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Smart, Bio-Inspired Polymers and Bio-Based Molecules Modified by Zwitterionic Motifs to Design Next-Generation Materials for Medical Applications

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In philosophy, yin and yang symbolize opposing and simultaneously correlated forces. This pre-defined scenario occurs in nature as well, e.g., for zwitterionic materials. Both charges, either positive or negative, act individually, and it is not surprising that their interaction with, for example, tissue surfaces or cell membranes differs. However, the combination of the individual binding affinities allows for establishing and tuning strong and/or surface-specific interactions. To emphasize this relationship, this review describes novel, naturally-derived and bio-inspired (semi-)synthetic materials with zwitterionic motifs designed for medical applications. Accordingly, it is not only mentioned how these materials are further modified, functionalized, or synthetically designed to obtain zwitterionic charge profiles for addressing various pathological scenarios. It is equally important to highlight how the physicochemical properties of zwitterions contribute to achieving this goal. For this purpose, the detailed understanding and basic knowledge of mediated binding mechanisms and electrostatic interactions of zwitterionic materials with the physiological, aqueous environment and body/artificial surfaces are discussed in-depth to clarify the dynamics of zwitterionic moieties.

1. Introduction

One of the most intriguing attributes of the human body is the balanced maintenance of a wide range of mechanisms.[1] On the macroscopic scale, organs and tissues communicate in a complex hierarchical manner to ensure system functionality.[2,3] A microscopic analysis demonstrates how this may be facilitated: Cells converse biochemically via cross-talks with biomolecules such as proteins,[4] signaling molecules,[5] and nucleic acids (e.g., DNA),[6] and their chemical mechanisms, e.g., van der Waals (vdW) forces,[7] hydrogen bonds,[8] electrostatic[9] and hydrophobic[10] interactions, which allows them to achieve the required action. Nature's huge variety of biomolecules and interactions highlights the sophisticated structure of the human organism and its efficient functioning. Nevertheless, diseases cause a systemic imbalance and, depending on the degree of severity, specific physicochemical functions are either slightly or drastically restricted.[11] Indeed, drugs exist to retain body functions and fight diseases; however, it is also possible to combine or substitute pharmaceuticals with other strategies to enhance human health. For example, many researchers worldwide are inspired by zwitterionic motifs to develop bio-based or (semi-)synthetic materials for medical applications to combat pathological scenarios and regenerate affected body functions.[12–15] Those zwitterionic moieties comprise mostly naturally originating structures, e.g., amino acids,[16] since the body recognizes them as signal molecules and thus, triggers certain desired endogenous reactions.[17] In most cases, the zwitterions are derived from animal or plant sources and are either gently extracted from those materials[18] or recombinantly produced by microorganisms and purified.[19] Such approaches allow for the production of large-scale quantities of zwitterionic components, which can be covalently grafted to (bio)molecules via various functionalization and post-modification strategies[20,21] or synthetically assembled into polymers.[22]

However, scientists are not only highly creative in finding novel zwitterionic sources and in the development of innovative, zwitterionic materials by selected synthesis strategies, but also in the design of tailored material structures for medical applications which substitute commercially available solutions (e.g., sutures).[23] In addition to micro- and nanoparticles[24] – such as micelles, dendrimers, polymersomes, liposomes, metal–organic frameworks (MOF)s[25] – other structures such as hydrogels,

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films, patches, (microporous) scaffolds,[24] (nano-)capsules, (nano-)emulsions, (nano-)fibers,[26] protein conjugates,[27] membranes, sponges, and nanocomposites.[28] Those advanced materials facilitate the fabrication, for example, drug carriers,[27] coatings,[14] and lubricants[29] for medical purposes. Combinations thereof are equally important to address multiple disease-induced defects and enhance the material performance to quickly or long-term alleviate/cure the disease.[30] Through synergistic effects of the developed zwitterionic materials achieved by physicochemical characteristics, the zwitterions interact with each other via electrostatic interactions to improve the cohesion (e.g., hydrogels) and/or bind to water or tissue in their physiological environment to improve the integrity or adhesion of the material.[31] Furthermore, zwitterions can serve as signal motifs to, e.g., promote drug interactions as carrier materials to transport and release them under demand (e.g., triggered by variations to the pH-value).[32]

The benefit of zwitterionic, innovative alternatives for medical applications depends on the advantages of the material combinations. One example is naturally-derived molecules, which are modified with zwitterions.[15,33] so-called semi-synthetic molecules: Those materials are mostly biocompatible and biodegradable[15] without causing toxic products;[34] however, large amounts of further functional groups within the biomolecule may result in unwanted side effects and trigger further body reactions.[35] On the other hand, synthetic polymers could improve the mechanical strength,[36] blood circulation time,[37] and biodistribution[38] which is required for several applications and is achieved by controlling the structural, biochemical composition of the material.[39] Yet, the biodegradability of synthetic alternatives is often discussed critically in the literature since it is either incomplete or absent.[40] Moreover, some polymers are insoluble in aqueous environments – a physiological challenge for in vivo applications of the material.[41] For the creation of novel bio-derived or (semi-)synthetic, zwitterionic materials, it is equally important to address the endogenous demands (e.g., biological surroundings) as well as the desired structural and material properties required for the specific treatment of diseases.

In this review, we highlight the functionalization of bio-derived molecules with zwitterionic motifs and the formation of (semi-)synthetic, polymeric alternatives to generate different materials for medical applications. In detail, we focus on selected medical diseases and provide an overview of different zwitterionic materials which are specifically tailored to the affected tissue areas – compared to other reviews emphasizing specific zwitterionic materials for different application perspectives. Moreover, we want to pave the way for inspiring researchers for new zwitterionic materials since the goal is to define the material's demands for each pathological scenario on a deeper material and mechanistic analysis. Thus, we show the individual physicochemical mechanisms of zwitterionic moieties conveying multiple functionalities and render them prone to the medical field of application. We introduce selected examples of such materials and demonstrate the advances of electrostatic interactions by zwitterionic motifs for tailored, multifunctional demands in vitro and in vivo. Overall, this review provides an overview of biologically relevant zwitterionic moieties, as well as chemically modified and synthesized zwitterionic materials (of the next generation) and the various mechanisms and tasks fulfilled by zwitterions for complex biomedical purposes.

2. Physicochemical Characteristics of Zwitterionic, Bio-Based, and Bio-Inspired Materials

2.1. Naturally Occurring and Synthetic Motifs Endowing Materials with Dual Electrostatic Properties

From a chemical perspective, polyzwitterions are classified as a subgroup of polyelectrolytes since each charged repeating unit contains both, a positive and a negative charge.[42] In more detail, the zwitterionic moieties are located in coexistence of positive and negative charges within the same monomer unit, which are distributed over the entire polymer.[43]

In nature, zwitterionic amino acids are abundantly found and offer a large number of different physical properties.[44] The typical structure includes the so-called head group – with a central carbon atom and the zwitterionic moieties: a cationic amino group and an anionic carboxylic group – and a specific side chain connected to the carbon atom, which differs depending on the amino acid.[45] The side chain or residue group contains a range of various structure motifs providing further charge by other carboxylic (e.g., glutamic acid, aspartic acid) and amino moieties (e.g., lysine, arginine, histidine) or contributing to a hydrophilic (e.g., serine, cysteine)/hydrophobic character (e.g., glycine, alanine, leucine).[46] The surrounding pH value influences the charge profile of the zwitterionic amino acid motifs: at acidic pH values, those zwitterionic groups are protonated and thus, the amino group shows cationic character, the carboxylic group is uncharged, and vice versa in basic conditions.[47] In contrast, when the pH value is at the amino acid-specific isoelectric point, the zwitterionic nature of the corresponding amino acid dominates (**Figure 1A**).[48] All of those amino acids enable the formation of both intramolecular and intermolecular interactions when incorporated in naturally occurring compounds.[49] Based on covalent and non-covalent interactions which are mediated by disulfide bridges via thiol groups (e.g., cysteines),[50] electrostatic interactions by charged motifs,[51] hydrogen bonds via proton acceptors and donors of amino acids hydrophilic character[52] or hydrophobic interactions by corresponding hydrophobic amino acid residues,[53] the materials can provide interfacial[54,55] and material toughness.[56]

Proteinogenic amino acids offer a huge range of building blocks, which are well-known for forming different classes of biomolecules such as peptides.[57] Typically, the formation of those long chain structures in the human body occurs during a condensation reaction. In detail, the carboxylic motif (in the head group) of monomeric or peptide- terminating amino acids interacts with amino moieties of other amino acid head groups by releasing water molecules.[58] Of course, the resulting biomolecules are degradable by hydrolysis (i.e., proteolysis) as well to reconstitute single amino acids again.[59] The aforementioned endogenous synthesis pathway, which connects the amino acids with certain functional groups to each other to form biomolecules, is problematic for biomedical applications since the zwitterionic head groups are covalently linked. To produce zwitterionic materials for medical purposes, however, that aim at using the advantage of charged moieties,

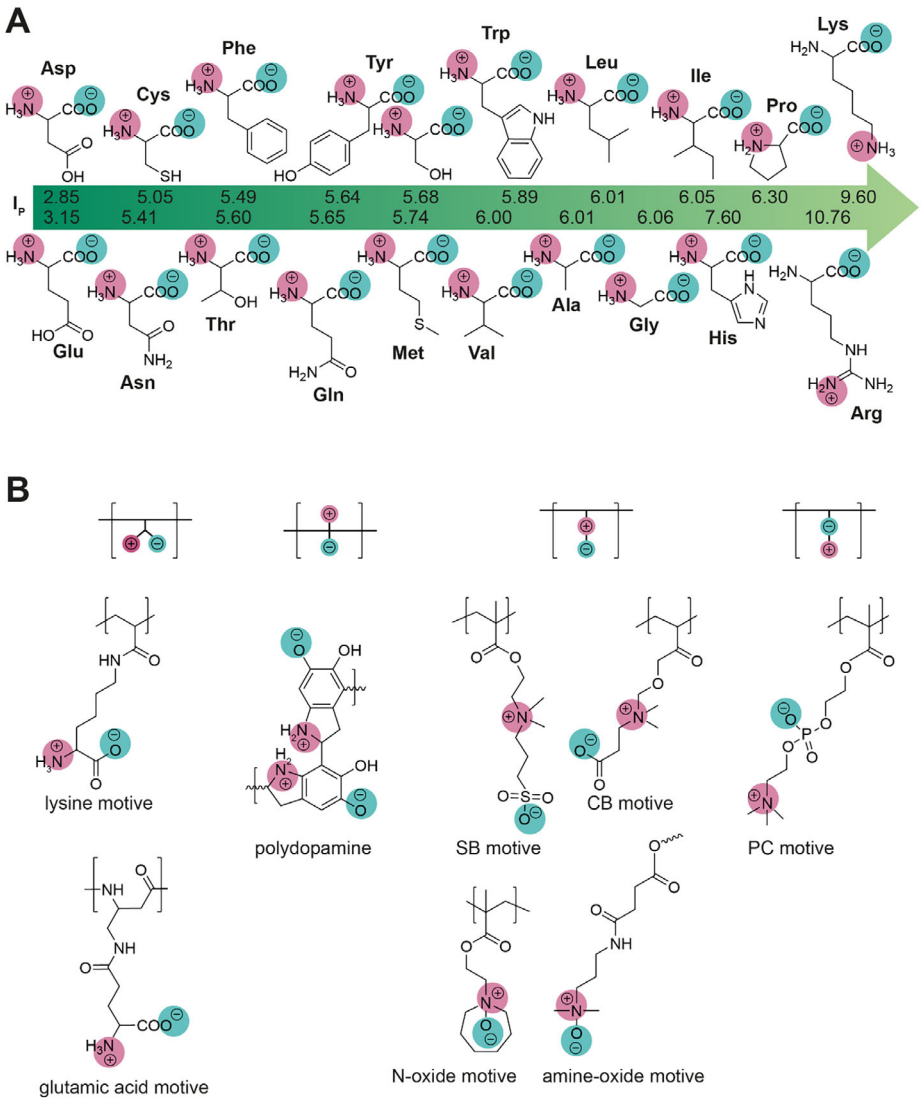

Figure 1. Overview of different zwitterionic structure motifs. a) The zwitterionic nature of each amino acid depends on its isoelectric point (I_P). b) Examples of zwitterionic moieties – a subclass of polyelectrolytes – that are discussed in more detail in the various medical applications in this review. Asp = aspartic acid; Glu = glutamic acid; Cys = cysteine; Asn = asparagine; Phe = phenylalanine; Thr = threonine; Tyr = tyrosine; Gln = glutamine; Ser = serine; Met = methionine; Trp = tryptophan; Val = valine; Ala = alanine; Leu = leucine; Ile = isoleucine; Gly = glycine; Pro = proline; His = histidine; Lys = lysine; Arg = arginine; SB = sulfobetaine; CB = carboxybetaine; PC = phosphorylcholine.

linking amino acids via residue groups, is a very promising alternative to ensure accessibility of the zwitterionic character. Owing to their several modification strategies, such as (i) amino-acid-functionalized[43] or -like norbornenes (e.g., polymerized via ring-opening metathesis polymerization)[60] corresponding electrostatically charged structures are formed. For this purpose, a Steglich coupling of the amino acid α-carboxylic moiety with 5-norbonene-2,3-*endo,endo*-dimethanol[61] or the synthesis of amino acid α-amino – which interacts directly with 5-norbonene-2,3-*endo,endo*-dicarboxylic anhydride – is performed to create (novel) molecular zwitterionic structures.[62] Moreover, (ii) amino acid-derived poly(meth)acrylamide or poly(meth)acrylates (e.g., polymerized via radical polymerization)[63] were generated to obtain protein or peptide mimicking structures. The first method is based on activated vinyl compounds interacting with the amino acid α-amine group,[64] and the second strategy made use of Steglich esterification between a hydroxyl-group-containing a vinyl compound and an activated carboxylic acid.[65] Relying on a (iii) post-polymerization modification approach using, e.g., amidation of activated esters,[66,67] amino acid-derived monomer synthesis allows for to formation of highly diverse classes of zwitterionic molecules.[68] Although this review belongs mostly to polymers with zwitterionic moieties in the side chain, we also want to mention another mechanistic principle governed by zwitterionic groups in the main chain. Mazo et. al.[69] described that those polymers are obtained by ring-opening polymerization of *N*-carboxyanhydrides derived from α-amino acids.

Furthermore, zwitterionic betaines are frequently found in nature as well, e.g., in microorganisms, plants, and animals.[70]

In the human body, betaines are not part of the protein synthesis itself, but rather serve to post-modify biomolecules with methyl groups during transmethylation mechanisms.[70] In terms of chemical properties, betaines behave similarly to amino acids, which is in line with the origin of betaines since those molecules are amino acid derivatives.[71] Betaines possess trimethylammonium motifs instead of primary amino groups, which are permanently positively charged.[72] Moreover, betaines may comprise three different negatively charged groups – either a carboxylate (= carboxybetaine; CB), a phosphate moiety (= phosphobetaine; PB), or a sulfonate (= sulfobetaine; SB).[73] There are many examples of how the zwitterionic betaines are obtained: (i) alkylation of amines is the most performed coupling reaction.[74,75] In detail, tertiary amines such as dimethyl amino ethyl methacrylate (DMAEMA) contain target sites for chemical functionalization with lactones via ring-opening alkylation to obtain CBs.[76,77] In addition, (ii) post-modification reactions with 2-alkoxy-2-oxo-1,3,2dioxaphospholanes[78] and sultones[79–81] allow for the covalent linkage of phosphate[78] and sulfate group[79–81] to obtain PB and SB, respectively. Similar to the amino acid synthesis strategy, zwitterionic betaine monomer derivates show polymerization propensity driven by free radical polymerization,[82] reversible deactivation radical polymerization,[83] ring-opening metathesis polymerization[76; 84] or step-growth polymerization[85] (although applied rarely). The inter- and intramolecular interactions of the resulting betaine functionalized molecules are comparable to those of amino acids mentioned above: electrostatic interactions, hydrogen bonds, hydrophobic, and hydrophilic interactions.[86]

There are also phospholipids in the human body carrying zwitterionic charges – namely phosphatidylcholine (PC), phosphatidylethanolamine (PE), and phosphatidylserine (PS).[87] All three share the ability to assemble in cell membranes and thus support the formation of compartments within cells.[88] Regarding the chemical complexity, those molecules possess a hydrophobic tail group including fatty acids, which are grafted onto the hydrophilic head group – either a cationic choline/amine or a zwitterionic serine – via glycerol and a negatively charged phosphate group.[89] Those tail and head moieties have the self-assembly propensity in in vivo environments using hydrophobic and hydrophilic interactions (the later moieties allow for water attachment, as well),[90] respectively, to create various (flexible) structures such as inverted/ spherical/ cylindrical, worm-like micelles, vesicles,[91] monolayer, and bilayer[92] which form macro- and micromolecular barriers[93] or carrier.[94] The contained zwitterionic motifs in those structures (PC and PE) are overall charged at physiological pH values, whereas PS shows an anionic net charge.[95] In other words, for the fabrication of zwitterionic biomolecules or (semi-)synthetic alternatives, the tails – fatty acids as well as glycerol – are negligible, however, the charged moieties such as PS, PC, and PE serve as zwitterions for designing new structures.

To conclude this chapter, we discuss the enzymatic and synthetic pathways to generate those three classes of zwitterionic phosphatidyl-based molecules. In humans and animals,[96,97] for example, PS is obtained once the enzyme phospholipase D has mediated the transphophatidylation of PC.[98] In comparison, PS is chemically synthesized either in liquid–liquid[99] or aqueous-solid systems,[100] or in completely aqueous suspensions,[101] however, with animal- and plant-derived phospholipids such as PC and soybean lecithin as raw materials. Afterward, synthesis strategies for fully artificial phosphoryl-based alternatives[101] were introduced – especially a highly convergent, multi gram scale synthesis of PS.[102] However, enzymatic treatment of PC precursors still offers the most economic opportunity for PS production.[101] Compared to PS, the primary *de novo* synthesis for PC and PE is based on the Kennedy pathway.[103,104] This synthesis strategy consists of three stages: first, choline or ethanolamine is phosphorylated to obtain phosphocholine and phosphoethanolamine, respectively. Then, those intermediates are converted into cytidine diphosphate-choline and cytidine diphosphate-ethanolamine. In the final step, the formed molecules are combined with diacylglycerol to produce PC or PE.[103,104] In addition, PC can also be obtained by enzymatic conversion of PE via phosphatidylethanolamine N-methyltransferase,[105–107] whereas PS decarboxylation – catalyzed by phosphatidylserine decarboxylase – results in PE in vivo.[108,109] Synthesis strategies to produce PE and PC are based on diacylglycerols, and to advance control over the reaction, organic solvents (e.g., DMF or propan-2-ol) are necessary.[110] However, novel approaches has recently enabled scientists to create fully synthetic[111–114] and less toxic pathways.[115,116] For example, Liu et al. developed an enzyme free PC synthesis via transacylation of lysophosphatidylcholine in water.[117] A general trend in synthesis is the formation of polymerous analogues, in this case of phospholipid-based ones. For example, Nakaya et al.[78] reported that various phospholipid analogous monomers were made from starting compounds such as 2-chloro-2-oxo-1,3,2-dioxaphospholane. It was now possible to synthesize vinylic monomers and polymers carrying phospholipid analogues in both, the side and the main chain. The most commonly used vinylic analogue, 2-methacryloyloxyethyl-phosphorylcholine (MPC), is commercially available and can be easily polymerized via various radical polymerization techniques.[118–131] Alternatively, phospholipid moieties can be integrated by end-group functionalization using post-polymerization modification,[132] modified via chain transfer agents in a reversible-addition-fragmentation chain-transfer (RAFT) synthesis[133] or by an initiator in atom transfer radical polymerization (ATRP).[134,135] Moreover, step growth polymerization was performed to obtain PC polymer analogues by the reaction of diisocyanates with zwitterionic diols[136] or dibromides with a zwitterionic dichloride.[85]

Naturally originating zwitterionic moieties of amino acids at their isoelectric points (mentioned above; Figure 1A) and further zwitterionic motifs (Figure 1B) discussed in the following chapters to design bio-derived or (semi-)synthetic zwitterionic materials for healthcare applications are summarized in Figure 1, which provides an overview of the potential offered by zwitterions.

2.2. Multifunctional, Zwitterionic Motifs Providing Materials for Biomedical Applications

2.2.1. Low-Biofouling – Coatings Based on Zwitterionic Materials for Biomedical Demands

Owing to the eukaryotic/prokaryotic cell and protein repellence (**Figure 2A**) of zwitterionic moieties originating from two mech-

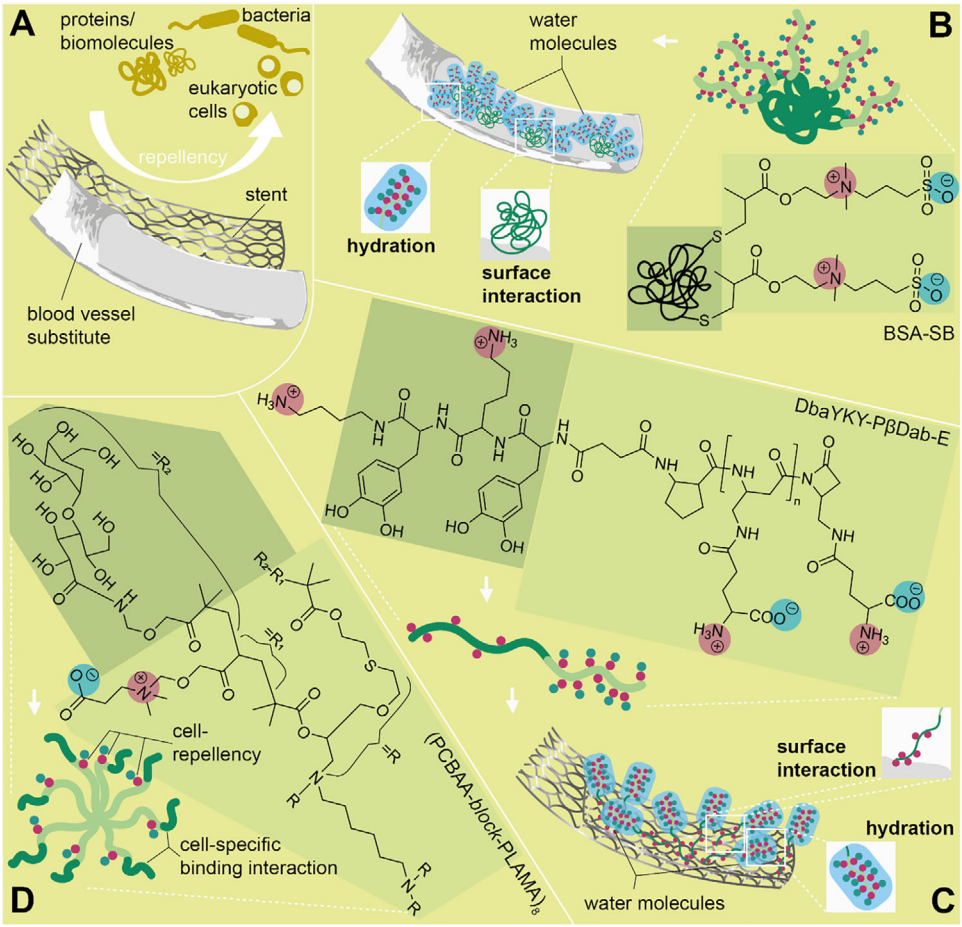

Figure 2. Selected examples of macromolecular coatings that confer low-biofouling characteristics to implant surfaces. a) Suitable coatings on artificial material surfaces of stents and blood vessel substitutes enhance low-biofouling properties. Either naturally-derived[150] (b), semi-synthetic[154] (c), fully synthetic[165] (d) zwitterionic molecules are generated to combat the adhesion of prokaryotic/ eukaryotic cells and biomolecules to maintain a healthy body state. BSA-SB = bovine serum albumin-sulfobetaine; DbaYKY-PßDab-E = dibutylamine-DOPA-lysine-DOPA-tripeptides-poly(*β*-diaminobutyric acid-glutamic acid); $(PCBAA\text{-}block\text{-}PLAMA)_8$ = eight-armed poly(carboxybetaine) acrylate-*block*-poly-2-lactobionamidoethyl methacrylate.

anisms – the formation of a i) hydration layer and the ii) steric hindrance by the coating – bio-based and bio-inspired materials act as a protective barrier on artificial, medical devices/implants. In detail, the zwitterionic motifs interact with water molecules via electrostatic interactions to create hydrogen bonds and thus enabling the formation of a hydrophilic water layer.[137] To overcome this arising barrier, proteins and cells have to modulate an energy-driven process (entropic effect) to facilitate physicochemical surface interactions. Moreover, the chain flexibility of the zwitterionic materials is crucial to ensure steric repulsion forces as a defensive protection mechanism against biofouling processes.[138] It is typically a combination of highly dense polymer/biomolecule surface distribution and long, linear or branched subunits that govern intrinsic binding interactions[138] such as chain entanglement, to obtain artificial implant surfaces with anti-adhesive properties.[139] In the absence of both mechanisms caused by bare substrates or insufficient surface coatings on medical products, which are inserted into the human body, a more pronounced unspecific accumulation of endogenous proteins occurs due to an immune response.[140] Once a protein-rich layer is formed on the artificial material, microorganisms can efficiently attach onto the surface and thus stimulate colonization, biofilm development, and finally cause infections and tissue inflammation.[141] The risk of being bacterially contaminated is problematic for medical products that remain short-term in the human body (such as catheters or contact lenses) as well. However, not only microorganisms but also endogenous cell adhesion is discussed to be associated with unwanted side effects. For example, the successfully deposited cell and protein components of the bloodstream (e.g., red blood cells, platelets, and fibrin) inside stent materials create a stable thrombus[141] which, in turn, leads to ischemia[142] and thus, a loss of implant functionality. Similarly, when neointimal hyperplasia occurs as a result of predominant inflammation reaction, e.g., in blood vessel substitutes. Hence, smooth muscle cells can attach to the implant surface, proliferate, form an extracellular matrix, and, in those cases, could trigger restenosis (leading to the internal closure of implants), a process potentially related to high mortality rates.[143]

To overcome the detrimental effects, low-biofouling coatings for medical implants and devices with zwitterionic motifs are introduced in the following. Importantly, the coating must be able to deal with the challenge of anchoring such zwitterionic

molecules on various medical substitutes. Depending on the physiological application, the substrates applied to the human body are metallic (e.g., joint implant),[144] glass (e.g., contact lens)[145] or plastic-based (e.g., catheter)[146] materials featuring either a high[147] or low surface energy[148] – the polarity of the medical product surface is crucial for attachment of the coating material.[149] The first dip-coating/spraying system,[150] which we discuss in the following subsection, shows how conjugates of native bovine serum albumin (BSA) molecules with zwitterionic SB (produced via radical-mediated thiol-ene click chemistry reaction between free thiol radicals of BSA and carbon–carbon double bonds of sulfobetaine methacrylate (SBMA)) adhere on metallic and (in-)organic surfaces and prevent biofouling processes. The substrate binding events of bovine serum albumin-sulfobetaine (BSA-SB) are brought about by multiple molecular interactions, such as hydrogen bonding, vdW, and hydrophobic interactions, of BSA. In comparison, cell repellence was rationalized by the zwitterionic SB units, which favor water interaction and thus, the formation of a hydrated film (Figure 2B). This generated water layer provides the coating with improved steric repulsion and reduces the electrostatic, cation-π interaction, ion bridging, hydrogen bonds, and vdW interactions with biofoulants such as simulated body fluid, proteins (e.g., mucin, lysozyme), carbohydrates (e.g., sucrose, fructose), and small signal molecules (e.g., dopamine). In an *ex vivo* study, the coating was applied to blood vessel substitutes, which allowed for investigating long-term blood circulation experiments (16 days) composed of the flowing rate in BSA-SB modified tubes (8.98 cm s^{-1}, 92.0% of the original flowing rate). Hence, coatings based on BSA-SB conjugates render this low-biofouling material an interesting candidate for medical application, when in-depth in vivo investigations successfully support the *ex vivo* data obtained.[150]

Of course, bio-inspired (semi-)synthetic polymers hold the potential to be used as a coating on medical implants, but those materials are limited to certain substrate surfaces.[151–153] Owing to the binding difficulty onto a wide range of implant materials and certain functional groups – which might cause side reactions – of those coatings, an anchoring alternative to BSA at the interface between substrate and macromolecular coating with similar adhesion properties is required. Inspired by the marine mussel adhesive L-3,4-dihydroxyphenylalanine (L-DOPA), Zhang et al.[154] developed a standard linker covalently binds to, for example, zwitterionic peptide chains (peptide chains formed via condensation reactions, e.g., the carboxyl group at the γ position of glutamic acid reacts with the amine group of the side chain of the β-lactam) using anionic ring-opening polymerization (AROP).[154] The DOPA molecules themselves can engage in substrate surface interactions,[155] including covalent and non-covalent bonds: Interaction with nucleophiles, hydrogen bonds, π–π electron interactions, cation–π interactions.[156] The formed semi-synthetic, zwitterionic, and adhesive dibutylamine-DOPA-lysine-DOPA (DbaYKY) tripeptides (DbaYKY)-poly(β-diaminobutyric acid-glutamic acid) (PβDab-E; Figure 2C) are less sensitive to proteolysis and have been shown to be suitable as a stable low-biofouling coating forming a protective barrier toward proteinaceous fibrinogen and cells, such as fibroblasts and gram-positive/gram-negative bacteria. Moreover, molecular dynamics simulations reveal how this is possible: Each repeat unit of PβDab-E is known for its high hydration free energy (−771.2 kJ mol^{-1}; 5 times higher than the gold standard coating with polyethylene glycol) and thus for its very high water-binding capacity to establish a protective layer on the substrate material. This controlled adhesion of DOPA (or tannic acid) anchors inspired many scientists to develop novel low-biofouling coatings with zwitterionic motifs (**Table 1**).[154]

Recently, Guo et al.[165] developed zwitterionic, semisynthetic eight-armed particles with antibacterial effect (Figure 2D). Those particles could open up new therapeutic possibilities when an (un-)coated implant surface has failed in the long term and biofilm formation occurs. For this purpose, the eight-armed molecules are synthesized from 1,6-hexamethylenediamine and 3-allyloxy-1,2-propanediol via thiol-ene reaction and esterification (open-loop substitution reaction) and, in a second step, modified by atom transfer radical polymerization with CB acrylate and 2-lactobionamidoethyl methacrylate. The zwitterionic CB inhibits the unspecific binding interaction with proteins and microorganisms, whereas the galactose subunit of 2-lactobionamidoethyl methacrylate targets lectin A (cell membrane protein) of, e.g., *Pseudomonas aeruginosa* and thus, prevents an optimal biofilm matrix formation by its strong binding affinity. In addition to those tasks, the resulting eight-armed particles improve the bacterial sensitivity toward antibiotics to combat ongoing infections. As already indicated by in vitro experiments, those particles combine biocompatibility and anti-bacterial properties – downregulation of both, antibiotic resistance and genes for biofilm formation. In vivo investigations with bacteria-colonized silicone surfaces (transplanted into the peritoneum of rats) confirmed those promising anti-biofouling properties after injection of the particles. It is likely that not only humans with post-implant acquired infections but also those with nosocomial infections could benefit from such innovative materials.[165]

2.2.2. Hydration Lubrication – Impact of Zwitterionic Molecules at Joint Interfaces

From the microscopic to the macroscopic scale, zwitterionic materials exhibit water-binding properties that are relevant for specific body functions.[13] For example, this feature makes them very interesting for tissue surfaces that are exposed to friction and need to undergo lubrication.[166] One well-known example is the naturally occurring joint. Together with the synovial fluid, the cartilage surface typically separates the two bone surfaces from each other to preserve the joint functionality (**Figure 3A**).[167] To obtain those required mechanical characteristics, articular cartilage consisting of extracellular matrix (e.g., collagen[168] and (glycosylated) proteins[169]) and chondrocytes,[170] and the main components of synovial fluid – namely lubricin,[171] hyaluronic acid (HA)[172] and zwitterionic lipids (e.g., PC)[124] – are suitable for friction and wear reduction by two mechanisms: i) boundary and ii) hydration lubrication.[166] The mechanism of boundary lubrication allows for the formation of a lubricating film, for example, via sacrificial layer formation, i.e., the frequent accumulation/shear-off of cartilage-bound proteins based on weak interactions during mechanical (un)load.[173] In contrast, hydration lubrication is best described by, e.g., zwitterionic phospholipids,[174] which easily establish hydrogen bonds,[175] ion-dipole,[176] dipole–dipole interactions[177] with water molecules via their charged moieties

Table 1. Overview of different low-biofouling coatings with DOPA-inspired linkers for medical applications discussed in the literature.

Surface-anchor	Polymer/biomolecule	Zwitterionic motif	Refs
Tannic acid	2-aminoethyl methacrylamide hydrochloride	phosphorylcholine	[120]
Dopamine	–	pSB	[157]
Dopamine	–	phosphorylcholine	[122]
Dopamine	–	CB	[158]
Dopamine	–	phosphorylcholine	[121]
Dopamine	4-formyl phenyl methacrylate	phosphorylcholine	[120]
Dopamine	*N*,*N*′-methylenebisacrylamide	SB	[159]
Tannic acid	polylysine, 2-(Diisopropylamino)ethylmethacrylat	phosphorylcholine	[119]
Dopamine	–	SB	[160]
Dopamine	starch	SB	[161]
dopamine	–	SB	[162]
Mussel-adhesive protein	peptide	zwitterionic peptide	[163]
Dopamine	N-(3-aminopropyl) methacrylamide hydrochloride	phosphorylcholine	[118]
Dopamine	2-(2-bromoisobutyryl) ethyl methacrylamide,	phosphorylcholine	[123]
Dopamine	*N*,*N*′-Bis(methacryloyl)selenocystamine, polyethylenimine, glycidyl methacrylate, *N*,*N*′-methylenebis(acrylamide)	SB	[164]

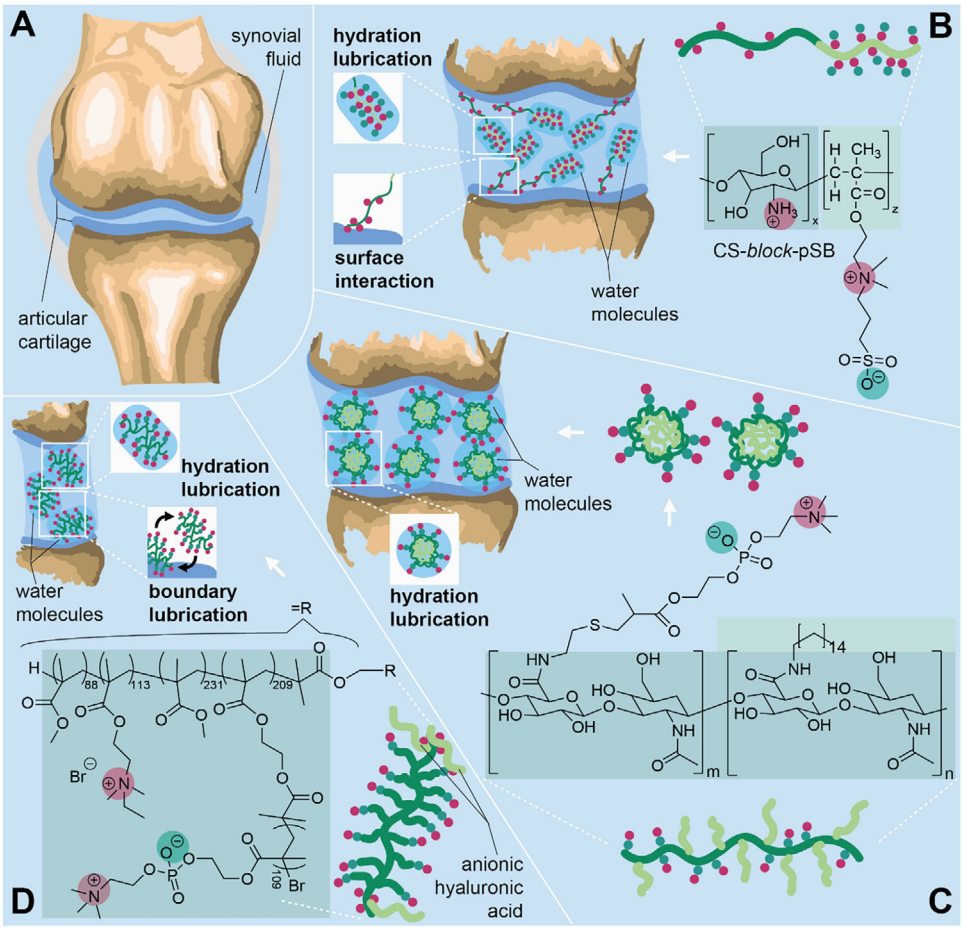

Figure 3. Schematic overview of different bio-based and inspired zwitterionic materials that are relevant for the lubrication of body surfaces. a) Depiction of a knee joint and its most important lubrication components. Artificial examples of naturally-derived[179] (b), semi-synthetic[186] (c), and almost completely synthetic[189] (d) zwitterionic materials to replace synovial fluid and their physicochemical properties once applied to their target. CS = chitosan; pSB = polysulfobetaines.

and thus, form a hydration water layer.[174] Furthermore, it is possible for water molecules to build hydrate shells surrounding the hydrophilic domains of the amphiphilic, lipid-favoring hydration lubrication.[174] Damaged cartilage or cartilage degradation (= osteoarthritis) caused by disease or age leads to even more friction in the joint.[178] The loss of interface integrity must be met by enhanced lubrication without adversely affecting further cartilage damage.[166]

To combat painful wear and abrasion, many researchers are inspired by zwitterionic motifs and both lubrication mechanisms. One example is the naturally-derived zwitterionic lubricant synthesized by betaine-modified chitosan (CS) via RAFT polymerization.[179] The carbohydrate CS – deacetylated chitin derived from crustacea, insects, and fungi[180] – is known for its long-term biodegradability and its ability to resist shear stress.[179] Owing to the acidic pH conditions in the joint originating from the inflammatory response, weak, electrostatic interactions between the protonated amino groups of CS and the anionic cartilage facilitate the formation of a protective film. In addition, the molecule-bound, zwitterionic polysulfobetaines (pSB) enhance the water-binding capacity through ionic interactions and support lubrication (Figure 3B). Linear tribological measurements with a cartilage pin-on-plate (Ti6Al4V alloy) system performed at a loading force of 10 N (= 1 MPa pressure; matches the physiological pressure of human articular cartilage) have shown that the coefficient of friction (COF) is 0.154. However, naturally occurring lubrication fluid in articular cartilage exhibits COF values between 0.001 and 0.01.[166] Only experiments with modified CS concentrations ≥1 mg mL^{-1} and artificial surface set-up (PDMS and Ti6Al4V alloy) revealed better COF values of 0.013 and hold the potential to be used for medical applications.[179] Moreover, in vivo experiments have indicated that the modified CS material limits the progression of osteoarthritis in mice.[179] There are many examples of such biomolecule combinations with similar physicochemical properties reported in the literature. Betaines[181–183] are frequently found as zwitterionic motifs, however, the amino acid proline,[184] the tripeptide glutathione (glutamic acid, cysteine, and glycine),[185] or the zwitterionic lipid component of synovial fluid, namely phosphorylcholine[29,125] are widely applied for biomolecule modification.

Another interesting but partially synthetic system was developed by Zheng et al.[186] using the bio-derived phosphorylcholine and HA. Owing to the shear-thinning effect of HA at high shear values, which predominate during mechanical load in the joint, the boundary lubrication efficiency of a single-component polyelectrolyte network is very low. Therefore, the naturally occurring carbohydrate was optimized by phosphorylcholine functionalization to ensure enhanced hydration lubrication through water molecule adsorption and to compensate for the viscosity loss at increased load. Modulated by the chemical synthesis strategy, thiolated HA molecules are created by carbodiimide coupling (carboxyl groups of HA react with amino groups of cystamine) to establish new target sites for further modification with methacrylated phosphorylcholine via thiol–ene click reaction. Moreover, to fabricate self-assembled, globular particle structures by hydrophobic interactions, HA was additionally functionalized with synthetic hexadecyl motifs using coupling amidation (Figure 3C). Atomic force microscopy has shown COF values of ≈0.03 when those resulting particles are evaluated at high contact stress (≈55 MPa; scanning rate: 2 Hz; ball-on-flat setup of polystyrene microsphere modified cantilever on Si wafer; particle concentration ≥ 5 mg mL^{-1}) and indicate high potential for application. Initial in vivo tests verified the globular molecule structure's contribution to reducing disease progression and preventing further cartilage damage.[186] There is a large body of literature available where combinations of, for example, lecithin/cholesterol and phosphorylcholine,[126] gelatine/dopamine and phosphorylcholine[187] or SB,[188] and PC lipid vesicles[127] are discussed as promising materials as well.

To develop tailored lubricants with even more properties, such as additional low-fouling characteristics, fully synthetic or (semi-)synthetic alternatives serve as friction and wear- reducing materials. Pham et al.[189] were inspired by lubricin, the well-known protein from synovial fluid, which facilitates lubrication by a sacrificial layer mechanism, in combination with the zwitterionic phosphorylcholine motif (hydration lubrication) to create semisynthetic, charged bottlebrush polymers. Those triblock polymers can be well manufactured by ATRP with the monomer units 2-(trimethylsilyloxy)ethyl methacrylate, DMAEMA, methyl methacrylate, and MPC. The bottlebrush polymer termini contain cationic moieties and thus, electrostatically interact with added polyelectrolyte HA to improve injection (shear-thinning behavior of HA) and promote cartilage protection (Figure 3D). First surface force measurements (cross-cylinder configuration with back-silvered mica surfaces and a constant sliding frequency of 50 mHz in back-and-forth motion) have highlighted that in comparison to bovine synovial fluid (BSF) from healthy animals (COF of ≈0.4), the synthesized triblock polymer can generate similar COF values (≈0.3). Hence, an ideal material to counteract further damage to the articular cartilage surface. Moreover, in vivo experiments proved the polymer to be biocompatible, less toxic, and may successfully postpone cartilage degradation in the early stage of osteoarthritis.[189] There are numerous (semi-)synthetic material examples demonstrating how such alternatives with different polymer geometries can be applied as lubricants for medical applications.[190–195]

Further lubricant modifications can be developed to create material properties such that the disease can be addressed more precisely. A very interesting multifunctional example is the semi-synthetic ɣ-aminobutyric-acid betaine functionalized resorcin[4]arene, which not only tunes joint lubrication after assembly, but may also embed drugs and release them over time to provide anti-inflammation and articular cartilage regeneration.[196] This example nicely shows that additional functions have improved those materials and convey the future prospects of lubricant innovations as well.

2.2.3. Immunology – Zwitterionic Moieties as Signal Molecules for Biological Response

Another area of biology where zwitterionic materials are an interesting component is the application as pseudo-immunomodulator[197] for the polarization and stimulation of, e.g., macrophages[198] and B cells;[199] however, the fundamental physicochemical interactions are complex and scarce in the literature. The immune system is classified into two main, interconnected categories: Macrophages, granulocytes,

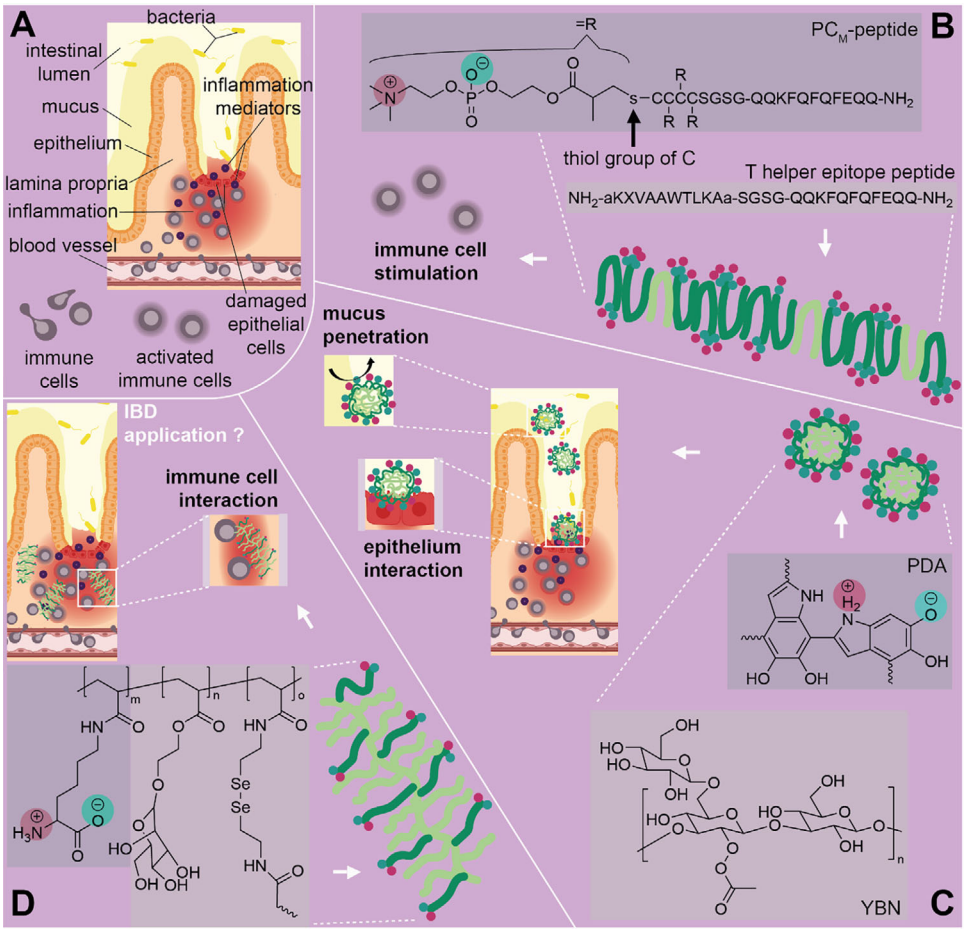

Figure 4. Selected examples of different approaches to combat inflammatory bowel disease. a) The pathological scenario is characterized by mucus loss and permeability of epithelial barriers toward inflammation mediators. To reduce inflammation and recover physiological functions, fully naturally occurring[225] (b), post-modified, bio-derived[231] (c), and semi-synthetic[198] (d) zwitterionic materials are created. X = cyclohexylalanine; a = D-alanine; PC_M = multi-phosphorylcholine; PDA = polydopamine; YBN = yeast β-glucan.

and natural killer cells are mainly involved in the innate immune system, whereas B and T cells play an important role in the adaptive immune system.[200] During inflammation, for example, by infections, sensor cells such as dendritic cells and macrophages[201] are attracted by the affected body area, activated, and either interact with specific molecules of the pathogen[202] (e.g., bacterial lipopolysaccharides)[203] or absorb the invading cell using phagocytosis.[204] Afterward, cells such as macrophages release chemokines or cytokines[205] – which act as signal molecules – to stimulate further cells (e.g., T cells) of the innate and/or adaptive immune system by interacting with specific surface-bound receptors.[206,207] Afterward, further chemokines and cytokines act as signal molecules inducing either an anti-inflammatory response[208] – indicating successful infection control and healthy body regeneration[209] – or a pro-inflammatory stimulus[208] which results in further immune cell activation, maturation, and helps in the fight against pathogens and infected endogenous cells.[210] Once the target objects are successfully fought, effector and memory T-cells are formed, which are able to differentiate into (central) effector memory $CD8^+$ and tissue-resident memory T cells.[211] When the latter memory T cells get in contact with those specific antigens, the active process of the immune response is triggered again.[212] In other words, the immune system is an intelligent defense mechanism of our body to protect the organism against pathogens.[213] However, when the immune system is permanently active, tissue damage might occur as a result of persistent inflammation in the targeted body area.[214]

For example, worldwide, many people suffer from chronic diseases that remain incurable up to now.[215] Inflammatory bowel disease (IBD) is one of those examples, including two pathology scenarios, namely Crohn's disease and ulcerative colitis, which are based on dysfunctions of the immune system (**Figure 4A**).[216] In both cases, the immune cells suffer from an exhaustive state due to a constant activation by inflammation mediators[217] and bacterial proteins, which increasingly penetrate the lamina propria via a defective mucosa and epithelium barrier.[218] Consequently, immune cell trafficking is affected since those cells are continuously recruited by the inflamed tissue, remain permanently active, and prime tissue-resident memory T cells emigrating off this target site and harming other tissues.[219] Based on current research, the disease is incurable – just the

symptoms can be alleviated.[220] Conventional drug therapies based on amino salicylates,[221] corticosteroids,[222] and/or biologics[223] are discussed in the literature. However, those medical applications may cause unwanted side effects and adverse, negative effects on physiological health, and impose further body diseases.[224]

This short disease overview indicates the need for specific alternatives to alleviate IBD symptoms. Curvino et al.[225] developed a peptide-based, zwitterionic system with immune cell modulating characteristics. For this purpose, the researchers applied solid-phase synthesis to create peptide fibers – the amino acid sequences show self-assembly (C-terminal). Some peptides possess zwitterionic PCs anchored N-terminally via Cys-(Ser-Gly)$_2$ linkers (max. 4 per linker): This is made possible by the reaction of 2-methacryloyloxyethyl phosphorylcholine with thiol groups of linker cysteines through Michael addition. Additionally, some peptide sequences comprise T-helper epitopes instead of PC units to probably enhance stimulation of a broad range of immune cells (Figure 4B). The physicochemical interactions of zwitterionic motifs involved in the immune cells targeting are neglected. It is well-known that intraperitoneally injected peptide fibers (colitis mouse model) stimulate B1a cells by multiple zwitterionic PCs.[225] As a consequence, those B1a cells[225] migrate to the spleen, proliferate into plasma cells and thus, form natural antibodies[226] (IgM) which control the inflammation in the gastrointestinal tract as follows[225]: These antibodies recognize PC epitopes in injured and/ or apoptotic epithelium cell membranes, as well as in gram-negative and gram-positive prokaryotic cell walls. This allows the neutralization of harmful cells or labels them for degradation by other immune cells. The physicochemical properties of IgM-PC interactions are not sufficiently discussed in the paper of Curvino et al.[225] Since antibodies are composed of amino acids, hydrophobic [227] or electrostatic interactions,[228] and/ or hydrogen bonds[229] can occur. The peptide-based system has even been improved by Curvino et al. to achieve oral application of the structures.[230]

Another interesting approach was developed by Yang et al.[231] The bio-derived system is based on yeast β-glucan (YBN) – a molecule with a linear β-(1,3) glucan backbone branched via β-(1,6)-linkages with further glucans – coated with zwitterionic polydopamine (PDA). To obtain the YBN particles, first, the polysaccharide is extracted from yeast, modified by esterification of the hydroxyl groups and then, stable YBN particles are formed after nanoprecipitation (Figure 4C). PDA molecules coat the polysaccharide-based structure by self-polymerization in alkaline solutions.[231] The formed PDA layer is zwitterionic, caused by negatively charged catecholic hydroxyl groups and cationic amino motifs; the latter are located in the indole ring arising after cyclization during auto-oxidation of PDA.[232] The zwitterionic YBN-PDA was found to penetrate the mucus barrier[231] by repulsive forces between the anionic moieties of PDA and mucin molecules.[233] Furthermore, electrostatic interactions improve internalization into epithelial cells by interactions with cationic choline groups within the cell membrane, and therefore, YBN-PDA can act as immunomodulators for T cell regulation and suppression of dendritic cell activity.[231] In contrast, yeast ß-glucan is prebiotic and alters the composition and diversity of gut microbiota to alleviate colitis. In in vitro and in vivo studies, YBN-PDA with hydrodynamic sizes of ≈190 nm demonstrated excellent biocompatibility, anti-inflammatory effects, they promote colon tissue regeneration and reduce reactive oxygen species (ROS).[231] Similarly, semi-synthetic particles with poly(lactic-*co*-glycolic acid) and PDA were successfully employed.[233] However, those structures have not been investigated in colitis models. Initial experiments proved efficient permeability of mucus and epithelial cell membranes for particles.[233]

Studies on synthetic alternatives targeting the treatment of IBD are hardly available in the literature. There are many examples of systems with semi-synthetic, zwitterionic materials that hold the potential to be applied in IBD.[234,235] For example, zwitterionic lysine-modified polymers with mannose and selenocystamine moities show anti-inflammatory properties (by M2 macrophage phenotype polarization).[198] The zwitterionic lysines interact via hydrogen bonds and electrostatic interactions with PC and PE of the macrophage cell membrane and thus, enhance the binding affinity of surface-bound receptors with polymeric mannose motifs (Figure 4D). In addition to antibacterial properties caused by, e.g., selenocystamine motifs, the system also accelerated wound healing in vivo, which renders this zwitterionic material a highly interesting candidate for IBD research.[198]

2.2.4. Drug Carrier – Transport Mechanisms Harnessing Zwitterionic Materials

Zwitterionic motifs show enhanced interaction with cancer cells and thus enhance the site-specific uptake of drug-loaded carriers.[236] Further particle characteristics, in addition to charge, such as polarity, stiffness, size, and shape, might have an influence on cellular uptake as well.[43] In detail, the highly conserved zwitterionic motifs are mainly present at physiological pH values.[237] In the cancer cell environment, at an acidic pH level, the zwitterionic particles carry cationic charges since the negatively charged functional groups are increasingly protonated. As a consequence, particle-cell interaction is facilitated by electrostatic interactions between the positively charged particles and the anionic cell membrane.[238] The mechanisms driving cellular particle uptake are similar to those of healthy cells. However, other site-specific uptake pathways in cancer cells are discussed as well, which are based on passive targeting by particle size and hydrophobic interactions. For example, zwitterionic motifs might contribute to cellular uptake across the membrane via amino acid transporters as well.[63] The interaction is not clear in every detail, since hydrophobic particle interactions or the particle size could also affect the uptake. Thus, further enhancing our understanding of transporter-based uptake mechanisms would be beneficial, since currently established, specific particle motifs such as peptides and receptor ligands target cancer cells efficiently but are also very expensive and less stable.[239] Moreover, a kind of biofouling is targeted for zwitterionic particles, since corona modification with blood plasma proteins, e.g., albumin, improves the blood circulation time and reduces the uptake by macrophages.[240] In addition, those bound proteins form a stealth corona that protects the particle itself, enabling intact drug delivery into the cells.[241] In other words, specific proteins associated with the particle corona are thought to enhance the cancer cell interaction and finally internalization.[242] A general trend for

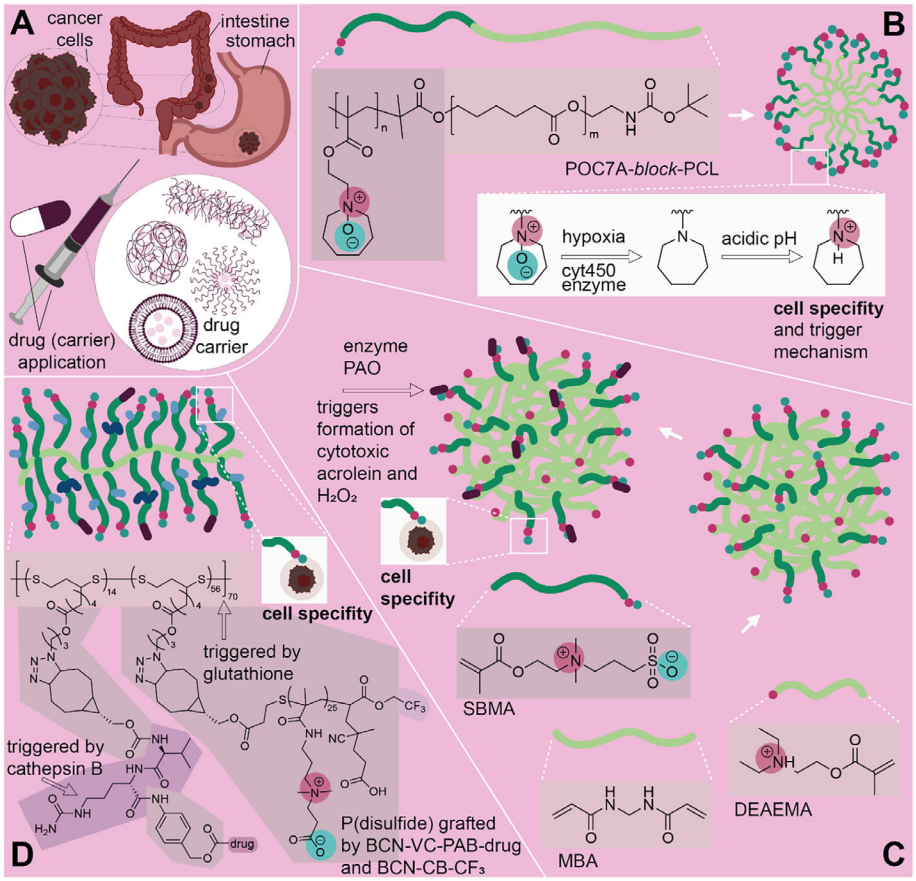

Figure 5. Overview of various zwitterionic drug carriers for combating cancer cells. a) The administration of drug carriers via injections and oral uptake is a common strategy to address cancer cells in the body. Zwitterionic drug carriers show naturally-derived structures such as micelles[259] (b) or assemble into artificial nanoparticles[263] (c) and bottlebrushes[264] (d) to specifically target cancer cells and release the drug in a sustained manner. POC7A-*block*-PCL = poly(2-(N-oxide-hexamethyleneimino)ethyl methacrylate)-*block*-poly(ϵ-caprolactone); cyt = cytochrome; PAO = plasma amine oxidase; SBMA = sulfobetaine methacrylate; MBA = *N,N′*-methylenebis (acrylamide); DEAEMA = 2-(Diethylamino) ethyl methacrylate; BCN-VC-PAB = bicyclononyne Val-Cit p-aminobenzyloxycarbonyl; BCN-CB-CF_3 = bicyclononyne carboxybetaine 2,2,2-trifluoroethyl acrylate.

zwitterionic particle systems is to tune cancer cell specificity and to incorporate mechanisms, e.g., to transport drugs more safely and release them in a sustained manner (**Figure 5A**). Different strategies are proposed to release therapeutic molecules intracellularly in malignant cells by stimuli such as pH and temperature changes, increased ROS and glutathione concentrations, or the presence of specific enzymes (e.g., esterase).[236] It is suggested that particles' zwitterionic motifs not only reach the cell site, but also trigger an endosomal escape within the cell to liberate the drug into the cytosol (and nucleus) and combat the cancer cell.[243,244] In-depth studies on the endosomal escape strategy of zwitterionic materials are rare; however, they would be useful for improving or developing new drug carrier materials since different mechanisms, such as particle swelling, membrane destabilization, and proton sponge, to overcome the endosomal membrane are discussed in the literature.[245]

Thanks to broad drug carrier research in the field of cancer therapy in recent decades, those systems might be able to attack malignant cells without affecting healthy tissue.[246–248] So far, chemotherapy[249] or freely administered drugs[250] have been applied for the treatment of cancer. However, those strategies are not limited to cancer cells and therefore, affect the overall human health state.[251] Yet there is a huge variety of potential particle systems with zwitterionic motifs for enhanced specific cancer cell interaction dealing with this challenge – although the uptake mechanisms are not deciphered in every detail.[12; 252] The ongoing progress in the field of advanced drug carrier design is not limited to bio-derived particle materials; instead, (semi-)synthetic alternatives with tailored properties are increasingly favored.[27]

Many scientists mimic naturally-derived structures to develop a unique strategy for addressing cancer cells. Well-known examples are the self-assembly of polyzwitterionic micelles and liposomes (**Table 2**).

Among those studies, we highlight the micelle-based system of Zheng et al.[259] in detail. This biomimetic system uses the zwitterionic key lipid variant, poly(2-(N-oxide-hexamethyleneimino)ethyl methacrylate) (POC7A)-*block*-poly(ϵ-caprolactone) (POC7A-PCL) which is produced by ATRP (Figure 5B). The hydrophilic particle corona is formed by POC7A, whereas the hydrophobic PCL is located in the core and encapsulates the anti-tumor drug doxorubicin (drug loading capacity: ≈7%; encapsulation efficiency: 71%). Those micelles

Table 2. Naturally-derived assembled structures, such as micelles and liposomes, are well-known examples of zwitterionic (semi-)synthetic drug carriers.

Structure assembly	Polymer/ biomolecule	Zwitterionic motif	Stimuli-responsive drug release	Refs.
Liposomes	1,2-Distearoyl-*sn*-glycero-3-phosphoethanolamine, cholesterol, hydrogenated soybean PC	pCB	pH	[135]
(Trojan for) liposomes	BBT with substituted bulkier 3,4-Ethylenedioxythiophene and terminal sulfonate groups	side chains with quaternary ammonium and sulfonate group	light	[253]
Micelles	poly(glycidyl methacrylate)-*b*-poly(SB methacrylate)	pSB	pH	[254]
Micelles	polytyrosine (PTyr); poly(oligo(ethylene glycol)monomethyl ether methacrylate-*co*-sulfobetaine methacrylate-*co*-disulfide dimethacrylate) (*P*(OEGMA-*co*-SBMA-*co*-DSDMA)) shells	SB	enzyme/glutathione	[255]
Liposomes	Zwitterionic amino phospholipid construct; cholesterol; PEGylated phospholipid	phosphoryl-choline	pH	[256]
Micelles	poly(1,4,5-oxadithiepan-2-one)-block-poly(2-(dimethylamino)ethyl methacrylate)-ZIP	CB analogue	pH/redox	[257]
Micelles	palmitoyl-poly(2-methacryloyloxyethyl phosphorylcholine)	polyMPC	micelle destabilization	[128]
Micelles	poly(2-methacryloyloxyethyl phosphorylcholine-*block*-poly(di(ethylene glycol) methyl ether methacrylate-*co*-4-formylphenyl methacrylate)	MPC	pH	[258]

– with an average size diameter of ≈42 nm – hardly interact with cells or proteins in vitro and exhibit a long blood circulation time (half-lives of ≈8 h), as well as tumor-specific accumulation (tumor inhibition of ≈84%) when injected intravenously into mice. Once the particles reach the target site (solid tumors), they are exposed to harsh environmental conditions such as hypoxia and acidity, triggering response mechanisms. First, N-oxide is converted to poly(tertiary amine) by cytochrome P450 enzymes, which are increasingly expressed by cancer tissue under hypoxia conditions. Afterward, the obtained poly(tertiary amine) is protonated at acidic pH, generating cationic motifs on the micelle surface. Those positively charged moieties combined with PC7A allow the particles to penetrate the tumor cell membrane more efficiently.[259] Further analysis on parameters such as stiffness could be beneficial to deciphering particle and material characteristics that enhance this uptake mechanism as well.

These initial drug carriers are aimed at making use of naturally occurring structures; however, numerous other material developments are investigated to further tune particle systems. For example, silica-based particle systems with zwitterionic motifs were shown to have potential as drug vesicles as well.[260–262] Moreover, modification strategies are not only restricted to enhancing the cellular uptake of zwitterionic materials, but those site-specific moieties can also serve as acceptors for active compounds, e.g., enzymes, via electrostatic interactions.[263] Upon particle internalization by targeted cells, surface-bound enzymes such as plasma amine oxidase convert polyamines, which are upregulated in cancer cells, to cytotoxic acrolein and H_2O_2 and thus trigger the apoptosis pathway. To create this smart system, zwitterionic SBMA and 2-(diethylamino) ethyl methacrylate (DEAEMA) are crosslinked by *N,N′*-methylenebis (acrylamide) (MBA) via free radical reaction. In a second step, the zwitterionic particles (average diameter of ≈186 nm) interact electrostatically with plasma amine oxidase (Figure 5C). As already indicated, the biocompatible particles have proven their antitumor efficiency both in vitro and in vivo in a mouse model, thus, it could be a beneficial innovation for drug carrier design in cancer treatment.[263]

Researchers also focus on drug carriers, which are neither comparable to membrane-based structures nor purely composed of natural materials. For example, Shao et al.[264] demonstrated that bottlebrush polymers hold the potential for drug carriers as well. To attain those structures, first, a polymer-backbone consisting of poly(disulfide) was produced by AROP. In a second step, building blocks of zwitterionic CB and 2,2,2-trifluoroethyl acrylate formed by RAFT synthesis, as well as the bicyclononyne Val-Cit p-aminobenzyloxycarbonyl linker, were covalently grafted to the backbone via click chemistry (Figure 5D). The linker motifs bind drug molecules, e.g., doxorubicin, and release them in a sustained manner in cancer cells by two mechanisms: Intracellular overexpressed cathepsin B cleaves Val-Cit and liberates drug molecules. Moreover, the cysteine bonds of the polymer backbone were degradable by the reducing environment in cancer cells (high glutathione level), which favors doxorubicin release. The zwitterionic functionalization, in turn, promotes cell specificity, and cell uptake is further supported by fluorocarbon, since it enhances the interaction with amphiphilic cell membranes.

Owing to their cell specificity, detailed investigations on additional parameters mediating uptake could be helpful to gain more selection criteria for novel zwitterionic carrier materials. Nevertheless, a suitable in vitro model has shown that the resulting bottlebrushes (hydrodynamic diameter of ≈35 nm) could be internalized by cancer cells. In the following, the protonated carboxylic groups of the bottlebrushes' zwitterionic motifs allow the endosomal escape (acidic conditions). Afterward, the loaded active compound is liberated from the drug carrier and kills the cancer cell. Such bottlebrushes have shown improved blood circulation time, satisfactory biocompatibility, anti-inflammatory properties, tumor specificity, and suppression when injected

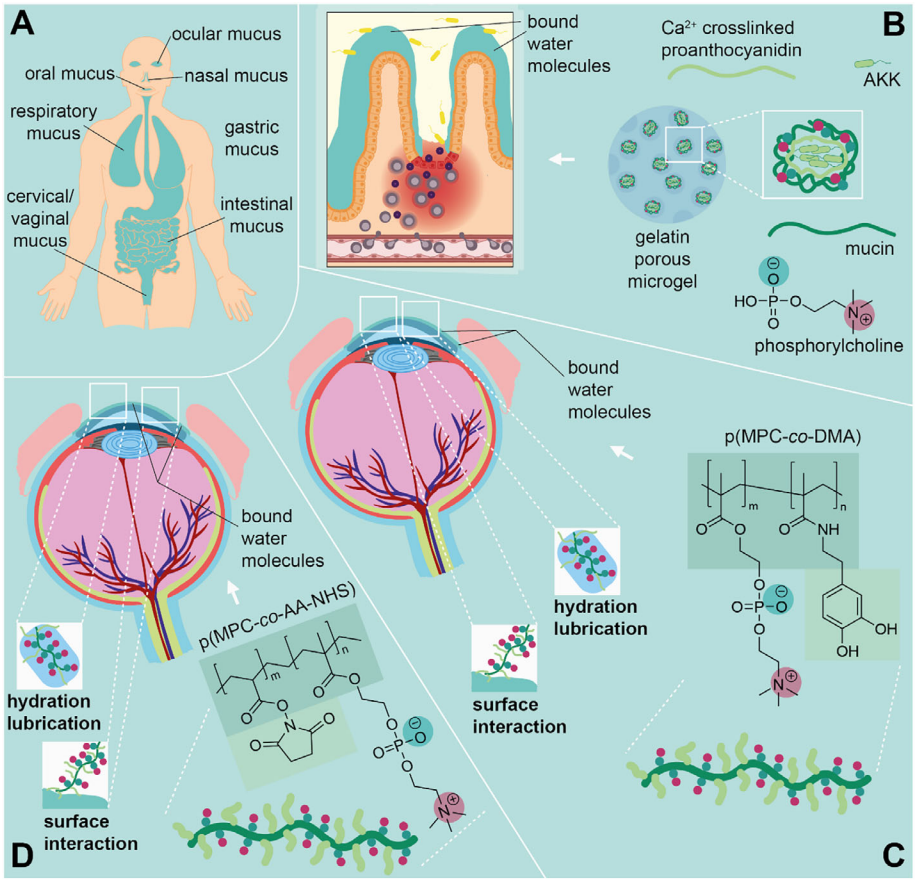

Figure 6. A few examples that show how naturally occurring physical mucus-based barriers in the human body are preserved. a) Tissues such as the lungs, the gastrointestinal tract, eyes, mouth, nose, and the female reproductive system are lined with mucus. To restore the mucus properties in inflammatory bowel disease (b), and dry eye syndrome (c,d), naturally occurring[280] (b), semi-synthetic[130] (c), and almost completely synthetic[285] (d) zwitterionic materials are developed. AKK = *Akkermansia muciniphilia*; p(MPC-*co*-DMA) = poly(2-methacryloyloxyethyl phosphorylcholine-*co*-*N*-(3,4-dihydroxyphenethyl)meth-acrylamide); p(MPC-*co*-AA-NHS) = poly[2-((methacryloyl)-oxy)ethyl]phosphorylcholine-*co*-N-hydroxysuccinimidyl acrylate.

intravenously in mice.[264] Similarly, other systems based on bottlebrush structures are available in the literature which could be used for drug delivery.[83; 265,266]

2.2.5. Hydrogel – A Combination of Crosslinking Properties and Hydration Lubrication

Hydrogels, relying on their composition, possess a wide range of properties including mechanical strength, porosity, and biocompatibility. It is likely that those characteristics are applicable to further biomedical settings.[267] To highlight some selected application areas: Hydrogels are created as depots to release therapeutics in a sustained manner,[268] patches to regulate wound healing,[269] coatings for medical devices to combat bio-fouling processes,[14] lubricants for joints,[270] and sensors to detect, e.g., cardiac function in vivo.[271] However, those prominent examples have already been addressed in this review or will be discussed in later sections in detail. Therefore, in this chapter, we will focus on the substitution of endogenous hydrogels or the protection of those layers. Mucus is secreted by goblet cells[272,273] and plays an important role as a natural hydrogel barrier found in the eyes, lungs, the whole gastrointestinal tract, as well as in the female reproductive system (**Figure 6**A).[274] Typically, mucus is composed of network-forming biomolecules, so-called mucins (≈5% w/v), ions, proteins, lipids, and water (≈95%).[272]

The resulting hydrogel layer serves as a selective barrier against the penetration of toxic substances, pathogens,[275] and regulates immunological responses.[276] Thus, loss of mucus barrier functionality is often associated with the development of diseases. On the other hand, an excessive mucus secretion (= hypersecretion) combined with reduced water deposition alters the viscoelastic properties of the hydrogel and thus, contributes to the development of complex pathological scenarios such as Chronic Obstructive Pulmonary Disease (COPD) and asthma.[272] In other words, maintaining the endogenous mucus layer balance could preserve the body's healthy state. Owing to the multiple negatively charged polysaccharides in the core domain of mucins, those biomacromolecules interact with water molecules via hydrogen bonds and thus, promote hydration lubrication.[277] Furthermore, the mucin-water molecule interaction helps to ensure low-biofouling properties.[278]

Inspired by those glycoproteins, scientists created tuned, zwitterionic materials – instead of just being anionic – to mimic

those hydrogel properties. Those zwitterionic molecules promote the successful formation of bio-inspired or bio-derived crosslinked matrices via intermolecular electrostatic interactions. In addition, the attractive forces of the formed network for water molecules allow matrix swelling and thus, endow it hydrogel characteristics.[15] Those materials could either replace mucus layers or strengthen the regeneration and integrity of endogenous mucus as natural barriers.

Although having shown the immunomodulatory properties of zwitterionic materials in IBD, we have not mentioned that this disease is based on a complex synergy of a dysregulated immune system and a reduced or lost physical mucus barrier.[279] Zhang et al.[280] developed a bio-driven solution based on naturally occurring material combinations and probiotics to successfully restore the mucus barrier function in colitis mice after oral uptake (Figure 6B). This system is made from bacteria *Akkermansia muciniphila*, which can degrade mucus; however, also stimulates goblet cells in the endogenous, intestinal environment to secrete those slimy molecules for barrier formation. For this purpose, a moderate dose of those bacteria (1×10^{10} colony forming units) is encapsulated in a multilayer coating: First, a network of antioxidant and anti-inflammatory active proanthocyanidins noncovalently coordinated by Ca^{2+} embedded the probiotics and interact with the next layer of mucin and zwitterionic phosphorylcholines – which forms a second hydrophobic, charged protective layer on *Akkermansia muciniphila*. The resulting compounds are transported in gelatin porous microgel, which creates a stable network for intestinal uptake of the system via oral administration. Proanthocyanidins, mucins, and phosphorylcholines adhere to the natural mucus layer of the inflamed intestinal tissue via hydrogen and disulfide bonds and prevent the passage of pathogenic bacteria and toxins from the intestinal lumen into the lamina propria. This selected example already indicates that naturally-derived systems could be very promising for application in IBD, however, other semi-synthetic, zwitterionic alternatives have been found in the literature.[280]

The following semi-synthetic materials hold the potential to be applied in a medical setting to protect the mucous layer. For example, a network of methacrylated alginate (methacrylation reaction of SA with glycidyl methacrylate) and thiolated pSB (hydrolytic reduction of poly(*N*,*N*-diallylcystamine-*co*-sulfobetaine methacrylate)) interacts with mucus in the uterus and blocking the premature slimy secretion.[281] This helps to increase the drug efficiency since those active compounds have to penetrate the selective mucus barrier to reach the underlying epithelial layer, and thus, a delayed secretion time of the slime increases the translocation effects.[282] For example, such a type of hydrogel could be placed on mucus layers, which, due to infection or disease, are only present as a thin barrier and thus are unable to effectively defend the body from contaminants. *Helicobacter pylori*, e.g., weakens the physical mucus barrier by attacking slime-producing cells in the stomach. Therefore, a suitable hydrogel offers its use as a replacement material for mucus in vivo.[283]

The next example is given by the semi-synthetic hydrogel based on copolymers synthesized via RAFT polymerization of adhesive DOPA motifs (*N*-(3,4-dihydroxyphenethyl)methacrylamide) and zwitterionic 2-methacryloyloxyethyl phosphorylcholine (Figure 6C).[130] Polymeric catechol groups serve as crosslinkers and strengthen the cohesion through interchain interactions by π-π stacking. The formed network could open novel application potential for the treatment of dry eye syndrome. This disease occurs as a result of damage to the protective tear film in the eye and is associated with itching and ocular surface defects.[130] In general, the tear fluid contains mucin molecules which provide hydration and lubrication to keep the eyes moisturized, healthy, and reduce friction.[284] The novel hydrogel is designed to compensate for the functionality loss and further properties are introduced to improve the material performance. For example, the hydrogel is formed by incorporating water into the matrix via electrostatic interactions between the zwitterions and water molecules, which offers several functions: It replaces or compensates the physical barrier function of mucus, i.e., the applied, biocompatible and zwitterionic hydrogel sticks to the eye for up to 4 days and promotes lubrication (COF value of 0.36, setup: silicon tube modified steel wires on flat silicon sheets, 2N, the sliding velocity of 150 mm/min) and hydration. On the other hand, muco-adhesion is achieved by catechol moieties that act synergistically through hydrogen bonds or covalent interactions (Michael addition and Schiff base reaction) with mucin molecules. Moreover, this zwitterionic material possesses additional features such as antioxidant, anti-inflammatory, and tissue resorption characteristics. Thanks to all those attributes, the hydrogel is able to alleviate the dry eye syndrome.[130]

Synthetic alternatives such as materials made from zwitterionic [2-((methacryloyl)-oxy)ethyl]phosphorylcholine and adhesive *N*-hydroxysuccinimidyl acrylate provide an artificial tear film substitute as well (Figure 6D).[285] The copolymer is synthesized via radical RAFT polymerization and supplies the eye with a hydration layer. This mechanism is based on the ion-dipole interaction of phosphorylcholine with water molecules. Moreover, *N*-hydroxysuccinimidyl acrylate forms amide bonds that allow the copolymeric hydrogel to interact with amino groups of the eye and reveal proper tissue surface adhesion. The formed material not only acts as a moisture and alleviates symptoms originating from dry eye syndrome but also conveys surface lubrication (COF value of 0.085 with a ball-on-flat setup of PTFE microsphere and Si wafer; load of 0.5 N and reciprocation frequency of 1 Hz) to protect the eye during mechanical stress such as blinking. Initial in vivo experiments proved this artificial tear fluid to be biocompatible, reduce protein absorption as well as pro-inflammatory cytokine expression, and successfully improve the retention time on the eye.[285]

In addition, self-healing, zwitterionic hydrogels with antioxidant properties also might offer high potential as mucus-bound copolymers for medical applications. Tao et al.[131] developed copolymers made from zwitterionic phosphorylcholine and phenylboronic acid-modified dihydropyrimidin(thio)one which interacts with mucins. Thus, this strategy could preserve the natural physical barrier functions of partially degraded mucus in the body.[131]

2.2.6. Tissue Engineering – Network Forming Properties of Zwitterionic Materials

Most studies focus on the tissue engineering of bone[286,287] and cartilage[288,289] with zwitterionic substitution materials, but instead, we attempt to discuss other important tissue structures

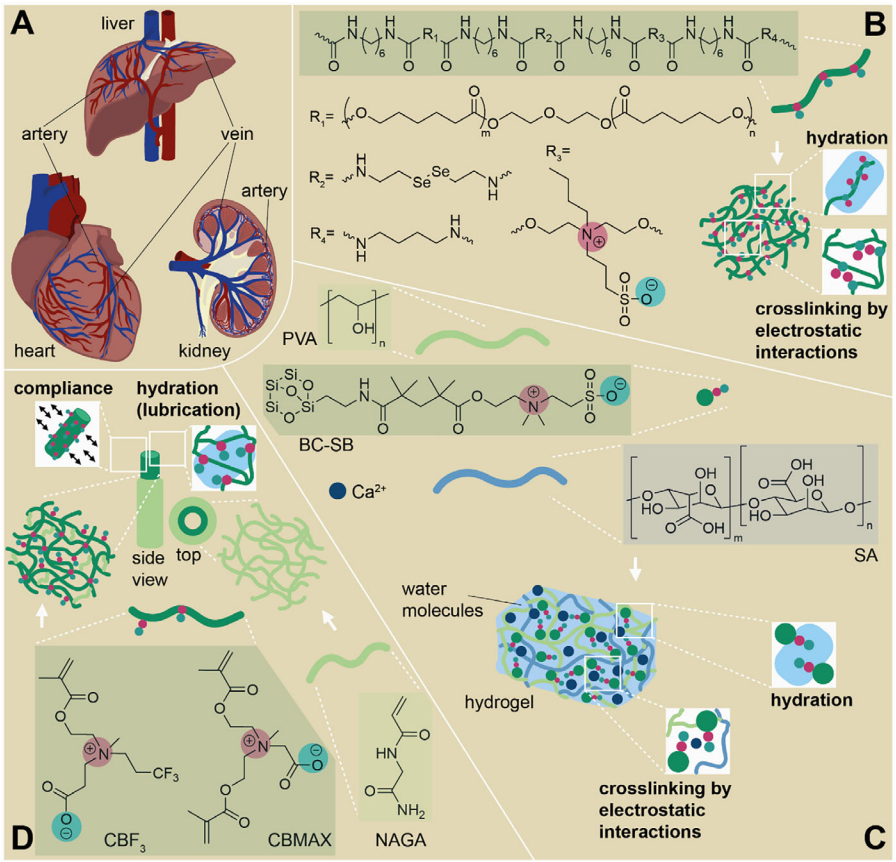

Figure 7. Selected examples of different macromolecular materials as a replacement alternative for small-diameter vascular grafts. a) Arteries and veins are contained in human tissue, especially in organs, to ensure oxygen and nutrient transport. Artificial substitutes of natural-based[299] (b), semi-synthetic[300] (c), and almost completely synthetic[301] (d) zwitterionic materials to create small-diameter vascular grafts for tissue engineering. R_1 = poly(ε-caprolactone)-diol; R_2 = selenocystamine; R_3 = sulfobetaine-diol; R_4 = 1,4-butanediamine; PVA = polyvinyl alcohol; BC-SB = sulfobetaine-methacrylate modified bentonite clay nanoparticles; Ca^{2+} = calcium ion; SA = sodium alginate; CBF_3 = zwitterionic fluorinated monomer; CBMAX = carboxybetaine dimethacrylate; NAGA = *N*-acryloyl glycinamide.

in this section. Typically, those (zwitterionic) substitution materials are known for their hydration, low-biofouling and immunological activity, as well as, for the support of cell adhesion and embedding.[288] The latter property makes zwitterionic motifs an interesting structural feature for the field of biofabrication and 3D bioprinting of artificial organs (e.g., liver and kidney;[290] **Figure 7**A). The formed tissue structures should act as replacements in certain cases, e.g., after endogenous loss of functionality. However, one common feature all of those printed constructs share is their insufficient formation of arteries (transport of oxygen-rich blood)/capillaries (nutrient, oxygen release)/veins (transport of oxygen-poor blood) to maintain tissue homeostasis.[290] To create corresponding materials, in addition to general material characteristics imposed by human physiological demands, technological and biological challenges are also present.

In general, polymer-based large blood vessels (diameter > 6 mm) are commercially available and used in clinical routine (e.g., polyethylene terephthalate and polyethylene terephthalate).[291] However, for the smaller blood vessels (diameter < 6 mm) infiltrating organs, alternatives are scarce since multiple parameters for satisfying blood perfusion remain, yet this is an unmet demand.[291] For example, material compositions with high mechanical strength are required that are able to deal with the blood pressure in vivo. Moreover, selective permeability of the blood vessel substitutes modulates the nutrient and oxygen supply of the organs,[291] as well as the disposal of CO_2.[292] In addition, the material characteristics are essential to circumvent immune reactions, thrombus formation, and biofouling events.[291] We discuss the latter aspect in more detail: Since the bio-derived and (semi-)synthetic blood vessel substitutes should integrate optimally into the cellular microenvironment of the printed organ, it is desired that vascular smooth muscle cell adhesion is suppressed on the inner surface of the tubes (= intimal hyperplasia; followed by risk of restenosis[293]), whereas cell attachment and growth is facilitated on the outer material interface. How do the physicochemical properties of zwitterionic materials influence the design of novel, suitable vascular structures?

The mechanistic principles responsible for anti-biofouling, i.e., the repulsion of blood components such as fibrinogen and platelets, which are relevant in the thrombus formation[294] – and immunomodulatory processes of zwitterions have already been discussed in the previous chapters. A pronounced accumulation of water molecules via electrostatic interactions[295]

and hydrogen bonds[296] causes further positive effects for tissue and cell interactions: the incorporated water alters the material's mechanical properties and thus affects cell proliferation and differentiation, as well as migration.[297] This first scenario is complemented by enhanced diffusion, e.g., of nutrients and oxygen toward cells, since the permeability of the material increases due to the high water-binding capacity.[297] An ideal zwitterionic material that fully satisfies all those complex demands is very difficult to find. This indicates not only how challenging the engineering of the advanced, artificial microvascular system is, but also the high potential of innovations in this field. Owing to the versatility in medical applications, such materials could also be relevant for vascular grafts as substitutes for lower limb vein disease or medium-diameter vascular grafts to improve the life quality of dialysis patients.[298] In the following section, we discuss a number of promising, novel zwitterionic materials to create future arteries, veins, and capillaries – regardless of their fabrication and processing technique. Naturally-derived zwitterionic materials hardly fulfil the required mechanical properties. This is the main reason for dysfunction of bio-derived vascular systems; instead, combinations with synthetic polymers are required and discussed in this section.

For example, Yuan et al.[299] synthesized zwitterionic diselenide-containing poly(ester urethane) urea polymers forming disordered systems based on the following monomers: hydrophilic, zwitterionic sulfobetaine-diol (SB-diol), hydrophobic PCL-diol, seleno-cystamine, and 1,4-butanediamine (Figure 7B). The formed material shows good biocompatibility, promotes proliferation of endothelial cells (ECs) and smooth muscle cells (SMCs), and possesses low-biofouling characteristics modulated by zwitterionic moieties. Moreover, SeCA stimulates endothelization in vitro through nitric oxide (NO; ≈1.5 mol cm^{-2} min^{-1}), an important regulator of vascularization. Mechanically strong vascular grafts were generated from the zwitterionic polymers with longitudinal and circumferential Young's modulus of≈12 and ≈3 MPa in the wet state, tensile strength of ≈10 MPa (longitudinal) and ≈3 MPa (circumferential) as well as a breaking strength of ≈200% (longitudinal) to ≈250% (circumferential). In comparison, human saphenous veins show an elastic modulus up to ≈1.5 MPa and a tensile strength up to ≈11.4 MPa (break at elongation: ≈160%). Indeed, stability and flexibility are crucial for in vivo applications, however, burst pressures similar to those of human saphenous veins (up to 2273 mmHg) are also required. Polymeric tubes (thicknesses of 300 µm) exhibited values of ≈2300 mmHg, a compliance of ≈1.7%/100 mmHg (human saphenous veins: 1.5%/100 mmHg), and a suture retention strength of ≈1 N. Once placed in the rat abdominal aorta interposition model in vivo, the formed vascular grafts with small diameter were found to be anti-thrombogenic, aneurysmal dilatation was absent, and modulated macrophage polarization enhanced wound healing as well as fast endothelization on the luminal surface. Although hyperproliferation has not yet been observed, enhanced growth of SMCs was detected on the luminal surface compared to the control (poly(ε-caprolactone)-diol).[299]

Improving the material could be a promising strategy to circumvent those issues, such as SMC attachment. For instance, Dawit et al.[300] suggested that the incorporation of zwitterionic SBMA modified bentonite clay nanoparticles into ionically crosslinked sodium alginate (SA)/ polyvinyl alcohol hydrogels via physical crosslinking (electrostatic interaction, hydrogen bonds) could pave the way for novel material properties (Figure 7C). The material tests are limited to subcutaneous in vivo applications of those vascular tubes in rats. Thus, neither ECs nor SMCs adhesion could be observed. However, the strong material swelling by contained zwitterionic motifs inhibited inflammatory reactions and formation of fibrous capsules. This already indicates that material combinations could serve as an alternative, especially when considering the anti-thrombogenic, anti-inflammatory, anti-bacterial, and biocompatible characteristics in vitro. It was shown that those properties are achieved by embedding zwitterionic particles, which allowed for the formation of dense molecular network structures, preventing the adhesion/ ingrowth of biological components. In addition, the incorporated particles improve the material's mechanical properties (tensile strength of ≈100 kPa; break at elongation: ≈42%). Compared to the first example, mechanical strength in the range of human saphenous veins was not obtained; however, the reduced cell adhesion (based on SBMA-CBs) holds the potential to improve the luminal surface of one-layered vascular tubes by integrating such particles.[300]

Another possibility to successfully control SMC growth on luminal surfaces is the engineering of bilayer systems: Li et al.[301] showed the combination of the inner layer composed of zwitterionic fluorinated hydrogel – chemically crosslinked through CB dimethacrylate – with the outer layer consisting of poly(*N*-acryloyl glycinamide) hydrogel – stabilized by intermolecular hydrogen bonds – via step-by-step polymerization (Figure 7D).[301] Based on those materials, tubes are formed with a thickness of 250 µm per layer and a peel strength of 400 N m-1 (180° peel-off test between both layers). Moreover, the vascular grafts reveal a tensile strength of ≈2 MPa (elongation at break: >500%), a burst pressure of ≈1700 mmHg, a compliance of 5%/100 mmHg, and a suture strength von 247 gf, which is comparable to natural blood vessels. Hydration of the zwitterionic motifs and thus material swelling provides the inner layer with optimized lubrication – COF of 0.039, which is similar to the native vessel intima with COF of 0.04 to 0.15 – anti-thrombogenic and anti-inflammatory properties in vitro, whereas the outer layer promotes the attachment of cells and absorption of blood proteins/ platelets. Transplantation of the formed tubes into carotid arteries of rabbits and pigs confirmed a constant blood flow velocity of 1.1 m s^{-1} (rabbit) and 0.6 m s^{-1} (pig), indicating the absence of aneurysm and intimal hyperplasia. Furthermore, neither fibrous capsule formation nor collagen deposition on the outer membrane was visible, which emphasizes the biocompatibility of the zwitterionic bilayer system.[301]

These few selected examples of zwitterionic, semi-synthetic systems show the ongoing advances in the field of tissue engineering and biofabrication, however, challenges still exist to obtain small-diameter vascular grafts for medical and regenerative medicine applications.

2.2.7. Wound Healing – Tissue Interaction and Cohesion of Zwitterionic Materials

Epidermal wound defects occur as a result of trauma, chemical exposure, and burns; however, they also occur during surgery.[302]

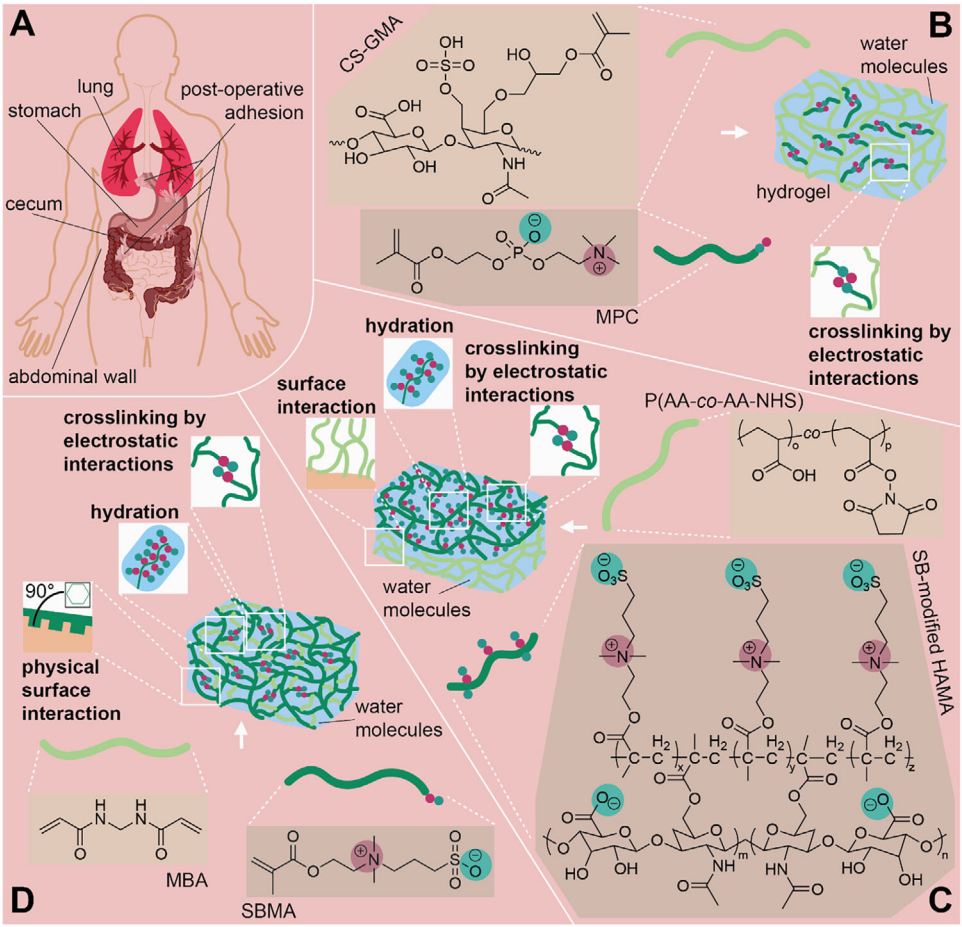

Figure 8. Overview of various zwitterionic materials for preventing post-operative adhesion. a) The pathological scenario is characterized by excessive fibrous bands and collagen formation connecting different human organs. To reduce complications during post-operative wound healing, fully naturally occurring[129] (b), semi-synthetic[322] (c), and almost completely synthetic[310] (d) zwitterionic materials are created. CS-GMA = methacrylate chondroitin sulfate; MPC = 2-methacryloyloxyethyl phosphorylcholine; P(AA-*co*-AA-NHS) = poly(acrylic acid-*co*-*N*-hydroxysuccinimide acrylate); SB-modified HAMA = sulfobetaine-modified methacrylate hyaluronate acid; MBA = *N*,*N*′-methylenebis(2-propenamide); SBMA = sulfobetaine methacrylate.

Typically, the healing process is precisely regulated by four different states: hemostasis, inflammation, proliferation, and remodeling.[303,304] In detail, hemostasis involves platelet adhesion induced by bleeding and, hence, the associated formation of a fibrin clot for wound closure. Furthermore, specific proteins such as cytokines are released, which stimulate inflammation. This allows neutrophils and macrophages to continuously infiltrate the wound and combat pathogens localized in the fibrin network. Over time, macrophages can liberate anti-inflammatory signal molecules to accelerate angiogenesis. Afterward, fibroblasts migrate into the wound, which are likely to contribute to deposition of extracellular matrix and boost collagen production to achieve re-epithelialization of the defective tissue. The last step includes the collagen network reconstruction and scar formation.[305,306] During wound healing, however, complications such as infections, hematomas, and excessive proliferation of new tissue are possible.[304] Especially, it has been discussed that unwanted adhesion with other tissues or organs arise from post-operative wound healing.[307] This process is mainly governed by the overproduction of ROS, which, based on oxidative stress response of the treated tissue, drives inflammation, and thus, promotes excessive fibrous bands and collagen formation favoring postoperative (abdominal) adhesion (**Figure 8**A).[308]

Several material combinations are introduced as a solution to this multifaceted problem. A wide range of zwitterionic systems, based on hydrogels and in the form of adhesive patches,[309] interact with tissue surfaces via hydrogen bonds,[310] dipole–dipole, and electrostatic interactions.[311] In addition, those non-covalent forces[312] provide the formed adhesive matrix with cohesion properties.[313] Maintaining the balance of zwitterionic motifs within the material is an important demand, i.e., the overall number of zwitterions present must be either below or above a certain threshold, depending on the material composition and required properties. Indeed, material adhesion to tissue is less efficient when a lower number of zwitterions is available, since the water-binding propensity of those motifs is reduced, and interfacial water prevents strong interactions with moist body surfaces. In comparison, excessive amounts of material-bound zwitterions leading to swelling, i.e., the formed network favors high water binding capacity[314] and thus, inhibit material-tissue interactions by lubricity.[315] The latter aspect is desirable in the

context of post-operative adhesion to protect the body against fibrous bridges to other tissues and organs.[314] Therefore, many researchers have been inspired by systems with two opposing surfaces – one containing fewer zwitterionic motifs, which faces the wound; and one surface, which confers swelling to the material (high number of zwitterions) and thus, minimizes post-operative tissue interactions. It is not surprising that those combinations enhance the wound healing process.

To obtain ideal wound healing conditions, researchers create different novel hydrogel and patch systems consisting of up to three layers and various material combinations. For example, Wen et al.[129] developed a naturally occurring, injectable, and self-healing, zwitterionic hydrogel (Figure 8B). This material was formed by free radical polymerization of methacrylate chondroitin sulfate (CS-GMA) and MPC. Zwitterionic motifs combine hydrophilicity and low-biofouling properties, whereas the CS inhibits the interaction of two tissue surfaces with each other via hydrogen bonds and promotes hydration. Moreover, non-covalent, electrostatic interactions and hydrogen bonds strengthen the material network such that an elasticity-dominated hydrogel (≈100 Pa at a frequency of 1 Hz) was formed at body temperature. In addition, the hydrogel could be injected via a syringe since it possesses shear thinning properties and, after curing, achieves the required physical barrier on the post-operative wound with biological demands such as biocompatibility and degradability; however, the hydrogel has shown cell- and protein-repellency in vitro. In addition to being bio- and hemocompatible, CS-GMA hydrogels have been found to be promising as a post-operative adhesive in rat models with cecum-abdominal wall adhesion: The material prevents not only primary but also recurrent adhesion and degrades easily in vivo over time. Furthermore, migration of fibroblasts, collagen deposition, and inflammation were rather low (e.g., by downregulation of chemokine ligand 2 and the corresponding receptor), and tissue regeneration was promoted. Similarly, those hydrogels were successfully employed for applications in the stomach and liver in rats, proving the broad versatility of CS-GMA to reduce postoperative adhesions.[129] Among those natural one-layers such as CS-GMA hydrogels[129] or poly 3-[2-(methacryloyloxy)ethyl](dimethyl)-ammonio]-1-propanesulfonate-based materials,[316] semi-synthetic alternatives are available in the literature as well.[308; 317–321]

For example, a semi-synthetic, biodegradable, bio- and hemocompatible, zwitterionic system (Figure 8C) with two opposing surfaces has been developed by Zhang et al.[322] The adhesive layer is composed of poly(acrylic acid-*co*-*N*-hydroxysuccinimide acrylate) [P(AA-*co*-AA-NHS)] polymer brushes which provide combinations of non-covalent (hydrogen bonds and electrostatic interactions) and covalent (NHS groups interact with amino groups of tissues) bonds with tissue surfaces. This sticky compound is linked by free radical polymerization to the zwitterionic, low-biofouling material, which consists of pSB-type zwitterion (SBMA) crosslinked by methacrylated hyaluronate acid via free radical polymerization in a mold. Network cohesion is modulated by the covalent crosslinking and electrostatic interactions of zwitterionic moieties. This results in enhanced mechanical properties such as a tensile strength of 114 kPa (2 M SBMA, 0.4 mol% methacrylated hyaluronate acid; elongation at break: strain of 684%) and an elastic modulus of 67 kPa at a compressive strain of ≈80%. Because of their mechanical stability, the material can deal with the challenges in vivo, for example, pressure changes (e.g., burst) and deformation (e.g., leakage of air and fluids) when applied to wounds. *Ex vivo* experiments with porcine skin confirmed a promising adhesion strength of ≈118 J m^{-2} during 180° peel testing (peeling rate of 5 mm min^{-1}; patch-skin pre-incubation of 24 h). Moreover, the patch strongly adheres to tissue and shows collagen deposition and minor inflammation – from a biological point of view, this is important for the wound recovery – in the rat intestinal abrasion-abdominal wall defect model. However, the zwitterionic material surface entails a hydrated state and thus, prevents binding interactions with contacting tissue surfaces.[322] Similarly, other semi-synthetic, bilayer, post-operative adhesive materials,[323–326] or even triple-layer systems[327] are well-known.

Liu et al.[310] developed a very interesting, zwitterionic system as post-operative wound healing material (Figure 8D). The adhesive patch is based on bionic hexagonal facets, enabling water displacement on the wet tissue surface and thus physical interactions instead of chemical binding. Once the physical barrier is formed, zwitterionic motifs efficiently protect the surface from attachment of bacteria, proteins, and cells in vitro. The material is based on building blocks of SBMA crosslinked by DMAEMA during free radical polymerization in a mold. The polymer network is further stabilized by electrostatic interactions between zwitterionic moieties. Indeed, the cohesive and adhesive properties of the patch show a tensile strength of ≈20 kPa (0.5% crosslinker concentration; elongation at break: strain of ≈180%) and interfacial toughness of 14 J m^{-2} on porcine skin (180° peel test; speed rate of 20 mm min^{-1}). After successful mechanical *ex vivo* tests with wet mouse tissues (e.g., liver), the excellent post-operative adhesion inhibition was confirmed by in vivo tests with an abdominal wall cecum injury mouse model. Moreover, the formed patch is considered a very promising material due to its biocompatibility, hemocompatibility, low inflammation, gradual biodegradation, and tissue regeneration.[310]

2.2.8. Sensor – Zwitterionic Materials Facilitate Electrical Impulses

Lastly, we introduce here the potential of zwitterion-modified materials as sensors for detecting and inducing electrical impulses in the human body. The different properties of zwitterionic materials for medical applications, e.g., low-biofouling, have been described in the previous sections. Biosensors combine multiple characteristics at the same time to connect both worlds – biology and artificial technology. In other words, zwitterionic materials are tuned to be associated with the interaction between cells/tissues and bioelectronics to either initiate specific cell processes or to measure cellular activities.[328] Those interaction events are brought about by electrical, (electro-)chemical, optical, mechanical, or magnetic/thermal pathways in both directions. To mention one selected example: Electrodes allow for recording cellular transmembrane potentials; conversely, electrodes also modulate an external stimulus for cell-based voltage-gated ion channels.[328] Thus, biosensors hold enormous potential for, e.g., state-of-health monitoring by the detection of blood glucose levels of diabetes patients or the heart function of people suffering from cardiac disorders. Moreover, those sensors were used as

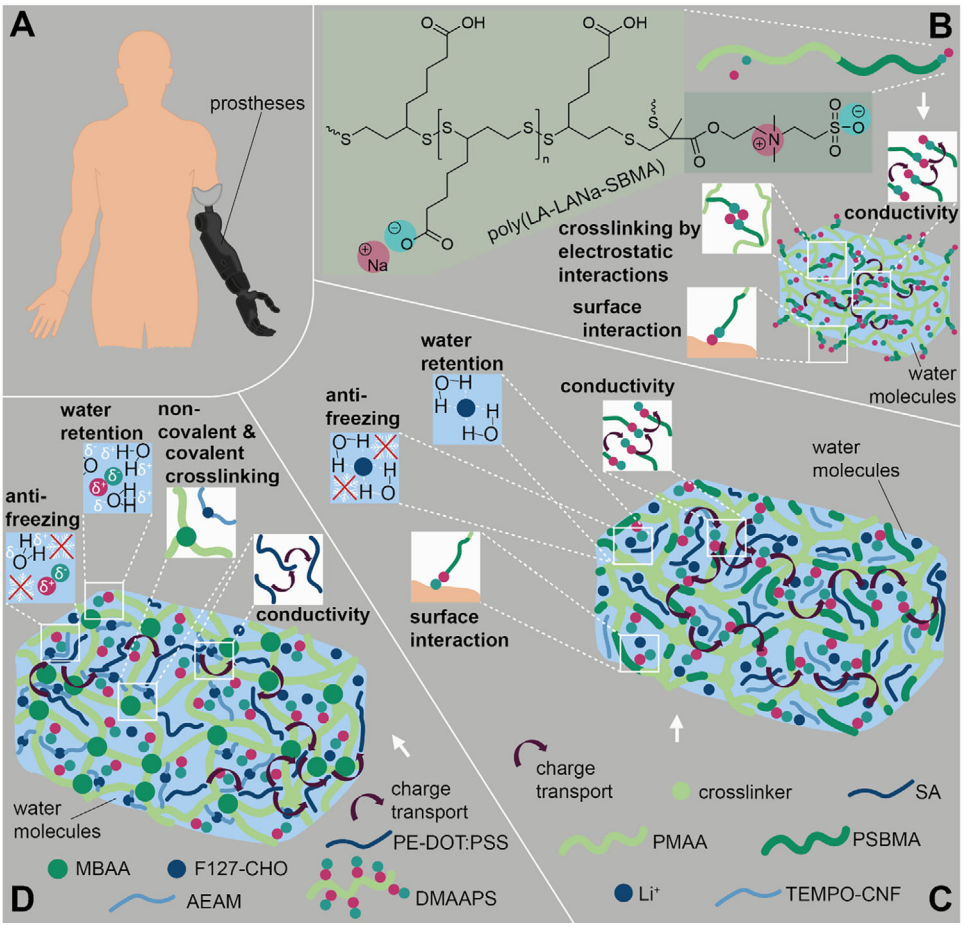

Figure 9. Schematic representation of different zwitterionic sensor materials which could be beneficial for the human-machine interface. a) The creation of specific sensors in the field of state-of-art research could be suitable for personalized, artificial prostheses. Tunable zwitterionic, naturally-derived[331] (b), semi-synthetic[333] (c), and almost completely synthetic[337] (d) materials show features to target this complex pathological scenario of human-machine interaction. Poly(LA-LANa-SBMA) = Poly(lipoic acid-sodium lipoate-sulfobetaine methacrylate); PMAA = polymerized 2-methacrylic acid; SA = sodium alginate; PSBMA =; TEMPO-CNF = TEMPO-oxidized cellulose nanofibers; Li^+ = lithium ion; MBAA = *N,N'*-methylenebisacrylamide; F127-CHO = aldehyde-functionalized Pluronic F127; AEAM = amino-modified monomer; DMAAPS = *N,N*-dimethyl (acrylamidopropyl) ammonium propane sulfonate; PE-DOT:PSS = Poly(3,4-ethylenedioxythiophene)-poly(styrene sulfonate).

detectors for biomarkers and proteins, which could allow for the investigation of early-stage cancer cell screening.[271] In addition to medical monitoring, sensors were suggested to be suitable for innovations in the field of robotics and at the human-machine interface.[329] The latter application area is likely to contribute to improved control over artificial limbs such as personalized prosthetic hands (**Figure 9**A). For this purpose, sensors are required to recognize signals from the neuromuscular system and to identify movement intentions – a machine learning algorithm is trained to track those signals and categorize them in predefined classes to obtain data, which is converted into movement signals – and trigger the artificial device to respond accordingly.[330] In particular, important features maintaining the system are the high sensor sensitivity, an artificial, intelligent machine learning approach, and the fast reaction to the input/output signals. It is worth mentioning that several sensor modalities are required within this system type to not only precisely identify the person's gestures, but also to reliably implement the measured signals to the prostheses. The complexity of those processes is further enhanced by the absence of fundamental data, such as tactile sensations or sensory input of gripping movements which aggravate the realization of such models and nicely illustrate that the development of personalized prostheses is still in progress.[330] Because of those reasons, we discuss in this section zwitterionic sensor materials which could be beneficial for applications at the human-machine interface in the future.

For example Yang et al.[331] use a naturally occurring material (Figure 9B) formed by lipoic acid (LA) and sodium lipoate (LANa) via ring-opening polymerization. These materials are functionalized with SBMA through nucleophilic addition reaction using thiol groups of poly(LALANa) to obtain poly(LA-LANa-SBMA) zwitterionic hydrogels as flexible sensor systems. Cohesion of the transparent hydrogel is thought to be facilitated by electrostatic interactions and hydrogen bonds of zwitterionic motifs. Covalent bound SBMA (60 mg per hydrogel) results in stable networks (tensile strength of ≈30 kPa; elongation at break: a strain of ≈700%), an interfacial toughness of ≈160 kJ m^{-3}, and Young's moduli of ≈70 kPa. Owing to the absence of covalent

crosslinks, however, the presence of dynamic disulfide bonds – in addition to hydrogen bonds and electrostatic interactions of SBMA in poly(LA-LANa) – the hydrogel possesses self-healing properties (tensile strength after 12 h healing ≈27 kPa). The zwitterionic moieties provide the hydrogel with antibacterial and adhesive properties on different surfaces via dipole–dipole interactions, hydrogen bonds, metal complexation, and electrostatic interactions (lap shear test with porcine skin: fracture strength of ≈16 kPa) as well as conductivity (0.55 mS cm^{-1}). Moreover, the zwitterionic nature of the hydrogel transports ions quite freely through the material network and offers bending detection on the wrist, knee, elbow, and finger, as well as breathing monitoring. The biosensor material features a low swelling ratio of ≈3%, retained water content of ≈70% – key factors to preserve mechanical properties – biocompatibility, degradability, non-toxic, antibacterial, antioxidant characteristics in vitro, and deformability when tested on humans.[331] Another promising cellulose-based sensor system can be found in the literature.[332]

Even though the biosensor example already indicates that naturally-derived zwitterionic materials combine a variety of properties, semi-synthetic alternatives may offer improvements such as an anti-freezing effect or retention of water at high temperatures, and thus, the human body application under various environmental conditions.[333] Han et al.[333] developed a promising material consisting of several components for biosensing-functionality (Figure 9C). A strong chemically crosslinked network was obtained by free radical polymerization of 2-methacrylic acid (MAA), 3-[*N,N*-dimethyl]-[2-(2-methylprop-2-enoyloxy)ethyl]ammonium]propane-1-sulfonate inner salt (SBMA), and *N,N*-Methylenebisacrylamide (MBA). The bonding strength of those covalent linkages between SBMA and PMAA is further improved by interactions with TEMPO oxidized cellulose nanofibers (TEMPO-CNF) and SA via hydrogen bonds. Lastly, a further crosslinker, namely Li^+, is integrated into the network through non-covalent, electrostatic interaction with SBMA or hydrogen bonds with SA. Like SBMA, Li^+ has an excellent water-binding capacity and thus contributes to the retention of bound water, prevents ice crystal formation at temperatures <0 °C, and maintains conductivity. Furthermore, Li+ helps to ensure the self-healing properties of the hydrogel-based sensor (81% recovery after 1.5 h) due to its non-covalent interactions. In comparison, the carboxyl groups of TEMPO-CNF improve the ion transfer and thus, indirectly enhance the material conductivity of the sensor material. Indeed, the conductivity is facilitated by SBMA within the system and differs depending on the temperature from ≈2.2 S m^{-1} at room temperature to ≈1.1 S m^{-1} at −22 °C. In addition, the zwitterionic moieties are responsible for the strong sensor adhesion on various surfaces by forming hydrogen and metal coordination bonds, as well as ion-dipole interactions. Lap shear experiments with porcine skin show a fracture strength of ≈4.9 kPa at room temperature and thus sufficient sensor-skin interaction for a medical application. TEMPO-CNF and SA considerably affect the mechanical properties of the sensor material. For example, the strain tolerance of the sensor at different temperatures proves the material integrity during deformation in use. The formed, biocompatible sensor material offers a very high information transmission fidelity, since hardly any signal losses and phase shifts were obtained during measurements with frequency (1 Hz–1 MHz) and voltage amplitude variations (60 mV–20 V). Applications of such zwitterionic sensors on human fingers, wrist, and elbow have already revealed the place of motion detection.[333] Other semi-synthetic sensors are available in the literature.[334–336]

Once the sensor material components are completely replaced by synthetic polymers, the anti-freezing properties can be enhanced further. Even though zwitterions have less impact on conductivity in the following hydrogel sensor system by Wu et al.,[337] we would like to emphasize this example to highlight the huge potential of zwitterionic-based materials (Figure 9D). In detail, the hydrogel composed of *N,N*-dimethyl (acrylamidopropyl) ammonium propane sulfonate, 2-aminoethyl acrylamide hydrochloride (AEAM), *N,N'*-methylenebisacrylamide (MBAA), and aldehyde-functionalized Pluronic F127-CHO was obtained via free radical polymerization. In addition to covalent crosslinking through MBAA, dynamic imine bonds facilitate micelle cross-linking formed by AEAM amino groups and aldehyde of Pluronic F127-CHO. This hydrogel network provides mechanical properties such as tensile strength of ≈0.22 MPa (elongation at break: strain of ≈2000%; toughness values of ≈2 MJ m^3), Young's modulus up to ≈120 kPa (relative humidity 40–80%), and self-healing properties (efficiency of 75% after 30 min). Poly-(2,3-dihydrothieno-1,4-dioxin)-poly-(styrene sulfonate) (PEDOT:PSS) embedded into the hydrogel further enhanced the material's conductivity (≈0.04 S m^{-1}). Moreover, the sensor functionality was retained during deformation, e.g., the gauge factor changes from 1.27 at 100% strain to 2.63 at 500% strain. Sensor application at the human forefinger demonstrated successful writing recognition. Since temperature variations between −80 and 45 °C do not limit the sensor function – zwitterions inhibited ice crystal formation within the hydrogel (≈30% water retention) – this kind of zwitterionic hydrogel sensor is highly suitable for human-machine interfaces.[337]

2.2.9. Zwitterionic Moieties Offer Excellent Material Innovations in Further Fields of Healthcare Applications

It is unlikely that zwitterionic materials can help in the treatment of all diseases, however, there are also several medical applications researchers have overlooked, so far, where zwitterions are found to be promising. Regarding the latter aspect, the number of studies harnessing zwitterionic materials for other therapeutic fields was mostly limited; however, in the following section, we discuss selected examples of semi-synthetic alternatives to target complicated pathological scenarios.

The first example includes the application of zwitterionic polymers as volume expanders in the blood during hemorrhagic shock (**Figure 10**A).[338] Naturally occurring molecules serving for treatments are hydroxyethyl starch, dextran, or succinylated gelatin, but they often accumulate in human tissue and might cause adverse side effects. In contrast, the fully synthetic polymers tend to interact with blood components and thus trigger bio-fouling processes. Kumar et al.[338] developed a semi-synthetic dextran system with zwitterionic amine oxides: Dextrans were post-modified with succinyl anhydride through their hydroxyl groups, and afterward, each anhydride motif reacted with an amine oxide via 1-ethyl-3-(-3-dimethylaminopropyl) carbodiimide/*N*-hydroxysuccinimide (EDC/NHS) coupling to

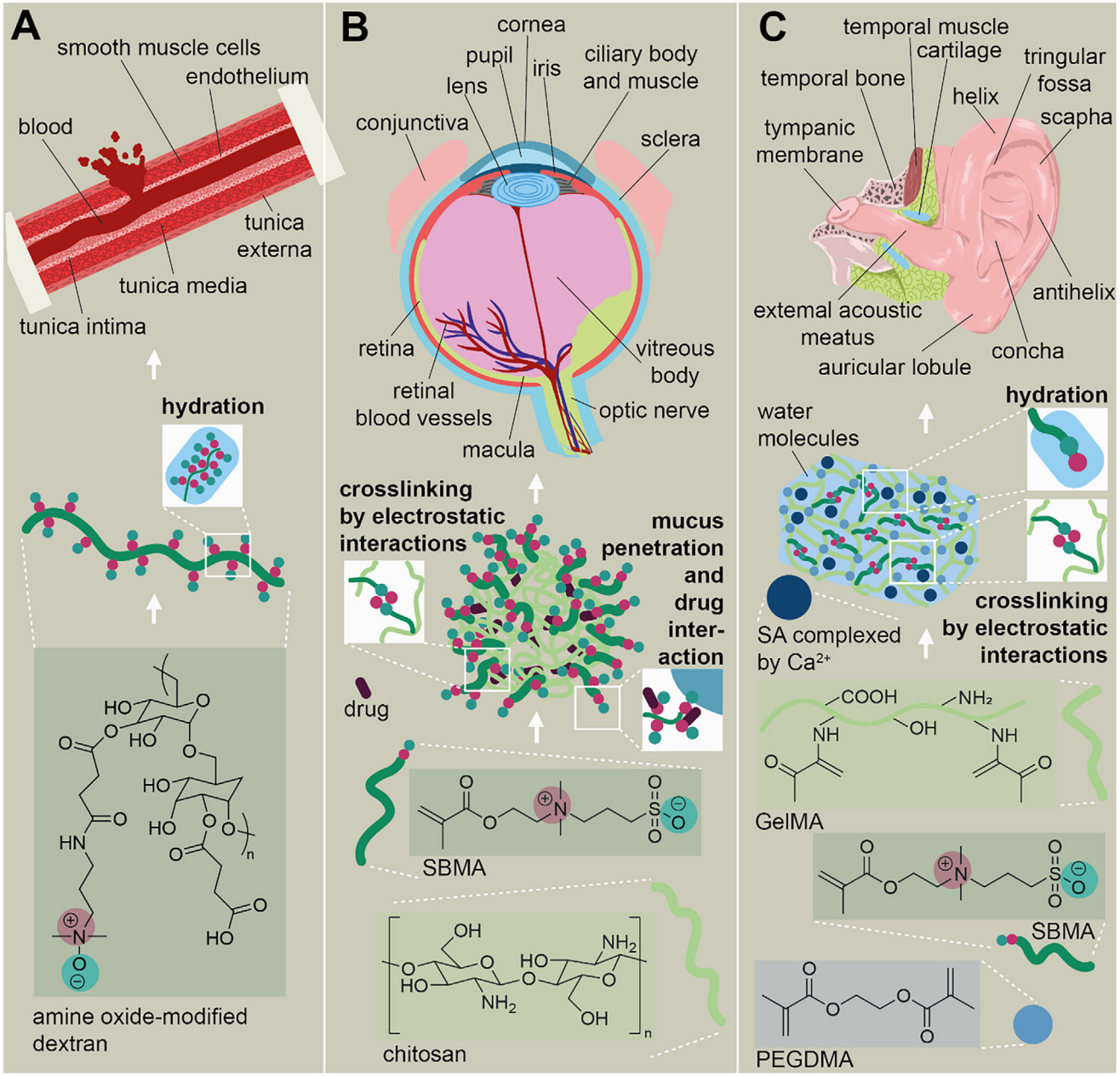

Figure 10. Selected examples of various zwitterionic materials for addressing different pathological scenarios. Shown are semi-synthetic alternatives to treat hemorrhagic shock[338] (a), chronic eye disease[339] (b), and tympanic membrane ruptures[340] (c). SA = sodium alginate; Ca^{2+} = calcium ion; GelMA = gelatin methacrylate; SBMA =[2-(methacryloyloxy)ethyl]dimethyl-(3-sulfopropyl) ammonium hydroxide; PEGDMA = polyethylene glycol dimethacrylate.

obtain molecules with zwitterionic character. The polymer low-biofouling mechanism is attributable to the formation of a hydration layer around the zwitterions. in vivo experiments have shown that dextran succinates with one zwitterionic motif per monosaccharide unit promotes biocompatibility, without adversely affecting coagulation, successfully restoring intravascular volume/ blood pressure, and limits cell/ tissue uptake. Long-term studies are still required, however, the potential of those zwitterionic semi-synthetic polymers is highly interesting.[338]

Chronic eye disease – dry and wet age-related macular degeneration – which results in vision loss is another example of the application of zwitterionic materials (affected only ≈200 million people in 2020).[339] Recently, Yutong et al.[339] developed eye drops with semi-synthetic polymers of bio-derived CS with zwitterionic SB produced by radical reaction at acidic conditions (Figure 10B). Intramolecular electrostatic interactions allow polymeric, self-assembly into stable nanocomplexes and drug (anti-inflammatory adalimumab or ROS reducing catalase) encapsulation. For example, the cationic moieties of CS-SB are involved in

Table 3. Overview of some zwitterionic moieties for medical applications addressed in this article in more detail.

Medical application	Physicochemical interactions	Refs.
Low-biofouling coatings	– Hydration layer (electrostatic interactions, hydrogen bonds) – Steric hindrance (in combination of highly dense polymer/biomolecule surface, e.g., entanglement)	[137, 138]
Hydration lubrication of joints	– Water-binding properties (hydrogen bonds, ion-dipole and dipole–dipole interactions)	[175–177]
Pseudo-immunomodulation	– Antibody-interaction (hydrophobic and electrostatic interactions, hydrogen bonds)	[227–229]
Drug carrier	– Cell uptake (electrostatic interaction) – Endosomal escape	[238, 243, 244]
Hydrogel	– Network-forming (intermolecular electrostatic interactions) – Water-binding (electrostatic interactions)	[15,284]
Tissue engineering	– Water-binding (electrostatic interactions, hydrogen bonds) – Pseudo-immunomodulation	[295,296]
Wound healing	– Tissue interaction (hydrogen bonds, dipole–dipole and electrostatic interactions) – Cohesion properties (non-covalent forces)	[310–312]
Sensor materials	– Conductivity – Cohesion, self-healing (electrostatic interaction, hydrogen bonds) – Tissue adhesion (dipole–dipole interactions, hydrogen bonds, electrostatic interactions)	[331,333]

the interaction with anionic IgG. So far, therapeutic agents have been administered via intraocular injection enabling delivery efficiency. Multiple process repetitions, however, can cause pain, bleeding, infection, and tissue damage. Zwitterionic CS-SB drug carriers prevent those side effects in vivo. The formed drug carriers penetrate the mucus barrier by repulsion (anionic charges in mucin and SB) and migrate into the retina/choroid through the reversible opening of tight junctions.[339]

Chen et al.[340] suggested a highly relevant example for tympanic membrane (TM) repair to prevent hearing loss (Figure 10C). The formation of covalent interactions between gelatin methacrylate (GelMA)/ polyethylene glycol-dimethacrylate (PEGDMA-crosslinker) and SB by free radical polymerization with UV through bound methacrylate groups introduced chemical crosslinks into a hydrogel; whereas hydrogen bonds of SB (sulfate moieties) with amino acids contained in GelMA (carboxylic and/ or hydroxylic groups) and electrostatic interactions between inter- and intramolecular SB groups reinforced the network. Moreover, the hydrogel contains SA microspheres complexed by Ca^{2+}, which are suitable for delivering basic fibroblast growth factor (bFGF) for cell proliferation. Creating those zwitterionic materials with promising perforation healing of dynamic body surfaces, such as TM, could replace myringoplasty, which leads to post-operative complications. Upon mechano-responsive stimulation, physicochemical interactions such as hydrogen bonds and electrostatic interactions within the network are weakened by vibration and simultaneously release bFGF by deformation of both particles and hydrogel. In addition to the excellent biocompatibility, the network structure induces the proliferation and migration of cells in vitro. *Ex vivo* experiments have shown that hydrogels made from GelMA/ SB solution with SA microspheres provide for the application required compressive, tensile, and adhesion (on rabbit fascia tissue) strength – values up to 6.6 MPa, 64.1 kPa, and 45.6 kPa, respectively, for SG_5M_5 (GelMA:SB ratio of 5 and GelMA/ SB:SA ratio of 5). The zwitterionic motifs are responsible for compressive and tensile strength since crosslinking of GelMA and PEG boosts the cohesive characteristics.[340] In comparison, the adhesion experiment focuses on the skin surface interactions of the zwitterions generated[340] via ion-dipole and dipole–dipole interactions. Zwitterions are fully surrounded by water molecules and confer the material with low-biofouling properties.[341]

There are many examples of further zwitterionic material for medical applications such as zwitterionic material from Wei et al.[342] for treating heart valve disease, a muscle repair material suggested by Pan et al.[343] or a hydrogel for Achilles tendon repair.[344] However, this brief overview already indicates that zwitterions offer different features beyond, e.g., immunomodulation, lubrication, or biosensing, and their potential to be tuned for other physiological scenarios.

3. Critical Aspects Regarding the Implementation of Zwitterions in Medical Applications

In conclusion, the selected examples of zwitterionic materials discussed, indicate a high potential as candidates for medical purposes. The functional moieties combine various physicochemical interactions, which are summarized in **Table 3**, to occupy many healthcare fields based on their specific requirements.

However, it should be emphasized that not all zwitterions fulfil the same criteria. For example, Zheng et al.[345] developed nano capsules to deliver therapeutic proteins side-specific to lung cancer cells. Nano capsules with a cationic corona turned out to be successfully internalized by cancerous lung cells, whereas particles with anionically and zwitterionically modified surfaces accumulated mainly in the liver.[345] The cationic charge is likely to contribute to vitronectin (contained in blood plasma[346]) attraction, which facilitates an intrinsic receptor-mediated endocytosis process by malignant lung cells.[345] This example highlights that selected zwitterions are required to adapt to defined, specific in vivo environments and thus, successfully meet medical demands by the bio-driven advantages of zwitterionic properties mentioned in the latter chapters.

In similar studies by Fujii et al.,[83] polymerization of bottlebrush-based nanoparticles grafted with one of three different zwitterions – namely CB, SB, and PB – results in a deeper cell penetration (in vitro spheroid cancer cell model), when CB

is the dominating motif. This dependency is typically discussed in the literature by the pK_a values of betaines[236]: Whereas sulfonate groups and phosphate moieties possess pK_a values of ≈4.0, the pK_a of carboxylate motifs is between 4.0 and 5.0. In other words, betaines' carboxylic group is predominantly protonated in the cancer cell environment (pH value ≈6.6) compared to other betaine variants which leads to a pronounced cationic tissue surrounding. The polycationic structure can interact with the negatively charged cell membrane and thus, promote cell adhesion and internalization.[236] Hence, once zwitterionic materials are placed in vivo, the cellular environment is crucial for the application efficiency of the charged compounds. Therefore, having an impact on successful material performance in vivo, identification of the key zwitterionic structures is necessary and sometimes pivotal for designing specific zwitterionic materials for different pathological demands. In both cases, the development of innovative machine learning approaches might be beneficial to discover the best zwitterions for the relevant physiological state and biomedical application, as well as the synthesis strategy to obtain tuneable, and specifically designed zwitterionic polymers.[347] However, the data for such procedures is currently scarce, and thus, synthesis of various zwitterionic materials on the basis of in vitro and in vivo results still holds true to generate empirical findings for future approaches.

Chemical challenges need to be considered as well, to generate materials on demand for specific medical purposes. Relying on the synthesis strategy, (zwitterionic) polymers and post-modified polysaccharides, for example, are easy to manufacture on a small scale. In comparison, up-scaling and reproducibility might be difficult, which limits access to industrially processed products for medical applications.[348] Moreover, industrial standards have shifted toward green chemistry and sustainability which further aggravate the production of (bio)polymers.[349] Owing to the creativity of scientists, however, it is not surprising that they focus on optimized synthesis solutions as well. One example is the air-tolerant and in-water photoinduced electron/energy transfer-RAFT method,[350–353] which is a simple method to form zwitterionic polymer brushes on a large scale for nano- and microparticles[352] and/or functionalize them on flat implantable surfaces.[354] Even when an appropriate synthesis strategy is found for some medical applications, specific materials such as hydrogels must be able to fulfil different criteria including mechanical strength, stimuli-responsiveness, and biodegradability. To have control over such multinetwork materials, combinations of different synthesis processes might be a better solution; however, such mixed synthesis methods already indicate system complexity on a small scale and, accordingly, the implementation of high-throughput principles is an additional challenge.[15]

When criteria such as the material production are tunable, novel zwitterionic materials with several advantages can be formed. For example, the long-term stability of zwitterionic materials functionalized on medical devices such as sensors[355] and implants,[356] as well as the prolonged circulation time in the bloodstream, when applied as drug delivery system, shows the excellent and promising application possibilities.[357] Interestingly, owing to the enhanced stability and solubility of drugs, uncharged, conjugated PEG has become the gold standard for drugs and/or their carriers to boost therapeutic activity. However, recent studies demonstrated that these PEG-modifications result in immunogenicity by anti-PEG antibodies in humans causing side reactions.[358,359] In comparison to PEGylated molecules, zwitterionic materials form a stable hydration layer on the surface to suppress the interaction with antibodies. Moreover, the reduced immunogenicity facilitates zwitterionic materials with a prolonged blood clearance and thus provides an alternative for stable delivery of active compounds.[360] Moreover, zwitterionic materials based on naturally-derived components such as amino acids or betaines are biocompatible; in comparison fully synthetic alternatives can be less or non-biocompatible, which is problematic for healthcare applications.[357] To circumvent those biological demands, synthetic molecules/polymers also benefit from the modification by naturally occurring zwitterionic moieties. A few examples which we introduced in section two, illustrate the in vivo and/or in vitro biocompatibility of designed natural-based, semi-synthetic, and fully zwitterionic synthetic materials and the versatile advances due to zwitterionic motifs for the medical sector.

Of course, numerous additional requirements, such as clinical testings', must be assessed before newly developed, zwitterionic materials can be considered for commercial availability and their application to improve the health status of a broad variety of patients. Indeed, some examples already show how medical devices such as catheters,[361] artificial hip joints, and stents are modified by zwitterionic polymers (e.g., PC and SB moieties) and used in daily clinical routine to improve the patient's life.[362]

Zwitterionic materials addressed in the literature are mostly limited to laboratory research, however, the broad versatility of zwitterionic materials to control multifaceted medical problems is of high relevance and more in-depth investigations might be beneficial. Moreover, inspired by the huge variety of promising zwitterions for medical applications and the availability of a broad toolbox of monomeric zwitterions, researchers continuously create new synthesis strategies to engineer novel polymers with advanced properties.

4. Conclusion and Outlook

Owing to the complex physicochemical synergies – diseases reveal multifaceted phenotypes – researchers must tune and tailor a broad range of materials to address those specific demands. Different structures modified with zwitterionic motifs might pave the way to meet the demands and fulfill the criteria to challenge diseases. In this context, selected examples of naturally-derived and (semi-)synthetic systems with zwitterionic moieties – and with additional features by material combinations thereof – have been used to provide positive, beneficial effects in healthcare by medical applications, which are introduced in detail. There is already a large body of literature available where a plethora of (bio)molecules and polymers are modified to create, for example, 3D networks, coatings, and immunomodulating structures, which are supposed to, e.g., regenerate tissue homeostasis, replace endogenous structures, or normalize immune cell trafficking events. All the examples of zwitterionic materials nicely show how the medical sector takes advantage of both chemical strategies – to modify various materials with sticky, stimuli-responsive, and/or zwitterionic motifs and further moieties relevant for each application – as well as the nature. The latter provides a broad range of biomaterials, which inspire researchers to derive them

directly from the natural source or mimic whole/partial structures for usage.

Bio-based molecules are known for their limited properties since they are highly specialized for certain body functions/tasks. In other words, all physiological processes are biochemically optimally interconnected. Diseases disrupt this efficient system, and the biomolecules are mostly unable to deal with the altered conditions since adaptations of molecule composition and structure evolutionarily require more time. Here, especially next-generation zwitterionic materials with tailored properties depending on the changed situation play an important role in targeting several disease symptoms. Enhancing our understanding by creating novel materials already indicates the potential of various material and motif combinations to obtain specific properties, however, researchers have to deal with challenges in the future as well. For example, unsolved questions remain, including: which and how many motifs are combinable until a composition limit is reached? For this purpose, suitable synthesis strategies have to be applied or developed for polymerization/post-modification. Furthermore, the material properties render physicochemical interactions in vivo. Increasing amounts of different motifs entail the risk of unspecific interactions and/ or undesired side reactions. Thus, interactions with random body surfaces and cells would reduce the medical benefit.

Furthermore, zwitterionic materials might offer enormous potential in the treatment of further diseases which affect only a small percentage of the general public (e.g., Hartnup disease) or for the improvement of medical imaging techniques (e.g., application of zwitterionic nanogels as contrast agent for real-time MRI[363]). Zwitterionic materials have shown promising characteristics for non-medical applications as well. For example, innovative, zwitterionic filters reveal the separation of oil-water mixtures or the removal of heavy metals to solve environmental issues.[364] The low-biofouling characteristics of zwitterionic coating materials provide solutions against the attachment of marine invertebrates to ships.[365] Zwitterionic materials open up interesting application fields – the use of energy storage devices to harness electricity for later purposes.[366] Those specific technical areas represent only a few examples; however, they demonstrate impressively how – on the microscopic scale – a positive and a negative charge within a polymer or molecule can macroscopically provide innovative materials and overcome problems that were previously impossible to solve.

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Conflict of Interest

The authors declare no conflict of interest.

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