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Engineering biomaterials to prevent post-operative infection and fibrosis.

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Abstract

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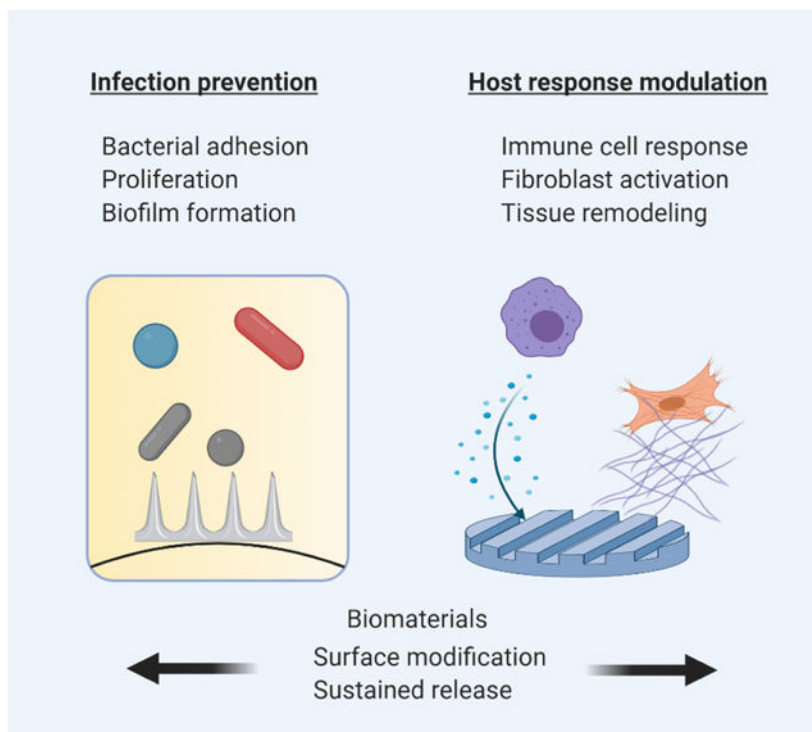
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Implantable biomaterials are essential surgical devices, extending and improving the quality of life of millions of people globally. Advances in materials science, manufacturing, and in our understanding of the biological response to medical device implantation over several decades have resulted in improved safety and functionality of biomaterials. However, post-operative infection and immune responses remain significant challenges that interfere with biomaterial functionality and host healing processes. The objective of this review is to provide an overview of the biology of post-operative infection and the physiological response to implanted biomaterials, and to discuss emerging strategies utilizing local drug delivery and surface modification to improve the long-term safety and efficacy of biomaterials.

Graphical Abstract



Keywords

Biomaterials; bacterial adhesion; surface modification; sustained release; inflammation; infection; fibrosis

1. Introduction

Biomaterials are implanted in tens of millions of patients globally, with more than 13 million procedures occurring annually in the U.S. alone (1). Biomedical implants have been employed in almost every domain of surgery, ranging from microscale implants in microvascular and ophthalmic surgery to macroscopic devices in orthopedic and general surgery. Interaction between the host environment and implanted biomaterials begins immediately upon introduction, after which biomaterials may become coated with serum

proteins, aqueous humor, mucosal secretions, microbiota, and/or extracellular fluids depending on their location in the body (2). This makes the biomaterial surface highly susceptible to microbial as well as host cellular adhesion. In 1987, orthopedic surgeon, Dr. Anthony Gristina postulated that “a race to the surface” would result in: (1) bacterial adhesion to the surface of the material and proliferation into a biofilm leading to infection, or (2) host cell encapsulation of the biomaterial with extracellular matrix to isolate it from host tissues (3). Accordingly, infection and inflammation are the two primary causes of medical device complications and failure, both of which are mediated by cellular interaction with the biomaterial. Thus, it is desirable to engineer biomaterials that are both resistant to contamination/biofouling and can successfully integrate with host tissue. Biomaterial associated infections lead to an increased annual economic burden of more than \$11 billion (4, 5). The first half of this review focuses on mechanisms involved in post-operative bacterial infection of long-term implants which are highly susceptible to bacterial adhesion and biofilm formation such as orthopedic prostheses, ureteral stents and sutures. We discuss advances in biomaterial design that may help prevent bacterial adhesion and proliferation. The latter half of this review discusses host responses to implanted biomaterials, particularly the role of innate immune cells and stromal cells in implant fibrosis. Recent approaches for modulating cellular responses to implanted biomaterials are also examined. Collectively, medical implants that are highly biocompatible and impervious to infection will significantly improve clinical outcomes and reduce healthcare costs.

2. Implants are susceptible to infection

Nearly half of all healthcare-associated infections in the U.S. occur with implanted biomaterials (6). Implant-associated infections increase duration of hospitalization, as well as rates of re-hospitalization and re-intervention (7–9). Microbiota from the patient, the operating room, and the surface of the implant itself have all been implicated in post-operative infections (10, 11). Bacterial adhesins interact with host proteins that coat the implant’s surface, aiding in bacterial adhesion to the surface of the device. Left unchecked, certain species of bacteria (predominantly commensal bacteria like *Staphylococcus aureus* and *Staphylococcus epidermidis*) can secrete signaling molecules to communicate and alter their metabolic states to form a biofilm (12–14). A biofilm is a matrix composed of proteins, DNA, and membrane structures from dead cells that protects the bacteria within the biofilm, including limiting penetration of small molecule drugs (15, 16). Systemic administration of antibiotics is often the first-line mode of prophylaxis and treatment of infections, although poor bioavailability and systemic toxicity may limit efficacy (17–19). Systemic antibiotic therapy has been associated with risk of allergic reactions, nephritis and enteric dysbiosis (20). Further, the lack of patient adherence to prescribed dosing regimen further limits both the safety and efficacy of antibiotics (21, 22). Subtherapeutic drug exposure contributes to the number of bacterial species that have become resistant to widely used antibiotics such as gentamicin and methicillin (23–25), as well as antibacterial agents such as triclosan (26). Thus, rather than relying on adjunct antibiotic administration for preventing post-operative infections, engineering functionality into the implant itself may lead to improved surgical outcomes. Figure 1 provides an overview of biomaterial-associated infection and strategies reviewed herein. In this section, we describe mechanisms of bacterial adhesion and biofilm

formation, followed by approaches for engineering implantable biomaterials that provide local, sustained antibiotic release and/or prevent bacterial adhesion.

2.1 Mechanisms of infection

Bacteria colonize a diverse range of surfaces, including host tissues and abiotic biomaterials (27). Bacteria may adhere to biomaterials via non-specific interactions, such as electrostatic interactions with the negatively charged bacterial cell wall, or by hydrophobic interactions. Alternatively, bacteria may interact with host tissue in a ligand specific manner (28, 29). Most bacteria have evolved to survive in a community adherent to solid surfaces where nutrient availability tends to be highest, and there is also positive selection for bacteria that form biofilms as a protection (30, 31). Biofilm formation on implants presents a challenge for effective treatment both because of poor penetration of antibiotics and metabolic heterogeneity within the biofilm which can allow some cells to survive high doses of antibiotics (32). Such resistant bacterial cells can proliferate once they sense a decline in the bacterial population, causing a recurrent infection (33). Below, we discuss strategies to prevent infections by eliminating early planktonic bacteria or by preventing adhesion.

2.2 Sustained release technologies for prevention of infection

Numerous anatomical barriers and clearance mechanisms significantly reduce drug concentrations at intended locations (34, 35). Local delivery of drugs overcomes these challenges and is a promising alternative to systemic therapies. There is increasing use of polymers for manufacturing medical implants due to the tailorable textural, mechanical, and physical properties (36). Moreover, a wide range of natural and synthetic polymers have demonstrated high strength, flexibility, and durability together with a favorable safety profile and long-term biocompatibility (37–40). More recently, the potential for loading polymeric implants with therapeutics for sustained, local release to prevent infection, as well as surface patterning to prevent bacterial adhesion, have been explored. Specific clinical applications for modulating implantable biomaterials properties to prevent post-surgical infection are described below (Table 1).

2.2.1 Orthopedic implants—Joint replacement surgery is performed more than a million times annually in the U.S. (41). Prosthetic joint infection is a major cause of revision surgery with a recurrence rate of 16% (42). The current standard of care to treat prosthetic joint infections involves explanting the prosthesis and using bone cement spacers loaded with antibiotics as filler materials for several weeks before implanting a new prosthesis, a timeframe in which mobility is limited (43). To obviate the need for intermediate bone cement spacers, Suhardi, et al. manufactured prosthetic joint implants containing eccentric drug clusters, which resemble highly elongated ellipsoids (41). They demonstrated that the *in vitro* release kinetics of the drug was dependent on the eccentricity of the drug clusters. Polymer processing methods that result in spherical drug clusters, such as solvent casting, can entrap drug for longer durations resulting in slow release kinetics. The authors demonstrate that compression molding results in eccentric drug clusters in the polymer matrix, which had faster elution rates. Implants loaded with a combination of vancomycin and rifampin released drug in a sustained manner for up to 6 months *in vitro*. In a rabbit joint *S. aureus* biofilm infection model, 100% of the animals that received drug loaded prosthetic

antifouling effect has also been shown for synthetic polymers such as poly[*N*-(2-hydroxypropyl) methacrylamide] (poly(HPMA)). In a study conducted by Gomes, et al. (52), poly(HPMA) was conjugated to a glass surface to form brush-like structures to characterize the attachment and biofilm forming capacity of *E. coli* on bare glass, poly(dimethylsiloxane) (PDMS), and brush-like poly(HPMA) surfaces. They observed 80% reductions in both total biofilm forming cells and viable cells on the poly(HPMA) coatings compared to bare glass surfaces *in-vitro* (52). Furthermore, BMAP-28, a cathelicidin peptide with intrinsic antimicrobial activity, was tested by Orlando, et al as a coating alone and in combination with antibiotics (53). When stents coated with either vancomycin or BMAP-28 were challenged with *S. aureus*, the bacterial burden was significantly reduced compared to uncoated stents. However, near complete elimination of infection was achieved when the BMAP-28-coated stents were used in conjunction with intraperitoneally administered vancomycin (53). Another study investigated the synergistic effects of combining antibiotics (54). They showed *in vitro* that there was an eight-fold reduction in the minimum bactericidal concentration of amikacin when used in combination with clarithromycin against adherent *P. aeruginosa*. In a rat model of *P. aeruginosa* bladder infection, they found that either systemically administered amikacin with an uncoated stent or clarithromycin-coated stents provided a reduction in bacterial colonization compared to an uncoated stent alone. However, near elimination of infection was achieved in rats that received systemic amikacin in combination with clarithromycin-coated ureteral stents (54). These results demonstrate that sensitization of bacteria to antibiotics by deterring attachment and the use of combinatorial drugs are significantly advantageous in preventing ureteral infections of biomaterials.

2.2.3 Antibacterial sutures—Surgical site infections (SSIs) are one of the most common post-operative complications, and have an incidence of 5.6 per 100 surgeries in developing countries and 2.6 per 100 surgeries in the U.S. (55). Additionally, in procedures like colorectal surgeries, incidence of post-operative infection can be as high as 17.5%, even in developed countries (56). While sutures are routinely used for wound closure in a wide variety of surgical procedures, the presence of sutures at a wound site has been associated with infection. This has led to the investigation, development, and approval of surgical sutures with antibacterial properties. In 2002, Ethicon received regulatory clearance for coated antibacterial sutures containing triclosan in general surgery (57). However, as mentioned previously, there is growing concern over bacterial resistance to triclosan (26, 48). One alternative strategy that has gained attention is employing sustained-release technologies to deliver antibiotics locally at the surgical site. Chen et al. (58) developed PCL-based levofloxacin hydrochloride coatings for silk sutures (sizes 2–0 and 0–0). The PCL/levofloxacin coatings demonstrated sustained release for up to 5 days *in vitro*, leading to measurable zones of inhibition against *S. aureus* and *E. coli* in agar diffusion assays for 7 days (58). However, suture coatings may require multifilament thread and increased suture diameter to achieve sufficient drug release, which limits use in surgeries requiring thin sutures (e.g., microsurgery). For example, Ethicon’s antibacterial sutures are only available in diameters suitable for general surgery (70–339 μm) One potential solution is to form a suture entirely out of polymer with drug embedded, which is achievable via electrospinning. In one study, Kashiwabuchi et al. manufactured poly(L-lactide) (PLA) nanofiber sutures

(size 8–0) loaded with the antibiotic levofloxacin, using a wet electrospinning method. By incorporating poly(ethylene glycol) within the PLA nanofibers, they achieved sustained release kinetics of levofloxacin for over a period of 70 days *in vitro*. Further, agar diffusion tests showed that the drug released from the electrospun sutures successfully inhibited *S. epidermidis* for a period of 7 days (59).

Historically, drug-loaded electrospun suture materials have failed to demonstrate sufficient mechanical strength as stipulated by the United States Pharmacopeia guidelines for clinical use (60–64). Parikh et al. (65) designed a novel electrospinning apparatus that was capable of manufacturing highly twisted nanofibers loaded with levofloxacin. Increasing the number of twists greatly improved tensile properties of the multifilament sutures. Sutures that were highly twisted (~1575 twists per 10 centimeters) surpassed United States Pharmacopeia breaking strength requirements (0.24 N) for a 28 μm absorbable suture with a maximum tensile strength of 0.35 N. Further, the sutures exhibited a direct dependency on the number of twists imparted to the nanofibers for breaking strength. This is the first report of electrospun suture materials demonstrating sufficiently high breaking strength required for use in clinic. In a rat model of corneal keratitis, the levofloxacin-loaded sutures successfully prevented multiple consecutive inoculations of *S. Aureus* over one week (see Figure 2), and detectable levels of levofloxacin in rat eyes for a month (65). Overall, the general approach of loading small molecules into polymeric suture materials to enable local and sustained delivery of antibiotics by means of direct loading of drug in the suture or via surface coatings have shown great promise in abrogating bacterial adhesion and proliferation.

2.3 Modulating material surface properties to prevent bacterial adhesion

Bacterial adhesion to materials is highly dependent on surface topography, chemistry, and hydrophobicity (66–68). Surface roughness has been shown to affect bacterial adhesion in dental implants (69), leading to many attempts to modify surface roughness to reduce the risk of infection (70–72). The rationale is that bacteria have evolved to detect patterns that are dimensionally similar to their own size (~1 μm), and thus, creating smoother surfaces (surface roughness <1 nm) reduces adhesion (73). For example, one study showed that titanium surfaces blasted with micronized aluminum oxide particles to produce a nanoscale surface roughness (>100 nm) had increased adhesion of bacteria derived from whole saliva. In contrast, naturally occurring nanopatterns, such as the self-cleaning hydrophobic surfaces on lotus leaves, and dragonfly and cicada wing patterns are highly resistant to bacterial adhesion and biofouling (74). Bhadra et al. (75) used hydrothermal etching to nanopattern titanium surfaces, and evaluated the attachment of *S. aureus* and *P. aeruginosa* compared to unmodified titanium surfaces. They noted a significant reduction in the total number of adherent bacteria and specifically live bacteria on the nanopatterned surfaces, indicating that certain nanopatterned surfaces have an inherent bactericidal nature (75).

Linklater, et al. (76) compared the bactericidal nature of dragonfly wings to a synthetic nanomaterial developed for use in photovoltaic applications and biosensors, termed black silicon (77–79). Black silicon was manufactured using a reactive ion-etching process to achieve nanoscale protrusions on the surface of silicon wafers. The authors then studied the adhesion and bactericidal properties of these surfaces using *S. aureus*, *P. aeruginosa*, and *S.*

subtilis. Nanotopographical features on black silicon resemble sharp protrusions and are capable of causing indentations and mechanical stress to the bacterial cell wall. The authors postulate that an imbalance between the hydrostatic pressure caused by the cytoplasm on the bacterial cell wall and the indentation stress caused by the nanopatterned substrate caused cell wall rupture and death of the bacteria. Further, certain bacteria such as *S. subtilis* are spore forming, and this property protects the bacteria from environmental stress and enhances their rigidity. Nanopatterned black silicon surfaces not only disrupted spores of *S. subtilis*, indicating an anti-adhesive nature, but also required a significantly higher number of bacterial cells of all three tested model organisms in order to achieve colonization of the material suggesting a bactericidal nature (76). Further research and validation is required in order to translate these technologies for clinical use.

3. Implants are susceptible to immunologic reactions

Implanted biomaterials generally illicit a chronic inflammatory response that eventually results in fibrosis, isolating the material from the rest of the body. This fate is common to materials made from natural and synthetic sources, and the speed and extent of the fibrotic response determines the functional lifespan of the implant. Surgical procedures and biomaterial implantation cause injury to the surrounding tissue, facilitating interactions with host proteins and cells. Non-specific protein adsorption to the material surface forms a “provisional matrix” which makes the microenvironment surrounding the biomaterial conducive to cellular adhesion (80). A complex set of infiltration, proliferation, fusion and degranulation events associated with various types of innate immune cells and stromal cells, such as smooth muscle cells and fibroblasts, culminates in fibrotic encapsulation (Figure 3). This physiological response to the implant is interlinked with bacterial colonization, as misguided host defenses can create a niche for bacterial adhesion and proliferation (10, 81). In particular, neutrophils and macrophages form part of an acute response to infection as well as abiotic implants and thus, dysregulation of their activity can result in infection, inflammation, and fibrosis (82, 83). In this section we provide an overview of recent advances in controlling the biological response to biomaterials, including providing local drug release, cell capture, and modifying surface topography. Lastly, we outline this evolution of concepts in the design and implementation of endovascular devices with improved surgical outcomes.

3.1 Immune cell responses to biomaterials

Immune cells are first responders that influence the nature of the microenvironment surrounding the biomaterial. Neutrophils are the predominant immune cell type at the site of implantation in the first hours (84). The role of neutrophils in generating reactive oxygen species (ROS) and vasodilation has been well studied (85, 86). While the primary function of neutrophils is to phagocytose foreign material and release inflammatory cytokines to recruit monocytes and macrophages, most implants are too large to be phagocytosed. In this case, neutrophils undergo degranulation and deposit neutrophil extracellular traps (NETs), or networks made from DNA, histones, and neutrophil elastase (84, 87, 88). NETs function to trap pathogens like bacteria and viruses and drive the sterile inflammatory response to implant materials. Jhunjhunwala, et al. (89) used a mouse model of peritoneal fibrosis to

examine the role of NETs in the fibrotic response to foreign materials. They implanted microcapsules made from alginate, glass, poly(lactic-co-glycolic)acid (PLGA) and poly(methyl methacrylate) (PMMA) in the peritoneal cavity of mice and observed an increase in histone H1 and neutrophil elastases on the surfaces of glass, PMMA and alginate microcapsules. Interestingly, PLGA microcapsules that degrade in 2 weeks showed lower levels of neutrophil recruitment as compared to PLGA microcapsules that take longer to degrade (89). Further, Cohen et al. (90) showed that cell adhesion has a deterministic role in neutrophil fate. The authors showed that neutrophil adhesion to polyethylene glycol (PEG) scaffolds resulted in increased secretion of ROS, matrix metalloproteinase-9 (MMP-9), and myeloperoxidase molecules in comparison to polydimethylsiloxane PDMS scaffolds (90). Further studies are required to elucidate the mechanisms underlying neutrophil-biomaterial interactions and device centric approaches to modulate neutrophil response to biomaterials.

Macrophage plasticity and diversity in phenotypes are essential to tissue restoration, repair and remodeling (91, 92). Macrophages begin to accumulate on biomaterial surfaces a few hours after implantation, and can remain there for several months (93). Macrophage recruitment is thought to be mediated by monocytes to enable further recruitment of immune cells (94–96). Monocytes can also differentiate into macrophages of many different phenotypes based on physical and chemical microenvironmental cues, typically classified as M1 or M2. M1 macrophages are involved in secretion of proinflammatory cytokines and are associated with host defense (97), while subtypes of M2 macrophages are generally associated with constructive tissue remodeling (98, 99). Therefore, it is generally desirable to skew macrophages surrounding biomedical implants to an M2 phenotype. Multiple studies have successfully demonstrated macrophage polarization to M1/M2 phenotypes by using immunomodulatory small molecule therapies (100–102). Recent data in RAG-2/ γ KO mice showed that macrophages are central to host fibrotic response and that macrophage depletion leads to the near absence of the foreign body reactions surrounding intraperitoneal implants in rodents and non-human primates (103). Further, inhibiting colony stimulating factor-1 (CSF-1) receptors on macrophages can lead to an equivalent effect in suppressing foreign body reaction to multiple classes of materials, including polymers, hydrogels, and glass microcapsules (Figure 4). Recent work has also implicated IL-17, a pro-inflammatory cytokine associated with Th-17 helper T cells and macrophage activation, in biomaterial mediated fibrosis (104–107). The absence of IL-17 signaling in mice was shown to mitigate fibrotic response to intraperitoneally implanted PCL (108).

Fibroblasts are the majority cell type in the healing stage of tissue restoration, and play a key role in inflammation, angiogenesis, and fibrosis. Fibroblasts are thought to be present in the neo-tissue for years, reprogramming their phenotype to become quiescent once tissue restoration is complete (109–111). Upon injury, a deluge of pro-inflammatory molecules activate fibroblasts present in connective tissue (112). Fibroblasts then differentiate into either fibrocytes, myofibroblasts or other phenotypes based on microenvironmental and chemical cues. Myofibroblasts are associated with highly dense ECM deposition in implant associated fibrosis pathologies (113, 114). Many pharmacological and materials-centric strategies to restrict fibroblast proliferation and activation have been successfully employed in preclinical models. Pitha et al. (115) detailed the use of Rho-kinase (ROCK) inhibitors (Y27632, fasudil, H1152) in suppressing the myofibroblast phenotype in scleral fibroblasts.

All three inhibitors reduced TGF- β -induced α -SMA expression and associated collagen contraction in primary scleral fibroblast cells *in vitro*. Further, in mouse models of bead-induced glaucoma, they showed that scleral fibroblast proliferation was restricted in mice treated with Y27632 and fasudil by sub-conjunctival injection (115). Biomaterial properties including implant size, surface topography, and porosity also influence fibroblast behavior. Veisoh, et al. (116) injected crosslinked alginate and glass spheres of 8 different diameters (0.3–1.9 mm) intraperitoneally in C57BL/6 mice to study the effect of size on fibrotic response. Interestingly, increasing sphere diameter inversely correlated with immune cell recruitment and cellular overgrowth on explanted spheres after 14 days *in vivo* as measured by flow cytometry and phase contrast imaging, respectively. Furthermore, expression of fibrotic markers such as α -SMA, collagen 1 (*COL1A1*) and collagen 2 (*COL1A2*) genes in cellular deposits on the sphere surfaces was significantly downregulated for 1.8 mm spheres as compared to 0.3 mm spheres. Additionally, when alginate spheres either 0.5 or 1.55 mm diameter were implanted subcutaneously in non-human primates, the 1.55 mm spheres were devoid of cellular growth, whereas the 0.5 mm spheres were encapsulated in fibrotic capsules up to 100 μ m thick (116). Taken together, these studies suggest that modulating fibroblast behavior either by material design or by using small molecules may deliver outcomes desirable for non-fibrogenic tissue remodeling.

3.2 Engineering biomaterials to modulate immune response

Restoration of function to injured tissues is crucial to the survival of organisms. The role of innate and adaptive immune responses to implanted materials, particularly shaping tissue architecture surrounding biomaterials in becoming increasingly clear. Early responders such as neutrophils have a very transient presence and therefore it is difficult to understand and modulate their behavior with meaningful consequences. On the other hand, macrophages have an extended presence at implant sites and a more robust and definitive response. As a result, emphasis has been placed on studying macrophage responses to biomaterials. It is important to note that while adaptive immune cells were initially thought to be peripheral to immune response to biomaterials, the role of helper T-cells in determining the fate of tissue regenerative biomaterials has been shown to be essential (117). Surface and physical properties of biomaterials have been described as mediators of macrophage activation. Macrophages respond to physical cues both *in vitro* and *in vivo*.

McWhorter, et al. (118) studied macrophage polarization on micropatterned surfaces. They manufactured substrates which had either 20 or 50 μ m thick alternating lines of fibronectin and pluronic F127 forming a micropattern. F127 is largely bioinert and deters cell adhesion, facilitating cellular elongation preferentially along the fibronectin components of the micropatterned substrate. The authors compared cell shape and markers associated with M1 and M2 macrophage activation in cells cultured on either patterned or non-patterned substrates. Macrophages cultured on micropatterned substrates displayed a distinct elongated shape, whereas those cultured on non-patterned substrates were more rounded with protrusions. Micropatterned substrates also induced increased expression of Arginase-1, which is an M2 biomarker. Molecules that are associated with inducing M2 polarization acted synergistically with physical cues to enhance Arginase-1 expression by up to 20-fold. In contrast, when macrophages on patterned substrates were exposed to classical

activation pathway stimulators LPS and IFN- γ , expression of iNOS which is a known biomarker for the M1 phenotype was only moderately increased suggesting that physical cues can have a protective effect against pro-inflammatory signaling molecules. Looking at actin microstructure, the authors found that inhibition of pathways involved in actin contractility lowered the expression of Arginase-1, but did not affect cell shape or spreading (118). This observation did not hold for cytokine mediated activation, suggesting that macrophages rely on cytoskeletal contractility after sensing physical cues to modulate polarization.

Another recent study performed by Tylek, et al. (119) showed that porosity heavily influenced macrophage polarization. They used a manufacturing technique called melt electrowriting to create three dimensional scaffolds of varying pore sizes (40–100 μm) and geometries (triangular, round, square shaped pores) from PCL. It was observed that a pore size of 40 μm induced definitive M2-like polarization in contrast to 50, 80, and 100 μm pore sizes. Interestingly, round geometry of the pores significantly decreased expression of the M2 macrophage marker CD-163 compared to rectangular, triangular, and disordered pore shapes. Additionally, a decrease in pore size from 100 to 40 μm significantly increased CD-163 expression. Further, the authors measured phagocytic activity of macrophages cultured on porous and 2-dimensional film scaffolds using a fluorescent bead assay, and observed significantly decreased phagocytic activity on all porous scaffolds at day 7 as compared to 2-dimensional films made from the same PCL polymer (119).

Li, et al. (120) studied composite structures made from PCL nanofibers and hyaluronic acid (HA) hydrogel networks as filler materials to restore tissue function and mechanical integrity. The composites had the combined advantages of mechanical stability, injectability and large matrix pore sizes which made the materials durable, easy to administer and capable of modulating immune cell response. *In vitro* cultures of macrophages in PCL-HA composites displayed a significantly higher degree of M2 polarization, whereas a greater extent of M1 polarization was observed in the HA hydrogels alone. They theorized that the compliant nature combined with the porous framework of the PCL-HA enabled tissue revascularization and cell infiltration in a model of rabbit soft tissue defect repair. Histological analysis showed that angiogenesis and integration with host tissue had occurred (120). Wolf et al. (121) studied the role of ECM in altering macrophage phenotype. In a rat model of abdominal muscle defects, the authors implanted polypropylene meshes coated with a urinary bladder ECM-derived hydrogel matrix. In the animals which received an ECM coated mesh, there was a reduction in the number of M1 macrophages as well as a reduction in the number of foreign body giant cells FBGCs on the surface of the implants at 7, 14 and 35 days compared to uncoated meshes (121). These results offer insights into the significant advantages of device centric approaches to modulate host immune response. Tailoring physical properties of biomaterials such as surface topography, roughness and porosity can induce a favorable immune microenvironment which is critical for the longevity of functional biomaterials.

3.3 Clinical case study: Coronary stents

Cardiovascular disease is the leading cause of death globally, accounting for nearly 18 million deaths globally in 2017 (122). An estimated 12–29% of elderly individuals suffer from peripheral artery disease requiring vascular intervention (123). Vascular intervention technologies have undergone a gradual evolution in parallel with advances made in understanding physiological responses to biomaterials. Table 2 provides an overview of coronary stent technologies that have been studied in clinical settings. Percutaneous coronary intervention is one of the most widely practiced surgical procedures involving the use of biomaterials in the U.S. The first balloon angioplasty was performed in the 1970s (124). Early enthusiasm around this procedure was dampened due to the occurrence of adverse events, such as in stent restenosis (ISR) due to excessive proliferation of smooth muscle cells after injury, elastic recoil, and abrupt closure of blood vessels (125). Patients then needed to undergo coronary artery bypass grafting surgery to restore homeostasis, leading to the development and use of bare metal stents (BMS), which were approved by the FDA in 1993 (126). However, both ISR and thrombosis remained issues with utilization of BMS. BMS therefore needed to be supplemented with systemic pharmacological agents, such as warfarin and aspirin, to avoid thrombosis and restenosis (127). Conventional BMS require placement using a balloon, which dilates the wall of blood vessels by exerting radial mechanical stress. The procedure is also associated with significant de-endothelialization and acute overexertion of pressure on the intimal and medial tissue, leading to smooth muscle cell proliferation and vessel constriction (128). Furthermore, injury to the endothelial cells and intimal tissue results in the secretion of pro-inflammatory signaling molecules, immune cell infiltration, and thickening of the intima (129–131). Attempts have been made to coat BMS with biocompatible polymers, such as polyethyleneterephthalate and polytetrafluoroethylene, though without any impact on restenosis or thrombotic events in large clinical trials (132, 133). Several efforts to modify the surface properties of stent coatings such as the use of nanofibers to enhance surface roughness and mimic ECM features are in preclinical development (134).

To circumvent the issues of thrombosis and neointimal hyperplasia, stents capable of delivering therapeutics locally have been developed (125). Drug-eluting stents (DES) are composed of a metal backbone to provide structural integrity with drug-loaded polymer coatings to provide local, sustained drug release. The TAXUS stent was the first DES, and delivered the anti-mitotic drug paclitaxel (135). Around the same time, the Cypher DES containing the anti-proliferative and anti-inflammatory drug, sirolimus, was also developed (136). Both stents reduced ISR compared to BMS, supporting the potential for sustained-release technologies (137). However, large trials showed no benefit in reducing stent-associated mortality compared to BMS (138). The second generation of DES (Endeavour, Xience, Resolute, Promus) incorporated either everolimus or zotarolimus, which are structural analogs to sirolimus and show similarities in effective cytostatic activity. These drugs also show potent immunosuppressive function and are used in transplant surgery to prevent pathological rejection. Large clinical trials and subsequent meta-analyses showed that overall, second generation DES were associated with reduced overall mortality, and lower rates of myocardial infarction, late stent thrombosis, and ISR.

There are however, key challenges that remain to be addressed concerning DES. Major among them is delayed re-endothelialization of the injured blood vessel, which is associated with late stage thrombosis events (130). The latest generation of stent technologies aim to promote the *in situ* cellularization of scaffolds. Endothelial progenitor cell capture stents (EPCCs) work by presenting a CD34 antibody on the luminal side of the stent to encourage EPCs binding and proliferation (139). Early studies of sirolimus-eluting EPCCs show non-inferiority to paclitaxel-eluting stents in mitigating neointimal hyperplasia and in the incidence of adverse cardiac events (140).

4. Concluding remarks and future perspectives

Biomaterials have substantially contributed to improving quality of life and extending lifespan of millions of people. Preventing biomaterial-associated infections and controlling host-material interactions will continue to be a critical factor for successful surgical outcomes. As biomaterials continue to evolve, it is becoming increasingly evident that a local, materials-centric approach offers distinct advantages in contrast to systemic therapies. Functionalizing biomaterials as drug depots to deliver high concentrations of antimicrobials locally, as well as employing surface modifications that deter bacteria from adhering and proliferating, are promising strategies to combat the increasing threat of antimicrobial drug resistance and circumvent issues with systemic toxicity and patient compliance. However, long-term surgical outcomes are often still poor due to fibrotic response, which can occur long after drug release has ceased. Strategies for modifying the biomaterial surface, such as patterning, may work to modulate the local immune cell signaling and stromal cell response to successfully integrate biomaterials with host tissue. We posit that the next generation of biomedical implants may incorporate topographical features as well as local drug delivery for both short- and long-term modulation of biological response. Biomaterials engineered to evade microbial colonization and instruct host cellular responses have great therapeutic and translational potential.

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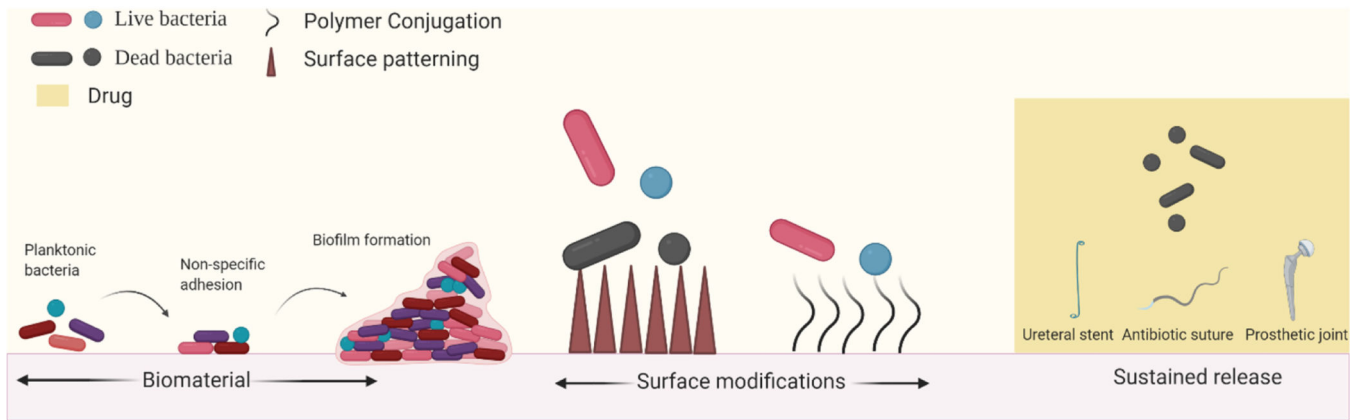


Figure 1. Stages of biofilm formation and strategies to prevent infection. Bacteria adhere to biomaterial surfaces via non-specific adhesion and proliferate to form biofilms. Modifying surface properties of the biomaterial such as biocidal patterning and polymer conjugation have been shown to be effective in preventing biomaterial associated infections in animal models. Biomaterials can also act as drug depots which can release bactericidal small molecules locally circumventing systemic delivery barriers.

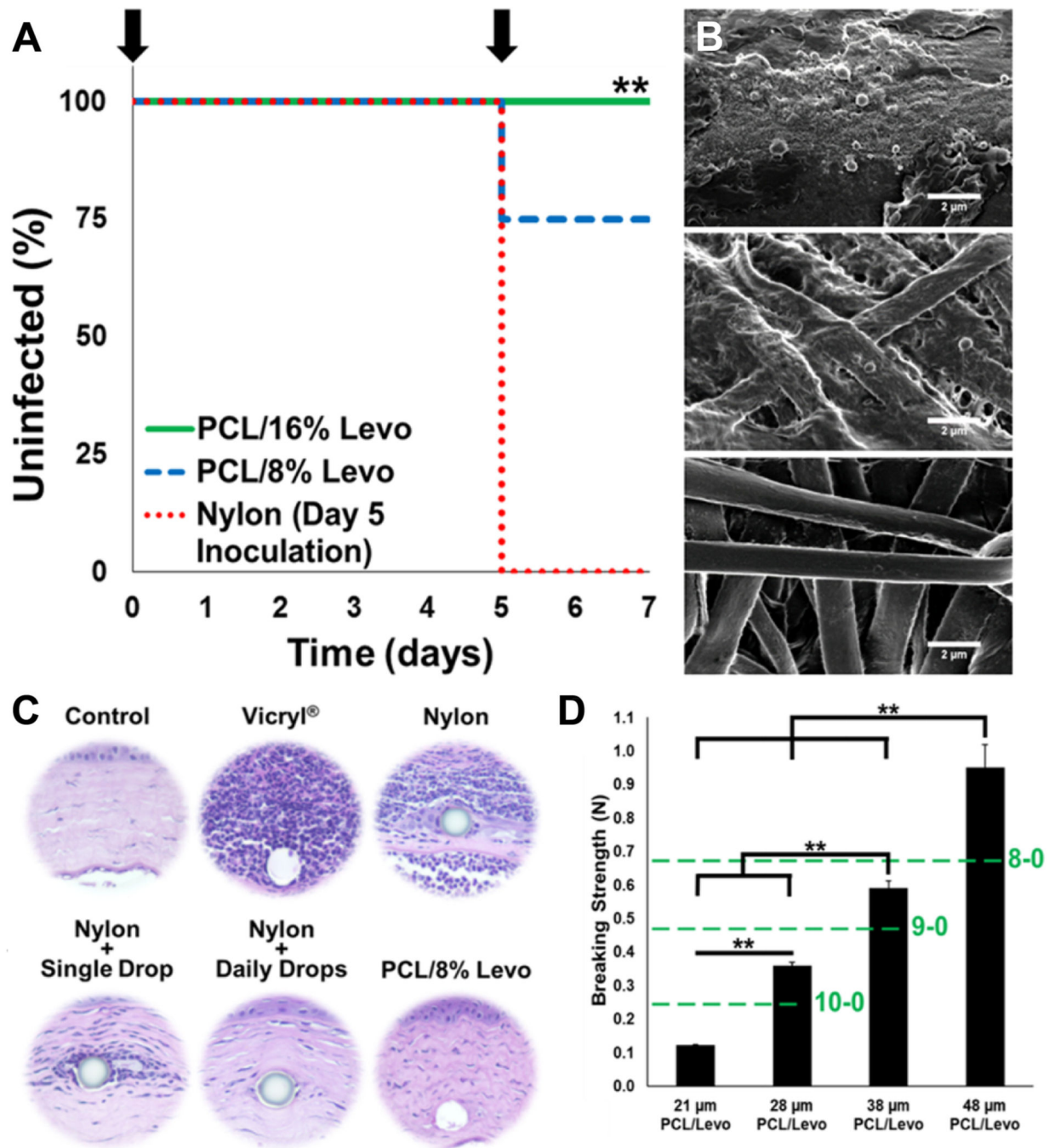


Figure 2. (A) Antibiotic-eluting ophthalmic sutures prevent *S. aureus* infection in a rat model of corneal keratitis (** indicates $p < 0.01$). (B) Scanning electron micrographs (scalebars represent 2 µm) of commercial nylon sutures (top), 8% (middle) and 16% Levofloxacin loaded nanofiber sutures (bottom) explanted from the corneal stroma after bacterial challenge with *S. aureus*. (C) H&E stained corneal tissue showing reduced inflammation in eyes which received drug eluting suture 48 h after bacterial inoculation. (D) Breaking strength of drug loaded sutures scaled with suture diameter. Dashed green lines indicate

minimum breaking strength requirement for absorbable sutures of 10–0, 9–0 and, 8–0 diameters. Modified with permission from [68].

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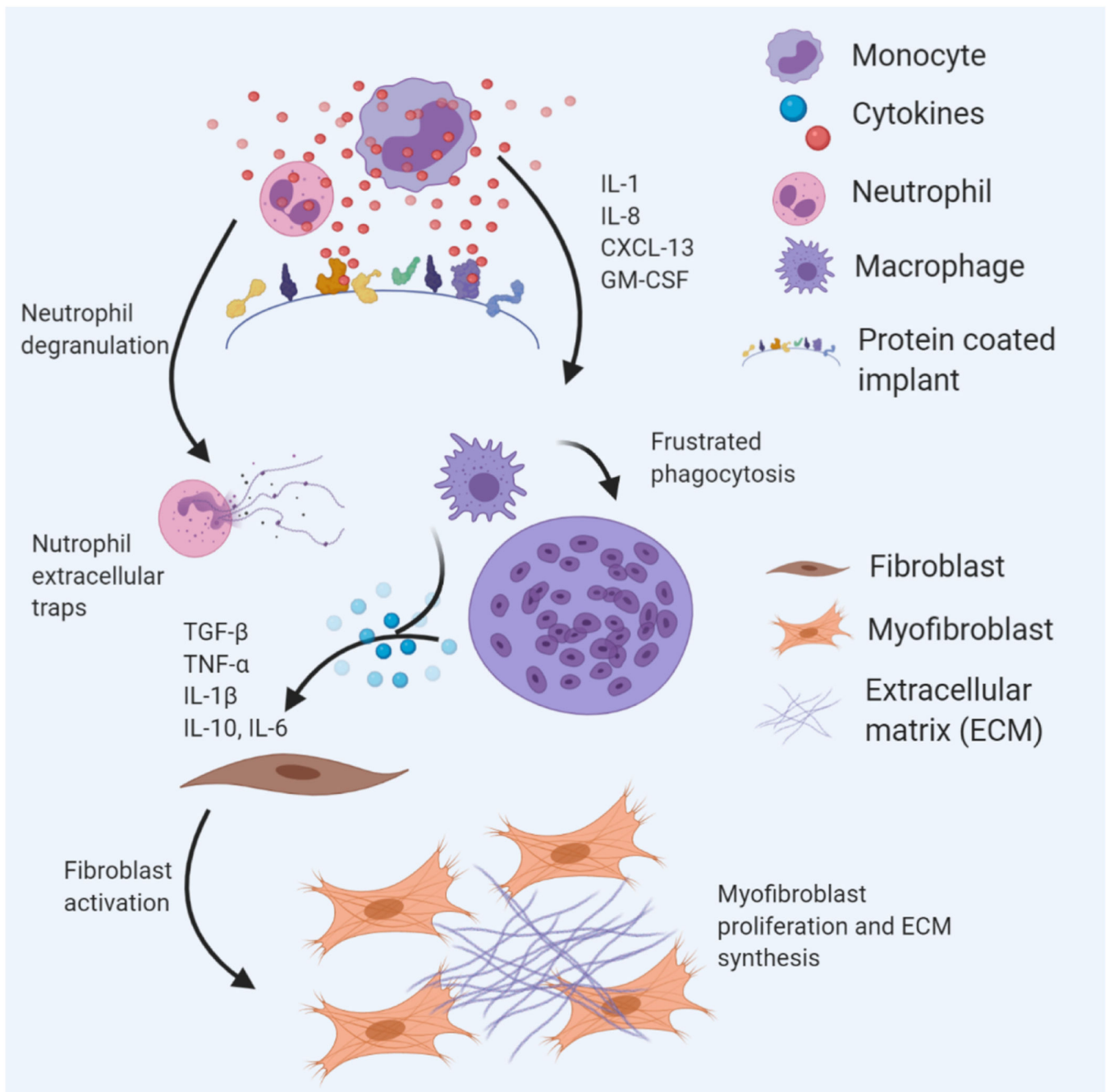


Figure 3. Local cellular response to implanted biomaterials. Proteins from blood or extracellular fluids adsorb to biomaterial surfaces upon implantation. Innate immune cells like neutrophils and monocytes adhere to protein coated surfaces through non-specific binding interactions. Neutrophils undergo degranulation and deposit neutrophil extracellular traps. Monocytes differentiate into macrophages which can fuse to form giant cells in an attempt to phagocytose biomaterials. Crosstalk between immune cells and stromal cells is an important step in wound healing and is a promising target for engineering biomaterials that can modulate host response.

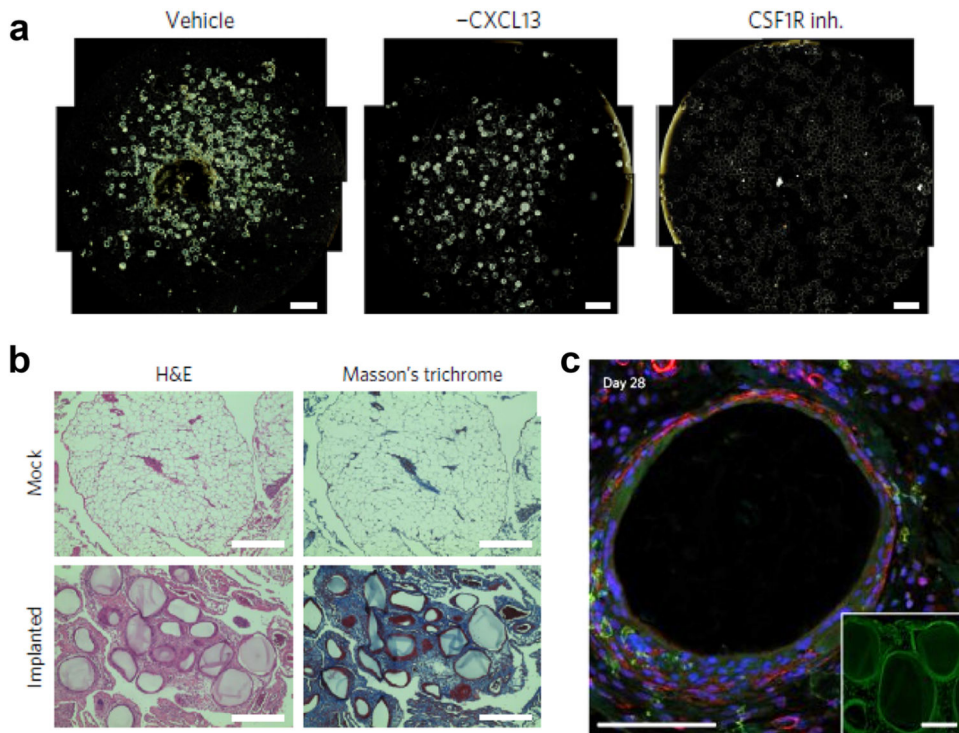


Figure 4. (A) Colony stimulating factor-1 receptor inhibition (CSF1R inh.) mitigated fibrotic overgrowth on intraperitoneally injected alginate spheres in mice as compared to vehicle only and CXCL13 neutralized wild type mice. (B) Histological examination of intraperitoneal alginate spheres in non-human primates. (C) Macrophage populations (green) and fibrosis associated α -smooth muscle actin (red) around explanted alginate spheres from non-human primates as visualized by confocal imaging. Modified with permission from [113].

Table 1.

Summary of manufacturing methods, materials and active ingredients used in implants described in section 2.2.1–2.2.3.

Device	Implant material	Processing method	Active ingredient	Clinical application	Reference
Prosthetic joint	LDPE	Compression molding	Rifampin, Vancomycin	Recurrent PJI prevention	[41]
Kirschner Wire	PLGA, PCL	Electrospinning	Vancomycin, Daptomycin, Linezolid, Rifampin	Preventing infection after bone fractures	[44]
Ureteral stent	Biosoft® polymer blend	-	Tachyplestin III	Preventing ureteral stent infection	[51]
Device coating	Poly(HPMA)	Surface-initiated atom transfer radical polymerization	None	Urinary catheter coating to prevent biofilm formation	[52]
Device coating	Biosoft® polymer blend	Dip coating	Vancomycin, BMAP-28	Ureteral stent coating to prevent bacterial adhesion	[53]
Antibacterial suture	Nylon, Polyglactin	High temperature extrusion	Triclosan	Preventing post-operative infection-general surgery	[57]
Antibacterial suture	PCL,PEG	Electrospinning	Levofloxacin	Preventing post-operative infection-ophthalmic surgery	[59]
Antibacterial suture	PCL	Electrospinning	Levofloxacin	Preventing post-operative infection-ophthalmic surgery	[65]

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Table 2.

Summary of vascular stent technologies approved for clinical use.

Device	Implant	Manufacturer	Material	Active agent	Reference(s)
Bare metal stents	Vision	Abbott	Cobalt-Chromium	None	[126,127]
	Rebel	Boston scientific	Platinum-Chromium	None	
	Integrity	Medtronic	Cobalt-Chromium	None	
Drug eluting stents	TAXUS	Boston scientific	Stainless steel, SIBS.	Paclitaxel	[135.136.137.138]
	Cypher	J&J	Stainless steel, PBMA/PEVA.	Sirolimus	
	Xience	Abbott	Cobalt-Chromium, PBMA/PVDF-HFP.	Everolimus	
	Promus	Boston scientific	Platinum-Chromium, PBMA/PVDF-HFP.	Everolimus	
	Endeavor	Medtronic	Cobalt-Chromium, Phosphoryl choline.	Zotarolimus	
	Resolute	Medtronic	Cobalt-Chromium, biolynx.	Zotarolimus	
	JANUS	Sorin biomedica	Cobalt-Chromium-Carbofilm.	Tacrolimus	
Bioabsorbable vascular scaffolds	ABSORB	Abbott	PLLA, PDLLA	Everolimus	[127]
	Synergy	Boston scientific	Platinum-Chromium, PLGA	Everolimus	
	Orsiro	Biotronik	Cobalt-Chromium, PLLA	Sirolimus	
Endothelial cell capture stents	Genous	OrbusNitech medical technologies	Stainless steel, Polysaccharide coating	CD34+ antibody	[139.140]
	COMBO		Stainless steel, ULG CD34 + antibody coating	Sirolimus, CD34+antibody	

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