

## REVIEW

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# Smart self-defensive coatings with bacteria-triggered antimicrobial response for medical devices†

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Bacterial colonization and biofilm formation on medical devices represent one of the most urgent and critical challenges in modern healthcare. These issues not only pose serious threats to patient health by increasing the risk of infections but also exert a considerable economic burden on national healthcare systems due to prolonged hospital stays and additional treatments. To address this challenge, there is a need for smart, customized biomaterials for medical device fabrication, particularly through the development of surface modification strategies that prevent bacterial adhesion and the growth of mature biofilms. This review explores three bioinspired approaches through which antibacterial and antiadhesive coatings can be engineered to exhibit smart, stimuli-responsive features. This responsiveness is greatly valuable as it provides the coatings with a controlled, on-demand antibacterial response that is activated only in the presence of bacteria, functioning as self-defensive coatings. Such coatings can be designed to release antibacterial agents or change their surface properties/conformation in response to specific stimuli, like changes in pH, temperature, or the presence of bacterial enzymes. This targeted approach minimizes the risk of developing antibiotic resistance and reduces the need for continuous, high-dose antibacterial treatments, thereby preserving the natural microbiome and further reducing healthcare costs. The final part of the review reports a critical analysis highlighting the potential improvements and future evolutions regarding antimicrobial self-defensive coatings and their validation.

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## Introduction

Short and long-term invasive medical devices are often related to a major complication, which is surface colonization from biofilm-forming bacteria. Among the wide variety of affected medical devices, cardiac valves and pacemakers,<sup>1–4</sup> silicone prosthesis,<sup>5–7</sup> dental<sup>8</sup> and orthopaedic implants,<sup>9</sup> catheters for several anatomical regions,<sup>10,11</sup> pulmonary ventilators endotracheal tubes,<sup>12</sup> ophthalmological contact lenses,<sup>13</sup> and also suture threads<sup>14</sup> can be considered the most critical. Once bacteria adhere to the device surface, they initiate the formation of a biofilm, organizing themselves into colonies. This biofilm

enhances their survival through enhanced adhesion, access to nutrients, and increased resistance to external stresses.

Particularly, bacterial attachment can be considered the first step of biofilm formation, triggering the production of extracellular matrix (ECM) composed of substances like polysaccharides, proteins, and DNA that are secreted by the bacteria themselves or by the host organism.<sup>15</sup> Furthermore, the ECM can embed and shield microcolonies while maintaining their cohesion.<sup>16</sup> The process of biofilm formation is continuously supported by communication among and within different bacterial species, a phenomenon known as quorum sensing.<sup>17</sup> The onset frequently takes place in healthcare settings, where it is impossible to completely eradicate every potential source of contamination from the surroundings, such as unsterile instruments, administered intravenous fluids, and weakly aseptic medical procedures. Also, pathogens are naturally present on human skin and some anatomical regions can be concealed, hence difficult to reach and clean.<sup>18</sup> Such infections are termed nosocomial and pose serious threats to the health and well-being of patients, especially considering that they might be already debilitated or immunosuppressed and could potentially perish in the worst cases.<sup>19</sup> In addition to the infection itself, the overgrowth of bacterial

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biofilm on medical devices leads to severe malfunctions and aesthetical deformities, causing unbearable discomforts for patients, thus necessitating their replacement or removal.

All these serious issues translate into an economic burden upon national healthcare systems because of frequent clinical visits, prolonged hospital stays and therapies, production of new devices and scheduling of multiple revision surgeries.<sup>20</sup> Given the high incidence of nosocomial infections, it is crucial to find solutions to mitigate this problem. Current systemic therapies, which rely on antibiotics, often lack suitable efficacy due to the increasing number of multi- and pan-resistant bacterial strains, rendering these drugs inadequate for eradicating bacteria in the biofilm mode of growth.<sup>21,22</sup>

Therefore, several research efforts have been made throughout the years to develop innovative engineered antimicrobial biomaterials.<sup>23–26</sup> These efforts have focused particularly on strategies that allow prevention and treatment of biofilms, aiming to exert their action at the initial interface between bacteria and medical devices. Surface functionalization can be a useful tool to develop biomaterials with a tailored antibacterial action, ranging from antifouling and quorum quenching to bactericidal and biofilm disruptive surfaces.<sup>15,27</sup> More interestingly, it is possible to design such antibacterial coatings to regulate their action in a controlled and targeted manner.

In this review, we provide an overview of strategies for fighting the infection onset through the recent design and manufacturing of engineered antibacterial surface coatings. Specifically, we present three promising surface functionalization techniques, offering description and outlining their general antibacterial applications before going into the details of their potential in achieving micro- and nano-structured self-defensive antibacterial coatings. In the final section, the potential improvements for the design and clinical validation of these smart and on-demand antimicrobial approaches are hypothesized upon, and their powerful innovative drive in the

fight against antimicrobial-resistant bacterial infections is stressed (Fig. S1†).

## Considerations and requirements for the design of antibacterial surface coatings

### Process of bacterial adhesion and strategies for their disruption

Bacterial adhesion is a three-staged process, including (1) bacterial transport towards a surface, (2) reversible adhesion, and (3) the transition from reversible to irreversible adhesion, that is governed by both physical and chemical interactions.<sup>28</sup> Specifically, the bacteria transport towards the solid substrate surface relies on the bacterial species as well as various environmental factors, where non-motile bacteria are influenced by gravitational and hydrodynamic forces, and Brownian motion, while motile bacteria are capable to navigate on an imperfect circular path close to the surface to facilitate their adhesion.<sup>29</sup> After their initial contact with the surface, bacteria undergo unstable and reversible adhesion. Particularly, Lifshitz-van der Waals interactions and electrostatic forces are responsible of the bacteria adhesion on the substrate surface under static culture conditions, characterized by absence of turbulent or laminar flow. Reversible adhesion typically occurs when bacteria reach the separation distance corresponding to the secondary minimum energy. Overcoming the energy barrier allows bacteria to approach the substrate closely and form irreversible adhesion. Additionally, acid-base interactions have been studied to affect the bacterial adhesion phenomena.<sup>30</sup>

The final stage, transitioning from reversible to irreversible adhesion, occurs through molecular-level interactions between



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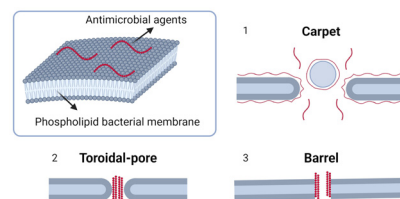
*author of >100 papers (H-index = 35) in the leading journals in Bioengineering, 5 book chapter and his research has led to 3 patents, >50 oral presentations at national & international conferences including >10 as invited speaker.*



bacterial surface structures and substratum surface components. These components include extracellular polymeric substances (EPS), lipopolysaccharides, fimbriae, pili, and slime.<sup>31</sup> As example, protein corneodesmosin (CDSN) has been identified as ligand for *S. aureus* and Towell *et al.* demonstrated that blocking the N terminus of CDSN is able to reduce the bacteria interaction with the corneocyte surface.<sup>32</sup> Throughout these stages of bacterial adhesion, surface properties play a pivotal role. Understanding the intricate relationship between bacterial adhesion and surface properties forms the foundation for designing surfaces with anti-adhesion properties against bacteria.

Among strategies aimed at bacterial eradication, targeting the cytoplasmic membrane is crucial due to their limited ability to self-renew after damage. Consequently, antibacterial agents can bind to the cell membrane, followed by hydrophobic insertion into lipid tails, resulting in its lysis.<sup>33</sup> Various models explain this mechanism to eradicate adhered bacteria. As example, the “Carpet” model suggests antimicrobial agents disrupt the bacterial membrane’s phospholipid structure at multiple sites, creating irreparable holes, while the “Toroidal-pore” model proposes antibacterial molecules insert spirally into the membrane, forming circular holes. Lastly, the “Barrel” model suggests antibacterial molecules assemble into spiral structures within the membrane, creating pores<sup>34</sup> (Fig. 1).

Another mechanism to eradicate bacteria involves targeting the peptidoglycans, that provide bacterial cell wall support. Indeed, targeting lipid II, a precursor for peptidoglycan synthesis, is a common strategy.<sup>35</sup> For example, a compound synthesized from D-glucal, resembling fragments found in the recycling process of bacterial cell walls, effectively inhibits the growth of *S. aureus* walls. This discovery suggests the potential of developing novel antibiotics that function by halting cell wall growth.<sup>36</sup> To note, Gram-negative bacteria possess an



**Fig. 1** Three popular models to explain bacterial membrane permeabilization, (1) high accumulation of antimicrobial agent parallel to the membrane leads to its disintegration and formation of micelles, (2) lipid monolayers are forced to bend from top to bottom forming a toroidal pore, (3) antimicrobial agents completely insert themselves into the membrane forming a channel.

additional outer layer that serves as a barrier to large hydrophobic molecules. As a result, many antimicrobial agents typically exhibit lower potency against Gram-negative bacteria compared to Gram-positive ones.

Finally, innovative synthesized biocompounds have been proved in their ability (1) to enter cells and target intracellular bacteria processes, *e.g.*, by inducing strong ribosomal inhibition in *E. coli*<sup>37</sup> and (2) to modulate the *in vivo* immune response by reducing IL-10 levels but increasing TNF- $\alpha$  and INF- $\gamma$  levels, considered representative immune cytokines and associated with high antibacterial activity.<sup>38</sup>

#### Defence mechanisms to adopt in the design of antimicrobial coatings

Since bacterial adhesion, proliferation and further colonization occur at the interface between microorganisms and medical devices, antimicrobial surface functionalization of biomaterials represents a valid approach to face the issue. There are several ways to fight the onset of an infection, acting at different stages of surface colonization and with different



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partners, enabling him to translate his research from the lab to industry.

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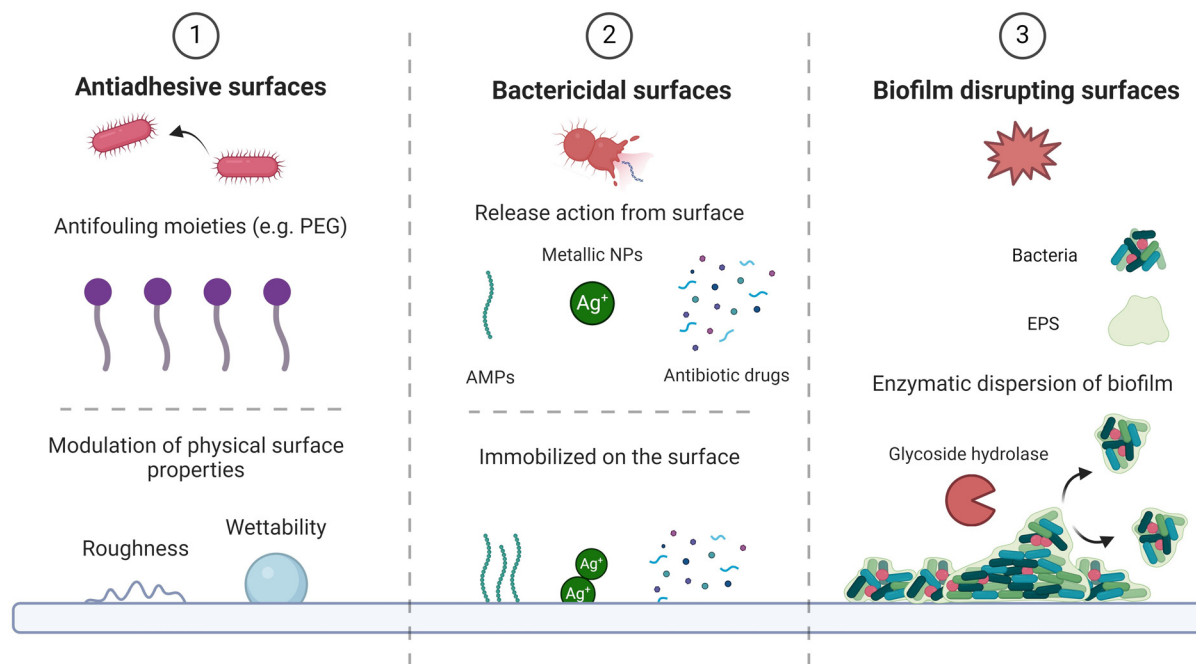


**Gianluca Ciardelli**

Biomaterials for Tissue Engineering, Controlled Drug Delivery, and more recently Nanomedicine, Tissue and Organ Models. The scopus database reports over 240 documents, 8 book chapters; 12 patents are cited by espacenet. His h-index is 48 with over 8900 citations (SCOPUS).

Gianluca Ciardelli graduated in Chemistry at the University of Pisa (Italy) and obtained a PhD in Natural Sciences at the ETH (Zurich, Switzerland). He is now Full Professor in Biomedical Engineering and coordinates the “Materials in Bionanotechnology and Biomedical Lab-Bioinside” group at the Department of Mechanical and Aerospace Engineering (Politecnico di Torino). He has over 20-years’ experience in research in





**Fig. 2** Scheme summarizing the three conventional defence mechanisms adopted in the design of (1) antiadhesive surfaces, exploiting physical and chemical modifications, (2) bactericidal surfaces and (3) biofilm disrupting antimicrobial coatings, that exploit immobilization or release of active molecules. The strategies and/or molecules mentioned are a few examples of the several options available in literature.

mechanisms, three of them are shown in Fig. 2 while Table 1 reports the applications of such defence mechanisms in literature.

Specifically, the first one is to prevent bacterial adhesion on the surface through non-adhesive coatings, that are predominantly based on antifouling moieties.<sup>39–41</sup> However, this mechanism can also exploit the modulation of the surface physical properties,<sup>42–47</sup> such as wettability or roughness, as

shown by Encinas *et al.* that reported the antiadhesive potential of micrometer and sub-micrometer sized patterned surfaces due to deformation stresses within the bacteria and also to piercing of their cell membranes by these superficial nano- and micro-structures, as long as their length scales fall just below the size of bacterial cells. Furthermore, once bacteria have adhered on the surface, antimicrobial coatings containing antibacterial and antibiofilm agents can still threaten microorganisms survival by interfering with their metabolism, physical integrity, and quorum sensing,<sup>48</sup> thus hindering their proliferation and biofilm formation, while a third possibility relies on disrupting biofilm at its early stages.<sup>49</sup> The second and third defence mechanism are usually achieved through integration of active molecules within the coating, such as antibiotics,<sup>50</sup> antimicrobial peptides,<sup>51</sup> metallic nanoparticles,<sup>52,53</sup> quorum sensing blockers<sup>54–56</sup> or degradative enzymes,<sup>57,58</sup> where the biocidal components could either be immobilized on the surface or a specific leaching action could be designed for the coating.<sup>27,49</sup> Advances in research have proven the benefits of combining these three defence methods in effectively fighting bacterial infections located in complex physiological environments.<sup>27,59–62</sup>



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*Irene Carmagnola earned her Ph.D. in Biomedical Engineering in 2013 and she is currently assistant professor at Politecnico di Torino. Her research activity is primarily focused on the design, fabrication, and characterization of polymeric-based scaffolds and on nanotechnologies applied to the biomedical fields, particularly Tissue Engineering. Specifically, she has utilized conventional and additive manufacturing techniques to*

*engineer scaffolds. She also has studied the preparation of hydrogels to be used as “ink” for 3D printing techniques to obtain cellularized constructs. In parallel, she has developed nanostructured coatings using innovative strategies for various applications, such as coronary stents, wound healing and antibacterial surfaces.*

## Responsive self-defensive antibacterial nanocoatings

Regardless of the specific strategy employed, contemporary trends in antimicrobial biomaterials emphasize the novelty of smart self-defensive coatings capable of reacting to specific



**Table 1** Summary of published works exploiting the three defence mechanisms for the development of antibacterial solutions

| Active molecules                                                                                              | Substrates                                                     | Bacterial/fungus strain                                                         | Application & Outcome                                                                                                                                                                                                                                                                                                           | Ref. |
|---------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| Antiadhesive surfaces<br>Polymethylmethacrylate-2-methacryloyloxyethyl phosphorylcholine (PMMA-MPC)           | Liquid silicone rubber (LSR)                                   | <i>S. aureus</i><br><i>S. epidermidis</i>                                       | PMMA-MPC modified LSR had a very high resistance against <i>S. aureus</i> adherence and biofilm formation. Interesting for cardiovascular implants applications.                                                                                                                                                                | 63   |
| R89 rhamnolipid                                                                                               | Medical-grade silicone                                         | <i>S. aureus</i><br><i>S. epidermidis</i>                                       | R89 has proven to be a good biosurfactant for implantable devices, strongly inhibiting biofilm formation in terms of biomass and cell metabolic activity.                                                                                                                                                                       | 64   |
| Polysulfobetaine methacrylate (PSBMA)                                                                         | Polydimethylsiloxane (PDMS)                                    | <i>E. coli</i><br><i>S. aureus</i>                                              | Beyond <i>in vitro</i> tests, <i>in vivo</i> assays on <i>S. aureus</i> were performed on hydrogel-coated catheters and found significant inhibition of bacterial adhesion and proliferation.                                                                                                                                   | 65   |
| Poly(sulfobetaine methacrylate) (pSBMA)<br>Poly(carboxybetaine methacrylate) (pCBMA)<br>Bactericidal surfaces | PDMS                                                           | Protein adsorption and fibroblast adhesion assays                               | Durable hydrogels with strong resistance to proteins and fibroblast adhesion have been optimized, representing an interesting coating for implantable materials to contain the foreign body response.                                                                                                                           | 66   |
| Cefuroxime sodium salt                                                                                        | Polyether ether ketone (PEEK) coated with nano hydroxyapatite  | <i>S. aureus</i>                                                                | Sonocoated nanoHAP layers were loaded with drugs, the release kinetics granted good antimicrobial activity up to 24 h. Structure and cristallinity of nanoHAP were not affected, suitable for bone implants.                                                                                                                    | 67   |
| Chlorhexidine                                                                                                 | Removable partial dentures                                     | <i>S. mutans</i>                                                                | A single application of the slow-releasing dosage coating on partial dentures effectively restrained <i>S. mutans</i> levels and reduced plaque score for a minimum of 1 week.                                                                                                                                                  | 68   |
| Octenidine-dihydrochloride (OCT)                                                                              | Polymeric tracheotomy tubes                                    | <i>S. aureus</i><br><i>P. aeruginosa</i>                                        | OCT coated tubes had good initial antimicrobial action and reduced superficial biofilm formation, but the effect rapidly decreased after reprocessing of the tubes because of poor adhesion properties.                                                                                                                         | 69   |
| Synthetic AMP (comprising KRWKWWRR)                                                                           | PDMS<br>Silicone Foley catheters                               | <i>E. coli</i><br><i>S. aureus</i><br><i>P. aeruginosa</i>                      | AMPs-impregnated PCL coatings achieved optimal release kinetics and did not support cells and biofilm growth up to 7 days. <i>In vitro</i> and <i>in vivo</i> studies on coated urinary catheters showed good antibacterial performance.                                                                                        | 70   |
| (9-amino-acid) cationic peptide 1037                                                                          | Polypropylene plates                                           | <i>P. aeruginosa</i><br><i>B. cenocepacia</i><br><i>L. monocytogenes</i><br>568 | Flagellum-dependent swimming motility was reduced, bacterial swarming was inhibited, twitching motility was stimulated. The result was a reduction in biofilm formation, its combination with a second powerful antimicrobial agent could be a good therapeutic strategy.                                                       | 71   |
| Silver Nanoparticles (AgNPs)                                                                                  | Medical-grade silicone elastomers<br>Elastic bandage dressings | <i>C. auris</i> 0390                                                            | Potent <i>in vitro</i> fungicidal effect of AgNPs tested against <i>C. auris</i> biofilms on medical and environmental surfaces. The inhibitory action was efficient on both biofilm formation and preformed biofilm and durable in time even after several washings with PBS.                                                  | 72   |
| Gold NPs biofabricated with <i>C. Annicus</i> aqueous extract (AuNPs-CA)                                      | Glass coverslips                                               | <i>P. aeruginosa</i> PAO1<br><i>S. marcescens</i><br>MTCC 97                    | Great antibiofilm and quorum sensing inhibition potential was observed, by dose-dependent reduction of QS-mediated virulence factors, biofilm formation and exopolysaccharide production.                                                                                                                                       | 73   |
| Magnetic Fe <sub>3</sub> O <sub>4</sub> @PEG-Ag nanocomposites                                                | Polystyrene plates<br>Petri dishes                             | <i>C. albicans</i><br><i>S. aureus</i><br><i>E. coli</i><br><i>L. major</i>     | Promising magnetic field-guided smart drug delivery system and antibiotic agent with insignificant toxicity, its efficacy was comparable to commercial drugs and could be further combined with antibiotics that can form a shell on its structure.                                                                             | 74   |
| AgNPs                                                                                                         | Silicone elastomers (PDMS)                                     | <i>S. aureus</i><br><i>E. coli</i><br><i>P. aeruginosa</i>                      | Great antimicrobial activity against <i>S. aureus</i> and good also against <i>E. coli</i> and <i>P. aeruginosa</i> , the effect depended on the particle size and NPs retained good cytocompatibility below 10 mM of silver. The synthesis allowed simultaneous reduction of silver and PDMS surface grafting.                 | 53   |
| Synthetic halogenated furanone compound (furanone 56)                                                         | Flow-cell based<br><i>P. Aeruginosa</i> biofilms               | <i>P. aeruginosa</i>                                                            | Interference with AHL-mediated quorum sensing by repressing expression on target genes of the <i>las</i> quorum sensing circuit and reducing production of virulence factors. It affected the architecture of biofilm and promoted the bacterial detachment process. Promising for novel non-antibiotic anti-pathogenic agents. | 75   |
| Biofilm disrupting surfaces<br>Streptococcal-specific bacteriophage-encoded endolysin (PlyC)                  | Polystyrene plates                                             | Group A<br><i>streptococcal</i> (GAS)<br>strain D471                            | PlyC, a cell wall hydrolase, directly lysed GAS cells as it diffused within the biofilm matrix acting on more than one bond.                                                                                                                                                                                                    | 76   |



Table 1 (Contd.)

| Active molecules                                                                                         | Substrates                                                  | Bacterial/fungus strain                                                                                           | Application & Outcome                                                                                                                                                                                                                                                                                                                              | Ref. |
|----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| DNase-mimetic artificial enzyme                                                                          | <i>S. Aureus</i> biofilms                                   | <i>S. aureus</i>                                                                                                  | In the first hour of incubation bacterial attachment was found to be less than 10%, followed by low biofilm formation after 120 h thanks to the artificial enzyme better stability. Against formed biofilms of ages 12 to 120 h, artificial DNase showed high disruption efficiency, better penetration and reusability compared to natural DNase. | 54   |
| Engineered quorum-quenching lactonase (GKL)                                                              | <i>A. Baumannii</i> biofilms                                | <i>A. baumannii</i>                                                                                               | Biofilm formation was significantly reduced by the engineered mutant enzyme in thickness, biomass and surface area. Good functionalization strategy for catheters or implants to yield a new generation of bioactive biomaterials.                                                                                                                 | 56   |
| 5 lytic bacteriophages (vB_PaeM_USP_1, vB_PaeM_USP_2, vB_PaeM_USP_3, vB_PaeM_USP_18, and vB_PaeM_USP_25) | Polystyrene plates and circular endotracheal tube specimens | 15 strains of <i>P. aeruginosa</i> (including multidrug-resistant ATCC 2108, ATCC 2110, ATCC 2112, and ATCC 2113) | Remarkable mature biofilm reduction through biofilm disruption and production of cell debris. The antibiofilm action could be attributed to deep penetration within the biofilm thanks to the degradation of the polysaccharide matrix. The lytic effect was significant in biofilm control on infected endotracheal tubes.                        | 77   |

changes in the surrounding microenvironment triggered by bacterial colonization.<sup>78</sup>

More generally, triggers for smart antimicrobial coatings can be (1) external, such as temperature,<sup>79</sup> electromagnetic field,<sup>80</sup> exposition to specific wavelengths of light<sup>54,61,81</sup> or to ultrasound,<sup>82</sup> and (2) internal, including changes of pH or presence of specific biological molecules/ions.<sup>79,83,84</sup> When the stimulation originates internally and is associated with the presence of adhering and proliferating bacteria, it leads to an on-demand, targeted antibacterial response initiated solely from the coating. This response should occur only when a bacterial infection is actively developing, and the surface of the biomaterial is indeed colonized by microorganisms.<sup>85</sup> As a result, this triggered response enables a sustained retention of efficacy over time, preventing premature loss of activity. Moreover, it enhances the biosafety of the coating by minimizing secondary negative effects on adjacent healthy cells and reducing the risk of developing multidrug-resistant bacterial strains.<sup>86,87</sup> These coatings are commonly known as self-defensive coatings because they are engineered to activate their antibacterial properties when threatened by the onset and proliferation of bacterial colonies. Particularly advantageous is their responsiveness to local pH variations or the presence of virulence factors.<sup>88</sup> During their metabolism, several strains of bacteria for example secrete organic acids (e.g., lactic acid by *S. aureus*, acetic acid by *E. coli*) that produce a local acidification of pH. Additionally, bacteria utilize various cellular structures, molecules, and regulatory systems known as virulence factors, which aid in their colonization of the host at the cellular level.<sup>89,90</sup> Among the various biomolecules released, degradative enzymes can be utilized to trigger a response and subsequent activation of antibacterial potency in self-defensive coatings. This mechanism can potentially result in the delamination of the coating, consequently removing attached bacteria and early-stage biofilm (a process known as self-polishing).<sup>88</sup>

Therefore, smart design and manufacturing of micro- and nano-structured coatings on the surfaces of medical devices are crucial for achieving these responsive mechanisms. This is accomplished by fine-tuning the physical and chemical properties of the coating, such as maximizing the surface-to-volume ratio and exploring various options for grafting bioactive moieties.<sup>85,91</sup>

In the next sections of this review, we will discuss the current applications of three techniques to develop responsive self-defensive antibacterial coatings: Layer-by-Layer (LbL) self-assembly, hierarchical polymer brushes and mussel-inspired adhesive coatings (Fig. 3).

All these coating technologies incorporate bioinspired features, whether through their highly organized architecture (polymer brushes), akin to the multifunctional and adaptable surfaces found in biological materials, or through the natural inspiration behind their building blocks (biomimetic mussel adhesive proteins) and their bottom-up construction methods (LbL self-assembled nanoscale systems).

### Layer-by-layer (LbL) nanostructured coatings

**Overview of the technology and its antibacterial applications.** Layer-by-layer assembly of complementary building blocks is a particularly versatile bottom-up approach for the fabrication of nanostructured coatings. These coatings can be manufactured on any type of substrate composition and geometry, by alternating polyelectrolyte layers, which are bound together through specific interactions. Examples of possible driving forces for assembly include electrostatic attraction, hydrogen bonding, hydrophobic interactions, covalent bonding, biologically driven assembly, depending on the specific materials used.<sup>92</sup> The multilayered coating can be designed and assembled to target several applications, because the LbL assembly can be tuned to achieve the required thicknesses and topographies through the incorporation of





**Fig. 3** Schematic representation of suitable coating techniques to achieve responsive self-defensive antibacterial coatings. (1) LbL electrostatic self-assembled nanocoatings are achieved through alternate deposition of oppositely charged polyelectrolytes, (2) Hierarchical polymer brushes can either be polymerized directly on the surface thanks to an initiator (graft from) or polymeric chains can later be grafted to the surface *via* a linker (graft to), (3) Polydopamine-based coatings can adhere to several surfaces *via* their catechol groups while their amino groups can be exploited to bind an antibacterial polymer or a linker-drug complex.

bioactive compounds.<sup>93</sup> Thus, the accurate selection of building blocks, particularly such as inorganic nanoparticles, synthetic and natural polymers or their combination as polyelectrolytes, as well as biomolecules like peptides, drugs, antioxidants, can tailor the structure and physico-chemical properties of the resulting coating.<sup>94</sup> The deposition technology can also be chosen from a wide range of possibilities, each yielding distinct features in the final film. The assembly could be performed through traditional dipping, spinning, or spraying of polyelectrolytes solutions, but also through modern 3D printing or microfluidics systems. With this array of possibilities and technology advancements, the deposition process has become increasingly suitable for automation and, therefore, easily scalable from an industrial perspective.<sup>95,96</sup>

Layer-by-layer coatings offer a wide range of possibilities when implementing an antibacterial strategy, which can be divided into two main categories: (1) encapsulation of antimicrobial compounds and (2) intrinsic antifouling/antibacterial activity.<sup>97</sup>

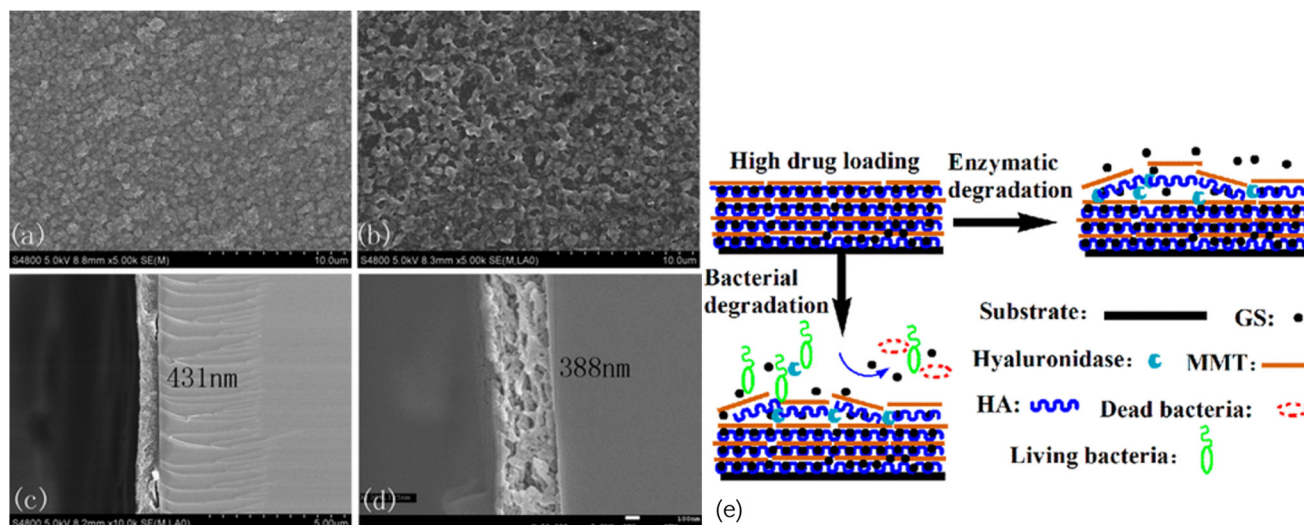
Integration of active antibacterial substances (*e.g.*, antibiotics, antimicrobial peptides (AMPs), metallic nanoparticles) during construction of LbL coatings leads to the establishment of a good reservoir and to the possibility of sustained release over time. To achieve this, therapeutics can either be complexed with polyelectrolytes or directly alternated as PEMs during the deposition process, allowing for tunability of their concentration and release profile based on the number and conformation of layers.<sup>98–100</sup>

**Self-defensive antibacterial LbL coatings.** Significant advances have been made in the development of self-defensive antibacterial LbL coatings. The most investigated bacteria-related triggers are acidic pH and degradative enzymes, such

as hyaluronidase (HAS) or chymotrypsin (CMS), commonly secreted by bacterial colonies.<sup>85</sup> The integration of enzymatic substrates as LbL building blocks triggers a degradative action that leads to partial delamination of the coating, resulting in both gradual release of therapeutic cargo and detachment of previously adhered biofilm-forming bacteria along with the most superficial layers.<sup>88</sup> Several cases have been presented in literature using hyaluronic acid (HA) as substrate for HAS. For instance, Wu *et al.*<sup>101</sup> alternated two polycations, 1,2-ethanediamine (EDA)-modified polyglycerol methacrylate (PGMA) and lysozyme in a LbL coating containing HA as polyanion to coat antibiotic-loaded silica nanoparticles. The action of hyaluronidase broke down hyaluronic acid, leading to coating superficial delamination. The polycations provided both bacteriolytic (lysozyme) and membrane-disruptive (cationic EDA-modified PGMA) action against bacteria. Furthermore, coating delamination also triggered the release of amoxicillin (AMO) drug only when AMO-resistant *E. coli* and *S. aureus* bacteria were present (both *in vitro* and *in vivo*). A similar approach, without the release of antibiotics, was proposed by Yao *et al.*,<sup>102</sup> in which a LbL coating was developed containing HA alternated with chitosan (CHI) initially and with polylysine (PLL) in the last layers. PLL and HA provided the coating with susceptibility to both CMS and HAS degradation, while PLL and CHI acted synergistically as bactericidal compounds. The enzymatic delamination of the coating reduced both *E. coli* and *S. aureus* adhesion, improving and prolonging the bactericidal action of PLL and CHI of the underlying exposed layers (as demonstrated by LIVE/DEAD staining up to 72 h).

Another HA-containing LbL coating was developed by Wang *et al.*,<sup>103</sup> which was deposited on medical silicone substrates. The alternating polyelectrolytes were montmorillonite (MMT)





**Fig. 4** SEM images of surface topography and thickness before (a and c) and after (b and d) GS release for 48 h in 105 CFU mL<sup>-1</sup> of *E. coli*. (e) Graphical representation of the (MMT/HA-GS)<sub>n</sub> self-assembled coating and enzymatically triggered delamination with release of GS. Reprinted with permission of B. Wang, *et al.*, Construction of High Drug Loading and Enzymatic Degradable Multilayer Films for Self-Defense Drug Release and Long-Term Biofilm Inhibition, *Biomacromolecules*, 2018, **19**(1), 85–93, <https://doi.org/10.1021/acs.biomac.7b01268>. Copyright © 2018, American Chemical Society.

and HA, both electrostatically interacting with positively charged gentamicin sulfate (GS) to yield high loading of antibiotic within the coating (MMT/HA-GS)<sub>n</sub> (Fig. 4). The progressive degradation by HAS led to a dual antibiofilm-antimicrobial action due to a combination of gradual drug release and controlled film peeling. MMT has been found to be interesting in LbL antibacterial coating applications thanks to its high loading and retention properties of antimicrobial compounds, encapsulating small molecular antibiotics and possessing low thickness combined with high specific surface area. Therefore, it is extensively featured in related literature, for example in a similar work by Xu *et al.*<sup>104</sup> in which MMT was loaded with GS and alternated with PLL to be degraded by CMS.

This interesting self-polishing ability of responsive antibacterial coatings can also be triggered by a pH variation by integrating pH-cleavable linkages between layers, as some works have already investigated exploiting imine links obtained through Schiff base chemistry.<sup>105,106</sup> Alternatively, responsiveness towards acidification of local pH can be easily achieved through integration of weak polyelectrolytes that are usually pH sensitive in terms of swelling, decomposition and/or permeability.<sup>84</sup> The enhanced permeability of the film could either release antimicrobial agents integrated within the coating or, more simply, expose specific bioactive dominions of the molecules making up the layers.

Several research efforts in this field have been made by Prof. Sukhishvili's research team using different pH-responsive polyelectrolytes. Tannic acid, a natural polyphenol and weak polyelectrolyte (pK<sub>a</sub> = 8.5) often used in LbL antimicrobial coatings due to its intrinsic antibacterial properties,<sup>107–109</sup> was integrated in PEMs thanks to both electrostatic interactions and hydrogen bonding with several cationic antibiotics (genta-

micin, tobramycin and polymyxin B) at neutral pH. No antibiotic release was observed at neutral conditions up to 4 weeks but, upon acidification, tannic acid became strongly less ionized triggering the release of antibiotic molecules until electroneutrality was reached. Following this principle, a further decrement of pH would have again triggered antibiotic release, so to not deplete the drug all at once.<sup>110</sup> Another interesting strategy investigated was LbL hydrogel coatings with a hydrated, open molecular structure able to host antibiotic and display antiadhesive properties. The hydrogel was composed of cross-linked poly methacrylic acid (PMAA) and loaded *via* electrostatic interaction with positively charged antibiotics or AMPs until complete neutralization. The pH-triggered release was fast in this case, demonstrating no diffusional constraints from the coating.<sup>111,112</sup> Hydrogel coatings composed of poly (2-alkylacrylic) acids were also investigated for their intrinsic bactericidal properties related to their hydrophobicity. The antibacterial effect was attributed to the conformational transition from coil to globule of the polyacid chains caused by the pH drop, thus exposing hydrophobic moieties that penetrated within the bacterial membrane.<sup>113</sup> The same researchers also exploited inorganic polyelectrolytes like MMT<sup>114</sup> and polyphosphazenes<sup>115</sup> for self-defensive antibacterial coating development.

Developing a coating responsive to multiple triggers in such a complex environment like the bacterial niche can be advantageous, as some have already started to investigate by developing a pH-responsive multilayer coating with an enzyme-responsive outer shell. Wang *et al.*<sup>116</sup> have designed a pH-responsive multilayer composed of antibiotic (gentamicin), silver nanoparticles (Ag NPs) and tannic acid on magnetic nanoparticles. The coating was finally covered by a hyaluronic acid external



layer to improve the biocompatibility of the system while also imparting responsivity towards HAS. Such magnetic nanoparticles are supposed to be selectively guided within the bacterial biofilm and respond to the bacterial infection microenvironment by releasing the antimicrobial agents on-demand.

These latest strategies represent the current desirable solutions for tackling bacterial infections because they can perform on-demand delivery of antimicrobial agents while also overpassing biofilm.

### Hierarchical polymer brushes

**Overview of the technology and its antibacterial applications.** Polymer brushes represent a particular coating technique able to produce very thin and well-organized polymeric films, tightly bound to solid substrates and possessing very high mechanical and chemical robustness. Additionally, this technique allows for the simple tuning of parameters such as superficial grafting density, final thickness, and polymeric chain chemistry.<sup>117</sup> It also offers the possibility of post modifications with additional functional groups. As a result, the coating displays finely regulated interfacial properties such as wettability, surface energy, capability of molecules adsorption/binding, cell adhesion, and rheological behaviour. These properties are related to the nanoscale architecture of the generated polymeric patterns, which is typical of the native ECM of biological tissues, making them highly suitable for biomedical applications.<sup>118</sup> The deposition process can be achieved through either a 'grafting-to' or a 'grafting-from' strategy. In the first case, previously polymerized chains are anchored to the surface *via* physisorption or chemisorption, while in the second the monomers start to polymerize and form chains on the substrate due to its functionalization with an initiator molecule, a process also known as surface-initiated polymerization. This method can be achieved through a multitude of controlled polymerization techniques.<sup>119</sup> Surface-initiated atom transfer radical polymerization (SI-ATRP) is one of the most popular methods to obtain biomolecule-functionalized polymer brushes.<sup>120</sup>

Furthermore, polymer brushes can serve as a powerful tool in the development of antibacterial surfaces, and several efforts have already been made in this direction, where the main antibacterial strategies are: (1) actively biocidal brushes, (2) non-biofouling brushes and (3) their combination.<sup>121</sup> Biocidal polymer brushes can either encompass intrinsic biocidal polymeric blocks, like poly- $\beta$ -peptides,<sup>122</sup> quaternized polymers,<sup>123,124</sup> polyguanidines,<sup>125,126</sup> cationic<sup>127</sup> and fluorinated polymers<sup>128</sup> or be used as reservoirs of antimicrobial agents.<sup>129,130</sup> Another successful antibacterial strategy is the inhibition of bacterial adhesion and biofilm formation on the surface, exploiting the non-biofouling properties of specific brushes<sup>131–133</sup> linked to their high hydrophilicity or zwitterionic nature, which weakens attractive forces between colonizing bacteria and substrate, thus delaying biofilm growth.<sup>134,135</sup> The synergistic antimicrobial-antifouling action of specifically combined polymer brushes is also promising because it allows prolonging the coating's effectiveness.<sup>136</sup>

**Self-defensive antibacterial polymer brush coatings.** The conformation and structure of polymer brushes can be easily tuned by a wide range of external triggers, resulting in a responsive surface that offers significant potential for the development of smart antibacterial coatings. The stimuli may include *e.g.* temperature,<sup>137</sup> pH,<sup>138</sup> type of solvent,<sup>139</sup> and the presence of ions.<sup>140</sup>

Considering in particular pH variations, the brushes composed of charged groups in their repeating units are defined as polyelectrolyte brushes. When subjected to a specific pH, weak polyelectrolyte brushes undergo changes in the number and density of charges, a behaviour that can result in polymeric chains swelling/collapse.<sup>141</sup> The stimulus of pH acidification is the most investigated and exploited in self-defensive antibacterial polymer brushes. Over the last decade, several works have been published following this strategy, wherein the bactericidal activity is either related to the selected polymers or to the loading of antimicrobial agents.

Moreover, to avoid toxicity and premature depletion of the biocidal component, the active layer is typically shielded by an outer biocompatible and antifouling polymeric layer made of zwitterionic or highly hydrophilic polymers. For instance, Liu *et al.*<sup>142</sup> developed a hierarchical polymer brushes system for universal polymeric substrates. They utilized a hydrophilic outer layer of poly(hydroxyethyl methacrylate) (pHEMA) to hinder bacterial adhesion at neutral pH. Melittin (MLT), a cationic AMP, was electrostatically adsorbed onto an inner anionic layer of poly(2,3-dimethylmaleic anhydride) (PDMMA). The amide bonds of PDMMA were cleaved upon bacterial acidification of local pH, triggering a charge-conversion (from negative to positive) release mechanism of MLT. Similarly, Yan *et al.*<sup>143</sup> utilized a pH-responsive hydrophilic outer layer composed of poly(methacrylic acid) (PMAA) combined with a different AMP (cecropin B) covalently bound to an inner poly(2-vinyl 4,4-dimethyl azlactone) (PVDMA) layer. In this case, the hydrated PMAA chains collapsed at lower pH values due to their increasing hydrophobic nature, thereby exposing the AMPs bound to the inner layer. This allowed a smart reversible switch between antifouling and bactericidal coating behaviour over time, without the need of additional reloading of antibacterial agent, making it potentially suitable for reusable surgical devices (Fig. 5). Another feasible solution for pH-responsive polymer brushes is the incorporation of acid-labile Schiff base linkages within the coating. Jin *et al.*<sup>144</sup> implemented a hierarchical polymer coating for infected bone defect therapy, made of ethanediamine-functionalized poly(glycidyl methacrylate) (PGED) brushes conjugated with the antibiotic GS through Schiff base bonds. These bonds were reduced in acidic pH but remained completely stable in a neutral environment. PGED exhibited very low cytotoxicity, in agreement with *in vivo* applications, and the release of GS was a self-adaptive response, allowing for a sustainable action over time, as demonstrated by recycling antibacterial assays. Similarly, Zhang *et al.*<sup>145</sup> developed a switchable antifouling/bactericidal polymer brush coating exploiting the cleavage of Schiff base bonds at low pH. The strategy involved a dual layer polymer brush for catheter





**Fig. 5** *S. Aureus* attachment (106 cells per ml for 24 h) for (a) unmodified Si (b) AMP-grafted Si (c) one-layer PMAA (d) AMP-grafted one-layer P(VDMA-co-MAA) (e) AMP-grafted hierarchical P(VDMA-*b*-PHEMA) (f) AMP-grafted hierarchical P(VDMA-*b*-PMAA). Red arrows indicate damaged bacteria cells. (g) Schematic representation of the reversible nature of the coating. Reprinted with permission of S. Yan, et al., Nonleaching Bacteria-Responsive Antibacterial Surface Based on a Unique Hierarchical Architecture, *ACS Appl. Mater. Interfaces*, 2016, 8(37), 24471–24481, <https://doi.org/10.1021/acsami.6b08436>. Copyright © 2016, American Chemical Society.

biomaterials (e.g., polyurethanes), with the inner layer comprising bactericidal quaternary ammonium poly[2-(dimethyl decyl ammonium)ethyl methacrylate] (PQDMAEMA) and the outer layer made of antifouling polyethylene glycol (PEG). While quaternary ammonium polymer brushes are effective antibacterial agents, they have intrinsic cytotoxicity and are prone to fouling due to their positive charge, necessitating coverage with an antifouling and biocompatible layer.

Using the same type of biocidal polymers, Sun *et al.*<sup>146</sup> have reported an interesting approach for polymeric implants surfaces (e.g., polypropylene meshes) that exploited a different bacteria-related trigger. They converted poly(2-dimethyl amino) ethyl methacrylate (PDMAEMA) brushes into a zwitterionic structure through quaternization and phosphorylation reactions, and then covered it with an upper layer of zwitterionic poly(sulfobetaine methacrylate) (PSBMA), providing non-adhesive and biocompatible properties. Bacterial phosphatase, one of the key enzymatic virulence factors produced during bacterial colonization and biofilm formation, cleaved phosphatase side groups present on PDMAEMA chains, exposing bactericidal polycations. During the bacteria killing process, PSBMA synergistically prevented the attachment of dead bacteria and shielded the cytotoxic polycations.

### Mussel-inspired adhesive coatings

**Overview of the technology and its antibacterial applications.** Mussel adhesive proteins have proven to offer a simple and versatile approach for biomaterials functionalization, leading to the development of conformal thin polydopamine (PDA) coatings. Their adhesive nature draws inspiration from the way in which mussels securely attach to surfaces underwater, achieved through a combination of catechol (3,4-dihydroxybenzene) and amino groups (primary and secondary) present in their foot proteins. Catechols are attributed

to dopamine (DOPA), while amines to lysine (Lys) and histidine residues.<sup>147</sup> This adhesive strength is derived from strong intramolecular interactions formed at the substrate interface, including hydrogen bonding,  $\pi$ - $\pi$  stacking, electrostatic interactions, catechol-metal coordination, and covalent reactions. It stands out as one of the first single-step, material-independent surface chemistries that have found immense success in surface modifications across several engineering applications, owing to its high long-term stability, mild reaction conditions, low cost and substrate adaptability.<sup>148</sup>

The most basic coating approach requires no pre-functionalization steps and simply relies on the immersion of the sample to be coated in a basic solution of DOPA, followed by spontaneous polymerization of PDA on the surface in an appropriate reaction time. The resulting coating can be used as-is or further functionalized, serving as a primer coating for the grafting of several biomolecules and/or polymers to achieve multifunctional surfaces.<sup>149</sup> In biomedical applications, PDA coatings exhibit low cytotoxicity and excellent biocompatibility, making them powerful tools for modifying biomaterials. Among these applications, antibacterial strategies have gained popularity, owing to both intrinsic antimicrobial properties of PDA coatings and the potential to develop PDA-based composites with enhanced antibacterial capabilities.<sup>150</sup>

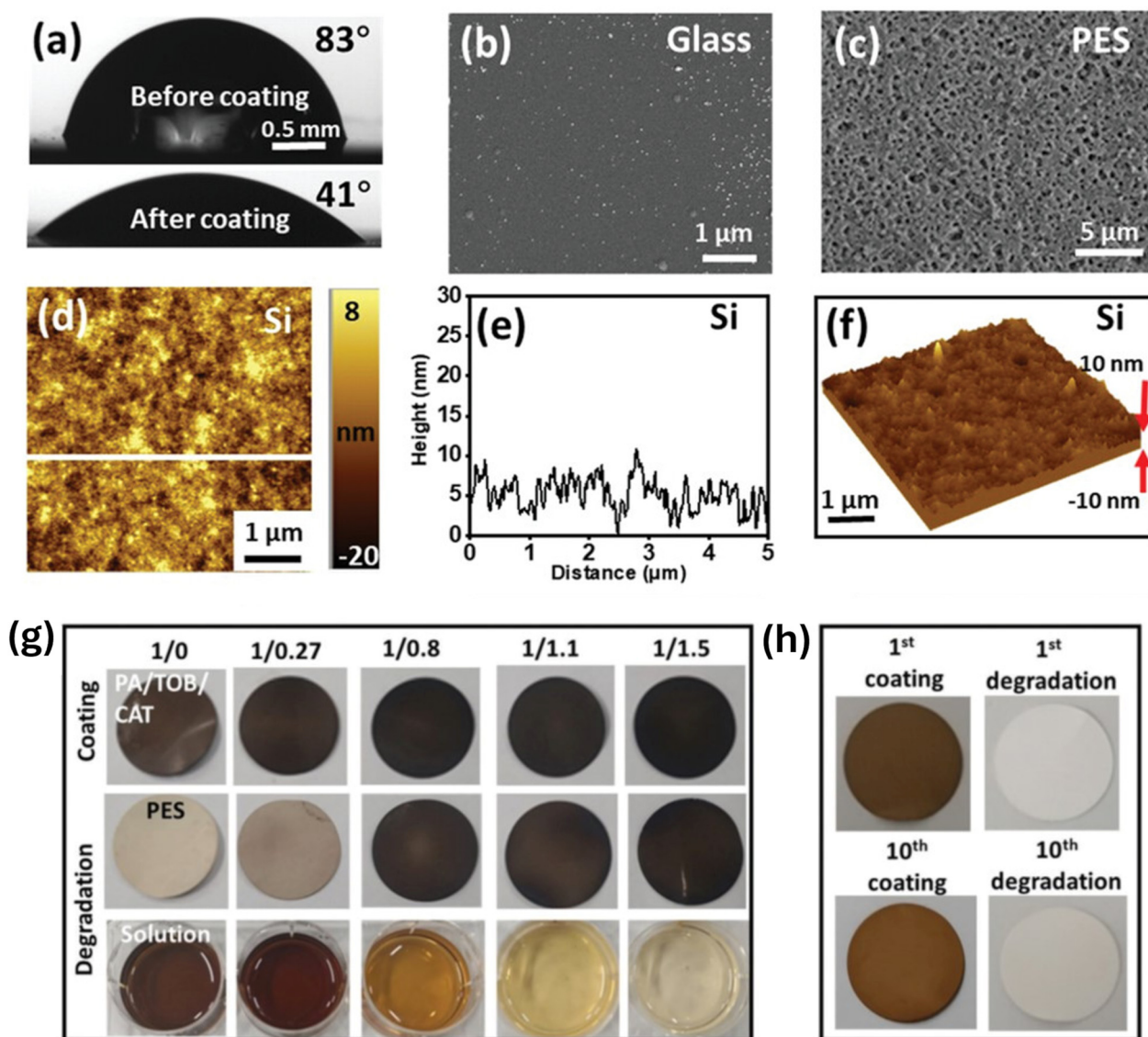
Stand-alone PDA exhibits surface-contact bacterial lysis action due to the high content of Lys residues in mussel foot protein-5 (Mpf-5), along with great oxidative killing capacity thanks to H<sub>2</sub>O<sub>2</sub> production.<sup>151–153</sup> Furthermore, PDA coatings offer notable bactericidal potential through photothermal therapy.<sup>154,155</sup> The synergistic activity of PDA with other antibacterial agents has also been widely investigated, leading to the development of PDA-assisted co-deposition of layers with outstanding multifunctional antimicrobial performance. Particularly, the combination with metallic ions, cationic and



zwitterionic polymers has enabled the implementation of anti-adhesive coatings with bactericidal potential.<sup>156–159</sup>

**Self-defensive antibacterial mussel-inspired coatings.** The integration of a bacteria-responsive feature in antimicrobial mussel-inspired coatings represents a very significant innovation towards substrate-independent, simple and smart antibacterial strategies. Some recent works have already been published, exploiting dynamic covalent chemistry to impart responsive features and PDA-like polymers to grant simplicity and substrate adaptability. Yang *et al.*<sup>160</sup> conducted research on mussel-inspired oxidative polymerization of 5,6-dihydroxyindole (DHI), a typical monomer of melanins, which presented catechol groups to ensure the formation of a stable

adhesive first layer on the surface. Then, sequential layers of formylphenylboronic acid linkers (FPBA) and aminoglycosides antibiotics (AGs) were deposited through boronate-catechol complexation and Schiff base reaction. The resulting bonds, boronate esters and imines, were both reversible and pH-sensitive, capable of being cleaved in acidic microenvironment during bacterial infections, thereby achieving triggered on-demand AGs release. The technology is completely substrate-independent, and the authors have tested it on both polymeric and ceramic surfaces. Concurrently, the same group<sup>161</sup> presented another coating approach (Fig. 6) that utilized solely natural molecules and reversible pH-sensitive bonds, deposited on organic, inorganic and metallic substrates (*e.g.*



**Fig. 6** (a) Water contact angle of glass w/(top) and w/o (bottom) PA/TOb coating (b and c) SEM images of PA/TOb coated glass and PES (d) AFM image of PA/TOb coated Si (e) coating height fluctuation derived from AFM images (f) 3D AFM coated surface reconstruction (g) coating appearance and degradation for different PA/CAT ratios (h) recyclability of the antibacterial coating. Reprinted with permission of L. Yang, *et al.*, Bioinspired Integration of Naturally Occurring Molecules towards Universal and Smart Antibacterial Coatings, *Adv Funct Mater*, 2022, 32(4), 1–10, <https://doi.org/10.1002/adfm.202108749>. Copyright © 2021, Wiley-VCH GmbH.



polyethersulfone PES, polyvinyl chloride PVC catheters and titanium bone nails). The two main constituents, AGs (*e.g.* tobramycin TOB) and protocatechualdehyde (PA), both exhibited antibacterial action. PA are polyphenolic molecules with aldehyde functionalities that provide a polycatechol structure with strong affinity and adhesion to several surfaces through mussel-inspired enzymatic polymerization catalyzed by horseradish peroxidase (HRP) in presence of  $H_2O_2$ . The investigated process was a one-pot reaction that also involved the formation of multiple dynamic imine bonds between the pendant aldehydes of PA and the amino groups of AGs *via* Schiff base reaction. The coating degradation and thus release profile of TOB could be tuned by addition of catechol (CAT) monomer for copolymerization. Moreover, the coating could easily be cleaned without altering the original surface properties and substrates could be coated again. It is a strategy that requires very mild conditions, low-cost natural materials, and simple instrumentation setups, while providing the coating with a smart antimicrobial performance.

Interestingly, such dynamic covalent bonds can be exploited also for a self-cleaning strategy, rather than self-defensive. Asha *et al.*<sup>162</sup> developed a smart antibacterial and antifouling coating with dual responsiveness. The primer adhesive layer was composed of PDA, onto which a zwitterionic and a cationic polymer were covalently grafted. Specifically synthesized for the application, 2-methacryloyloxyethyl phosphorylcholine (MPC) copolymerized with 5-methacrylamido-1,2-benzoxaborole (MAABO) resulted in the bioinspired zwitterionic (poly(MPC-st-MAABO)), chosen to impart antifouling properties, while the copolymer of quaternary ammonium cationic poly(2-(methacryloyloxy)ethyl trimethylammonium) and MAABO (poly(META-st-MAABO)) exerted bactericidal action. The benzoxaborole pendant groups contained in the polymers could be complexed with catechols, forming reversible covalent boronate ester bonds, responsive to both pH and sugars.<sup>163</sup> In this case, the bactericidal and antifouling activity was already solid and did not need a trigger to be activated but could greatly benefit from a cleaning step where all the dead bacteria and negatively charged proteins attached to the cationic brushes were detached from the surface. The self-cleaning action was related to dissociation of the boronate ester bonds and could be triggered either by bacteria-related acidification of pH or by addition of a competitive molecule containing *cis*-diols, so for example after administration of sugars/saccharides solutions. The coating had also regeneration ability if subjected to freshly prepared poly(MPC-st-MAABO) and poly(META-st-MAABO) solutions at physiological pH, thanks to a high affinity between benzoxaborole groups and *cis*-diols of the remaining PDA layer, demonstrating capacity for sustained long-term antibacterial performances.

## Conclusions and future perspectives

The advancement of on-demand responsive antibacterial coatings stands out as a compelling frontier in the ongoing battle

against microbial pathogens that holds the potential to revolutionize infection control strategies. Moving forward, the logical step appears to be a multifaceted approach that integrates various triggers for antibacterial activity within a single coating, as some of the previously cited works have already started to investigate, in favour of broadening the applicability of such coatings towards a multitude of different microorganisms, each one with specific pathogenic mechanisms that do not necessarily involve all the triggers discussed or not in equal measure. Thus, the strategic line of action to enhance the coating efficacy in eradicating bacterial colonization comes across as exerting a synergistic antibacterial action evoked by pH fluctuations, secretion of virulence factors by bacteria but also of reactive oxygen species (ROS) by proinflammatory immune cells in the infected tissue.<sup>164–166</sup> On this note, the complex case of polymicrobial infections that involve different bacterial strains could also be tackled by such a comprehensive approach.

Another significant improvement worthy of investigation would be the integration of active targeting mechanisms within the coating, so to refine the specificity of its action. Indeed, by selectively targeting bacterial cells while sparing healthy host tissues, these coatings have the potential to minimize off-target effects and mitigate the risk of collateral damage. This targeted approach not only enhances the efficacy of antibacterial treatments but also holds profound implications for the pressing global health concern of reducing the emergence of antibiotic-resistant strains. One possibility is offered by microbial lectins,<sup>167</sup> which are proteins expressed on bacterial membranes and biofilms to bind with host glycans, and their high affinity towards sugars and specifically multivalent polysaccharides.<sup>168,169</sup> The interaction between lectins and glycan-mimicking ligands within the coating could secure the immobilization of the microorganisms and promote the action of the antibacterial agents, as was proved in this work by Ye *et al.*<sup>170</sup> in which an active targeting mechanism based on dextran-lectin interactions enabled greater bioavailability of pH- and ROS-responsive nanoparticles containing antibiotic (rifampicin) and a cationic polymer while also promoting their selective internalization to also target intracellular infections.

Besides the implementation of potential improvements, another pivotal aspect to be addressed is how to facilitate the technological transfer of these coatings on commercially available medical devices. The translation of these advancements from the laboratory bench to clinical practice necessitates rigorous validation platforms that closely mimic the complex infection microenvironment.<sup>171</sup> Incorporating co-cultures of bacteria and cells into validation studies could enable researchers to assess the actual efficacy, biocompatibility, and safety profiles of these coatings under conditions that more accurately replicate real-world scenarios. Such validation efforts are paramount for ensuring the reliability and effectiveness of these coatings in clinical settings, where the infection control and patient care are highly important.

Finally, the development and refinement of on-demand responsive antibacterial coatings represent a crucial step



towards addressing the challenges posed by antimicrobial resistance and infectious diseases. Through interdisciplinary collaboration and innovative design strategies, these coatings offer a promising avenue for advancing infection control measures and improving patient outcomes in healthcare settings. By harnessing the power of targeted antibacterial action and adapting to the dynamic nature of microbial infections, these coatings could herald a new era in the fight against antibiotic-resistant pathogens, bringing in a future where effective infection control is within reach.

## Author contributions

Conceptualization – M. A. Cassa, I. Carmagnola; writing (original draft) – M. A. Cassa, P. Gentile, J. Girón-Hernández; writing (review and editing) – M. A. Cassa, I. Carmagnola, G. Ciardelli, P. Gentile, J. Girón-Hernández; supervision – G. Ciardelli.

## Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

## Conflicts of interest

There are no conflicts to declare.

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