng.* **2023**, *7*, 110−123.
(445) Roche, E. T.; Horvath, M. A.; Wamala, I.; Alazmani, A.; Song, S.-E.; Whyte, W.; Machaidze, Z.; Payne, C. J.; Weaver, J. C.; Fishbein, G.; Kuebler, J.; Vasilyev, N. V.; Mooney, D. J.; Pigula, F. A.; Walsh, C. J. Soft Robotic Sleeve Supports Heart Function. *Sci. Transl. Med.* **2017**, *9*, No. eaaf3925.
(446) Horvath, M. A.; Varela, C. E.; Dolan, E. B.; Whyte, W.; Monahan, D. S.; Payne, C. J.; Wamala, I. A.; Vasilyev, N. V.; Pigula, F. A.; Mooney, D. J.; Walsh, C. J.; Duffy, G. P.; Roche, E. T. Towards Alternative Approaches for Coupling of a Soft Robotic Sleeve to the Heart. *Ann. Biomed. Eng.* **2018**, *46*, 1534−1547.
(447) Rutkove, S. B. Effects of Temperature on Neuromuscular Electrophysiology. *Muscle Nerve* **2001**, *24*, 867−882.
(448) Janssen, R. Thermal Influences on Nervous System Function. *Neurosci. Biobehav. Rev.* **1992**, *16*, 399−413.
(449) Borgdorff, P.; Versteeg, P. G. A. An Implantable Nerve Cooler for the Exercising Dog. *Eur. J. Appl. Physiol.* **1984**, *53*, 175−179.
(450) Paggi, V.; Akouissi, O.; Micera, S.; Lacour, S. P. Compliant Peripheral Nerve Interfaces. *J. Neural Eng.* **2021**, *18*, 031001.
(451) Jia, J.; Pollock, M. Cold Nerve Injury Is Enhanced by Intermittent Cooling. *Muscle Nerve* **1999**, *22*, 1644−1652.
(452) Tang, N.; Peng, Z.; Guo, R.; An, M.; Chen, X.; Li, X.; Yang, N.; Zang, J. Thermal Transport in Soft PAAm Hydrogels. *Polymers* **2017**, *9*, 688.
(453) Chung, H. U.; Kim, B. H.; Lee, J. Y.; Lee, J.; Xie, Z.; Ibler, E. M.; Lee, K.; Banks, A.; Jeong, J. Y.; Kim, J.; et al. Binodal, Wireless Epidermal Electronic Systems with in-Sensor Analytics for Neonatal Intensive Care. *Science* **2019**, *363*, No. eaau0780.
(454) Nurse, E. S.; Marlow, K.; Hennessy, P. J.; Knight-Sadler, R.; Nelson, T.; Freestone, D. R.; Slater, K. D.; Cook, M. J. Water-Soluble Adhesive for Stable Long-Term Ambulatory EEG Recordings. *Clin. Neurophysiol.* **2022**, *142*, 258−261.
(455) Lee, S. M.; Kim, J. H.; Byeon, H. J.; Choi, Y. Y.; Park, K. S.; Lee, S.-H. A Capacitive, Biocompatible and Adhesive Electrode for Long-Term and Cap-Free Monitoring of EEG Signals. *J. Neural Eng.* **2013**, *10*, 036006.
(456) Zhang, A.; Shyam, A. B.; Cunningham, A. M.; Williams, C.; Brissenden, A.; Bartley, A.; Amsden, B.; Docoslis, A.; Kontopoulou, M.; Ameri, S. K. Adhesive Wearable Sensors for Electroencephalography from Hairy Scalp. *Adv. Healthc. Mater.* **2023**, *12*, 2300142.
(457) Wang, C.; Wang, H.; Wang, B.; Miyata, H.; Wang, Y.; Nayeem, M. O. G.; Kim, J. J.; Lee, S.; Yokota, T.; Onodera, H.; Someya, T. On-

Skin Paintable Biogel for Long-Term High-Fidelity Electroencephalogram Recording. *Sci. Adv.* **2022**, *8*, No. eabo1396.
(458) Vujic, A.; Tong, S.; Picard, R.; Maes, P. Going with Our Guts: Potentials of Wearable Electrogastrography (EGG) for Affect Detection. In *Proceedings of the 2020 International Conference on Multimodal Interaction*; ICMI '20; Association for Computing Machinery: New York, 2020; pp 260−268.
(459) Kumar, G. P.; Prakash, S. O.; Sangeetha, B.; Asha, R.; Suganthi, L.; Divya, B. Wireless Real-Time Electrogastrography Monitoring System. *J. Comput. Theor. Nanosci.* **2020**, *17*, 3724−3732.
(460) Vujic, A.; Krause, C.; Tso, G.; Lin, J.; Han, B.; Maes, P. Gut-Brain Computer Interfacing (GBCI) : Wearable Monitoring of Gastric Myoelectric Activity. *Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.* **2019**, *2019*, 5886−5889.
(461) Grishin, A. A.; Moshonkina, T. R.; Solopova, I. A.; Gorodnichev, R. M.; Gerasimenko, Y. P. A Five-Channel Noninvasive Electrical Stimulator of the Spinal Cord for Rehabilitation of Patients with Severe Motor Disorders. *Biomed. Eng.* **2017**, *50*, 300−304.
(462) Kapadia, N.; Moineau, B.; Popovic, M. R. Functional Electrical Stimulation Therapy for Retraining Reaching and Grasping After Spinal Cord Injury and Stroke. *Front. Neurosci.* **2020**, *14*, 718.
(463) Song, J. W.; Ryu, H.; Bai, W.; Xie, Z.; Vázquez-Guardado, A.; Nandoliya, K.; Avila, R.; Lee, G.; Song, Z.; Kim, J.; et al. Bioresorbable, Wireless, and Battery-Free System for Electrotherapy and Impedance Sensing at Wound Sites. *Sci. Adv.* **2023**, *9*, No. eade4687.
(464) Sel, K.; Brown, A.; Jang, H.; Krumholz, H. M.; Lu, N.; Jafari, R. A Wrist-Worn Respiration Monitoring Device Using Bio-Impedance. In *2020 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)*; 2020; pp 3989−3993.
(465) Frerichs, I.; Vogt, B.; Wacker, J.; Paradiso, R.; Braun, F.; Rapin, M.; Caldani, L.; Chételat, O.; Weiler, N. Wearable Electrical Impedance Tomography for Chest Monitoring. *Eur. Respir. J.* **2020**, *56*, 015006.
(466) Groenendaal, W.; Lee, S.; van Hoof, C. van. Wearable Bioimpedance Monitoring: Viewpoint for Application in Chronic Conditions. *JMIR Biomed. Eng.* **2021**, *6*, No. e22911.
(467) Wang, M.; Yang, Y.; Min, J.; Song, Y.; Tu, J.; Mukasa, D.; Ye, C.; Xu, C.; Heflin, N.; McCune, J. S.; Hsiai, T. K.; Li, Z.; Gao, W. A Wearable Electrochemical Biosensor for the Monitoring of Metabolites and Nutrients. *Nat. Biomed. Eng.* **2022**, *6*, 1225−1235.
(468) Nyein, H. Y. Y.; Bariya, M.; Tran, B.; Ahn, C. H.; Brown, B. J.; Ji, W.; Davis, N.; Javey, A. A Wearable Patch for Continuous Analysis of Thermoregulatory Sweat at Rest. *Nat. Commun.* **2021**, *12*, 1823.
(469) Kim, Y.; Prausnitz, M. R. Sensitive Sensing of Biomarkers in Interstitial Fluid. *Nat. Biomed. Eng.* **2021**, *5*, 3−5.
(470) Friedel, M.; Thompson, I. A. P.; Kasting, G.; Polsky, R.; Cunningham, D.; Soh, H. T.; Heikenfeld, J. Opportunities and Challenges in the Diagnostic Utility of Dermal Interstitial Fluid. *Nat. Biomed. Eng.* **2023**, 1−15.
(471) Lee, Y.; Howe, C.; Mishra, S.; Lee, D. S.; Mahmood, M.; Piper, M.; Kim, Y.; Tieu, K.; Byun, H.-S.; Coffey, J. P.; Shayan, M.; Chun, Y.; Costanzo, R. M.; Yeo, W.-H. Wireless, Intraoral Hybrid Electronics for Real-Time Quantification of Sodium Intake toward Hypertension Management. *Proc. Natl. Acad. Sci. U. S. A.* **2018**, *115*, 5377−5382.
(472) Nan, K.; Feig, V. R.; Ying, B.; Howarth, J. G.; Kang, Z.; Yang, Y.; Traverso, G. Mucosa-Interfacing Electronics. *Nat. Rev. Mater.* **2022**, *7*, 908−925.
(473) Ates, H. C.; Dincer, C. Wearable Breath Analysis. *Nat. Rev. Bioeng.* **2023**, *1*, 80−82.
(474) Chew, S. W. T.; Shah, A. H.; Zheng, M.; Chang, H.; Wiraja, C.; Steele, T. W. J.; Xu, C. A Self-adhesive Microneedle Patch with Drug Loading Capability through Swelling Effect. *Bioeng. Transl. Med.* **2020**, *5*, e10157.
(475) Waghule, T.; Singhvi, G.; Dubey, S. K.; Pandey, M. M.; Gupta, G.; Singh, M.; Dua, K. Microneedles: A Smart Approach and Increasing Potential for Transdermal Drug Delivery System. *Biomed. Pharmacother.* **2019**, *109*, 1249−1258.
(476) Cezar, C. A.; Roche, E. T.; Vandenburgh, H. H.; Duda, G. N.; Walsh, C. J.; Mooney, D. J. Biologic-Free Mechanically Induced Muscle Regeneration. *Proc. Natl. Acad. Sci. U. S. A.* **2016**, *113*, 1534−1539.
(477) Kim, J.; Salvatore, G. A.; Araki, H.; Chiarelli, A. M.; Xie, Z.; Banks, A.; Sheng, X.; Liu, Y.; Lee, J. W.; Jang, K.-I.; et al. Battery-Free, Stretchable Optoelectronic Systems for Wireless Optical Characterization of the Skin. *Sci. Adv.* **2016**, *2*, No. e1600418.
(478) Kim, J.; Gutruf, P.; Chiarelli, A. M.; Heo, S. Y.; Cho, K.; Xie, Z.; Banks, A.; Han, S.; Jang, K.-I.; Lee, J. W.; Lee, K.-T.; Feng, X.; Huang, Y.; Fabiani, M.; Gratton, G.; Paik, U.; Rogers, J. A. Miniaturized Battery-Free Wireless Systems for Wearable Pulse Oximetry. *Adv. Funct. Mater.* **2017**, *27*, 1604373.
(479) Kim, A.; Zhou, J.; Samaddar, S.; Song, S. H.; Elzey, B. D.; Thompson, D. H.; Ziaie, B. An Implantable Ultrasonically-Powered Micro-Light-Source (μLight) for Photodynamic Therapy. *Sci. Rep.* **2019**, *9*, 1395.
(480) Attili, S. K.; Lesar, A.; McNeill, A.; Camacho-Lopez, M.; Moseley, H.; Ibbotson, S.; Samuel, I. D. W.; Ferguson, J. An Open Pilot Study of Ambulatory Photodynamic Therapy Using a Wearable Low-irradiance Organic Light-emitting Diode Light Source in the Treatment of Nonmelanoma Skin Cancer. *Br. J. Dermatol.* **2009**, *161*, 170−173.
(481) Jeong, H.; Yoo, J.-Y.; Ouyang, W.; Greane, A. L. J. X.; Wiebe, A. J.; Huang, I.; Lee, Y. J.; Lee, J. Y.; Kim, J.; Ni, X.; et al. Closed-Loop Network of Skin-Interfaced Wireless Devices for Quantifying Vocal Fatigue and Providing User Feedback. *Proc. Natl. Acad. Sci. U. S. A.* **2023**, *120*, No. e2219394120.
(482) Shin, J.; Wang, H.; Kwon, K.; Ostojich, D.; Christiansen, Z.; Berkovich, J.; Park, Y.; Li, Z.; Lee, G.; Nasif, R.; et al. Wireless, Soft Sensors of Skin Hydration with Designs Optimized for Rapid, Accurate Diagnostics of Dermatological Health. *Adv. Healthc. Mater.* **2023**, *12*, 2202021.
(483) Sawyer, D. *An Introduction to Human Factors in Medical Devices* U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, and Center for Devices and Radiological Health, 1996, https://elsmar.com/pdf_files/FDA_files/DOITPDF.PDF.
(484) Amended Final Report on the Safety Assessment of Polyacrylamide and Acrylamide Residues in Cosmetics. *Int. J. Toxicol.* **2005**, *24*, 21−50.
(485) Harrington, R. E.; Guda, T.; Lambert, B.; Martin, J. 3.1.4 - Sterilization and Disinfection of Biomaterials for Medical Devices. In *Biomaterials Science*, Fourth ed.; Wagner, W. R., Sakiyama-Elbert, S. E., Zhang, G.; Yaszemski, M. J., Eds.; Academic Press, 2020; pp 1431−1446.
(486) Zhang, X.; Fevre, M.; Jones, G. O.; Waymouth, R. M. Catalysis as an Enabling Science for Sustainable Polymers. *Chem. Rev.* **2018**, *118*, 839−885.
(487) Horváth, I. T. Introduction: Sustainable Chemistry. *Chem. Rev.* **2018**, *118*, 369−371.
(488) Biswal, T.; BadJena, S. K.; Pradhan, D. Sustainable Biomaterials and Their Applications: A Short Review. *Mater. Today Proc.* **2020**, *30*, 274−282.
(489) Jarach, N.; Dodiuk, H. Debondable, Recyclable and/or Biodegradable Naturally-Based Adhesives. In *Biobased Adhesives*; John Wiley & Sons, Ltd, 2023; pp 427−461.
(490) Liu, Y.; Li, H.; Feng, Q.; Su, H.; Li, D.; Shang, Y.; Chen, H.; Li, B.; Dong, H. A Three-Dimensional-Printed Recyclable, Flexible, and Wearable Device for Visualized UV, Temperature, and Sweat pH Sensing. *ACS Omega* **2022**, *7*, 9834−9845.
(491) Kostag, M.; El Seoud, O. A. Sustainable Biomaterials Based on Cellulose, Chitin and Chitosan Composites - A Review. *Carbohydr. Polym. Technol. Appl.* **2021**, *2*, 100079.

https://doi.org/10.1021/acs.chemrev.3c00380
Chem. Rev. 2023, 123, 14084−14118