PART I

BACKGROUND AND CONTEXT

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ADDRESSING MEDICAL DEVICE CHALLENGES WITH DRUG–DEVICE COMBINATIONS

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1.1 INTRODUCTION

Implanted medical devices (IMDs) comprising synthetic biomaterials have seen exponential growth in their applications and clinical use over the past five decades [1]. The scope and fields of use for IMDs have increased multifold with the advent of new technologies, innovation, and improved understanding of human physiology and its underlying problems. Increasing rates of medical device adoption can be attributed to various factors, including aging median populations worldwide [2], innovations in design and function that increase performance and reliability, rising standards of living among patients in developing nations, and noted improvements in patient quality of life offered by the devices. New IMDs continue to offer improved treatment alternatives for cardiovascular, orthopedic, oncologic, and many other diseases [3]. Given these factors, the global medical device market is expected to continue growing, reaching approximately US$302 billion in 2017 with an annual growth rate of ~6% over the next 6 years (2011–2017) [4]. Tens of millions of people in the United States alone have some kind of IMD in their body. Despite enhanced safety and efficacy, new device design strategies are required to understand and address complex human factors affecting device performance *in vivo*. Innovations in design,

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biomaterials, surface modifications and biocompatible coatings, and device-based onboard drug delivery mechanisms are among strategies employed to improve clinical IMD performance.

1.1.1 Combination Medical Devices

Drug–device combination medical products are innovative biomedical implants with enhancements to device function provided by the onboard formulation and local pharmacology of selected drugs at the implant site [5]. Combination devices couple a drug loading and releasing mechanism onto an approved prosthetic implant. Together, these seek to provide several improvements to the *in vivo* performance and lifetime of implantable medical devices in various classes and capacities, including cardiovascular, ophthalmic, orthopedic, diabetes, and cancer applications. Drug–device combination products represent relatively new device class among implantable medical devices, one that is drawing increasing attention from both the pharmaceutical and device manufacturing industries and the clinicians to address several long-standing problems associated with IMDs. In 2003, the Food and Drug Administration (FDA) approved a coronary drug-eluting stent (DES) (Cordis CYPHER^{TM}, Johnson and Johnson, USA) opening the market to similar officially designated "drug–device combination products" in the United States [6]. Several notable medical devices with locally delivered drugs had earlier precedent, namely, steroid-releasing pacemaker leads, hormone-releasing intrauterine devices, antibiotic-impregnated catheters, aerosolized drug inhalers, drug-infused condoms, and several other precedents. Additionally, several combination products also existed earlier in Europe than elsewhere, for example, antibiotic-releasing bone cements, drug-eluting stents, heparin-coated catheters, and others (approved with the CE mark). FDA's Office of Combination Products (OCP) was established in 2002 to provide a pathway for assigning principal FDA oversite and review policies to drug–biologic–device combinations that could otherwise be confused or compromised by traditional FDA review file assignments [7]. The objective was to provide a streamlined and consistent process for assigning these new products to FDA Centers based on claimed primary modes of action (i.e., device or drug). The OCP defines a "combination device" under 21 CFR 3.2(e) as "A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; or two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products." Table 1.1 summarizes this classification system. Most combination devices add a drug bioactivity adjunct to an already-approved implanted device to counteract challenges faced by the device in the context of the local host tissue environment. This can include inflammation, fibrosis, coagulation, and infection, improving performance in several conditions. One prominent example is the use of the drug-eluting stent, where local release of micrograms of drug to the vascular bed has reduced the need for surgical intervention by 40–70% over bare metal stents [8–10]. However, combination products are often optimized into an integrated

TABLE 1.1 Diversity of Combination Medical Products Used in Physical or Chemical Combinations, or Copackaged as a Kit, or as Separate Cross-Labeled Products

Combination Product Type	Clinical Examples
Drug and device	Drug-eluting stents, antimicrobial catheters, tibial nail, and sutures
Drug and biologic	Autologous platelet concentrate delivery of gentamycin to an open fracture; demineralized bone matrix delivery of statins to bone defect
Biologic and device	Heparin-coated vascular grafts, insulin infusion pumps, spinal cages with rhBMP-2
Drug and biologic and device	No precedents approved; fictional example: adenoviral NfκB transgene delivery from Taxol-eluting vascular stent

system from separate drug and device products: They were never designed *de novo* to complement each other in structure and function, that is, controlled drug delivery is often an add-on feature to an existing FDA-approved medical device design that is suboptimally adapted to the structural, mechanical, or electronic function of the device [6]. New strategies and new technologies that combine drugs, devices, and biologics *de novo* as coordinated, unified new designs are expected to provide a new generation of combination products, more intelligently incorporating and merging new technologies, changes, and refinements of both existing drug delivery mechanisms and medical device functions, shifts from traditional devices and drugs, while remaining compliant with regulations [6].

Diverse classes of drugs are used in combination devices to enhance medical device and implant performance. Anti-inflammatory, antifibrotic, antiproliferative, antithrombotic, and antibiotic drugs are primary classes of pharmaceutical agents often combined with a controlled delivery mechanism suited to the application. Site- and implant-specific drug interventions before, during, and after medical device implantation can be used to alleviate several adverse host responses, providing a local therapeutic strategy when a device design or systemic drug delivery alone is insufficient. For example, anticoagulants are applied to cardiovascular and intravascular implants to reduce device-based thrombosis, while antifibrotic, anti-inflammatory, and antiproliferative drugs are used for soft tissue implants and endovascular stents susceptible to fibrous tissue in-growth and smooth muscle proliferation. Antibiotics are released from orthopedic implants, shunts, and percutaneous and urinary catheters that exhibit high infection incidence.

Conventional therapeutics are administered in different ways, including nasal, oral, parenteral (intravascular, intramuscular, subcutaneous, and intraperitoneal), topical, transdermal, and other administrative routes [11]. Although systemic administration has its merits, local drug administration can in some cases provide comparable results with significantly lower doses of drugs while limiting the drug efficacy and toxicity to the tissue surrounding the implant site. Drugs are combined with delivery technologies to control rates and local dosing of therapeutics to tissue beds surrounding implanted devices. Typically, drugs are released systematically from the device

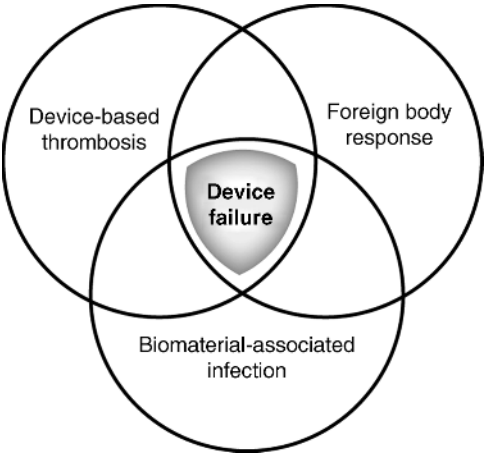

FIGURE 1.1 General host-interfacing challenges facing implanted medical devices.

surface using impregnated resins or rate-controlling polymer films. Occasionally, drugs are eluted from the bulk device as in the case of antibiotic-loaded bone cement. Local drug release limits drug dosing to low quantities, reduces systemic toxicity, increases duration of release, and limits the area of release to the tissue bed surrounding the implant [6]. Local drug release mechanisms offer several advantages over conventional systemic drug administration. An ideal drug delivery system with a combination device should provide continuous and effective drug doses to the site of implantation while also offering possibilities to continue drug release for prolonged periods [12]. Rates and durations of drug delivery depend on several factors such as the implant size, local tissue physiology and morbidity, drug pharmacology and potency in therapy, duration and location of drug release, its kinetics, drug and local clearance, and toxicity.

Due to the widespread development and use of combination products, a comprehensive understanding of drug delivery mechanisms and device functional improvements in the drug's presence is necessary to improve their efficacy and scope of medical applications. Mechanisms involved in drug delivery should be exploited to better match release to the local needs of each specific combination product. The major challenges faced by IMDs in clinical applications are shown in Figure 1.1: (1) nonspecific host response–foreign body reaction; (2) device thrombosis, and (3) biomaterial-associated infections. These all share some interrelated failure mechanisms that may amplify tissue-site adverse reactions and host responses. For example, the link between thrombosis and infection is increasingly identified to be synergistic, as is the relationship between the host foreign body response (FBR) and implant-centered infection. These increasingly complex host response relationships can be difficult to solve using a single device design or biomaterials-based approach alone. Use of local pharmaceutics with the device provides options to exploit device strengths and also drug targeting against multiple challenges in the implant site. The remainder of this chapter serves to describe combination device

approaches in the context of the current medical device and implant challenges in host tissue sites.

1.2 THE HOST FOREIGN BODY REACTION

The host's acute and chronic FBR remains an unsolved challenge for many IMDs. As the implantation of almost every medical device creates a wound (e.g., knee arthroplasty and pacemaker), or local disturbance of a tissue bed (e.g., contact lens), a normal host tissue wounding response is spontaneously initiated. This reaction is primarily an abnormal tissue healing response that alters normal wound site healing in the presence of a foreign body (IMD), yielding a chronic unresolved tissue response, often resulting in excessive fibrosis. Extending the functional clinical lifetime of IMDs while reducing their adverse events *in vivo* remains an important goal. Nonetheless, despite many device improvements and design changes, this goal remains elusive. For example, the host's acute and chronic FBR is well known to limit the lifetime of implanted sensors (i.e., glucose real-time monitoring devices) [13–15]. Lack of tissue mechanisms preclude rational implant improvements and other more direct therapeutic approaches. IMDs spontaneously adsorb a diverse array of plasma proteins within the first few seconds of implantation [16]. Neither the types and amounts nor orientations of these proteins on the implant can be controlled *in vivo*, but despite many assertions otherwise, this might not have much significance to the final tissue reaction. Surface properties of the implanted biomaterial certainly govern aspect of protein adsorption, but exactly how this then modulates the host reaction to the implant is less certain. Many biomaterials of distinctly different bulk chemical and surface composition result in very similar endpoints *in vivo* in soft tissue, encased by fibrous overgrowth and an avascular capsule. The IMD as a foreign body destabilizes homeostasis and hemostasis in host tissue and results in a modified "healing response" that adversely affects both the implant's performance and host tissue surrounding it.

The FBR is a consequence of aborted wound healing and the complex interplay between the complement and coagulation cascades with the host immune system. The complement system comprises cascades of blood and cell surface proteins triggered by pathogens and other "foreign" substances, including implanted biomaterials [17]. Blood's potent intrinsic and extrinsic protease cascades are triggered by procoagulant stimulus [18]. In both systems, procoagulant and complement proteins are zymogen proteases activated by the foreign body interacting with the precursor zymogens through proteolytic cleavage [19], and each acting to amplify host cell-signaling and cell-recruiting capacities. FBR results from continuous host exposure to combinations of specific (activating) and nonspecific (activating) proteins on the foreign body and their protease activation. Subsequent chemotaxis and reactions from host immune and inflammatory cells lead to unresolved chronic healing responses, sustained inflammation, recruitment of fibroblasts and fibrotic encapsulation, and foreign body giant cell presence as a terminal response to the implanted device. In this dynamic wound site response, normal wound site acute cell infiltrates comprising neutrophils and other leukocytes, and later monocyte and macrophage invasion stimulate release of

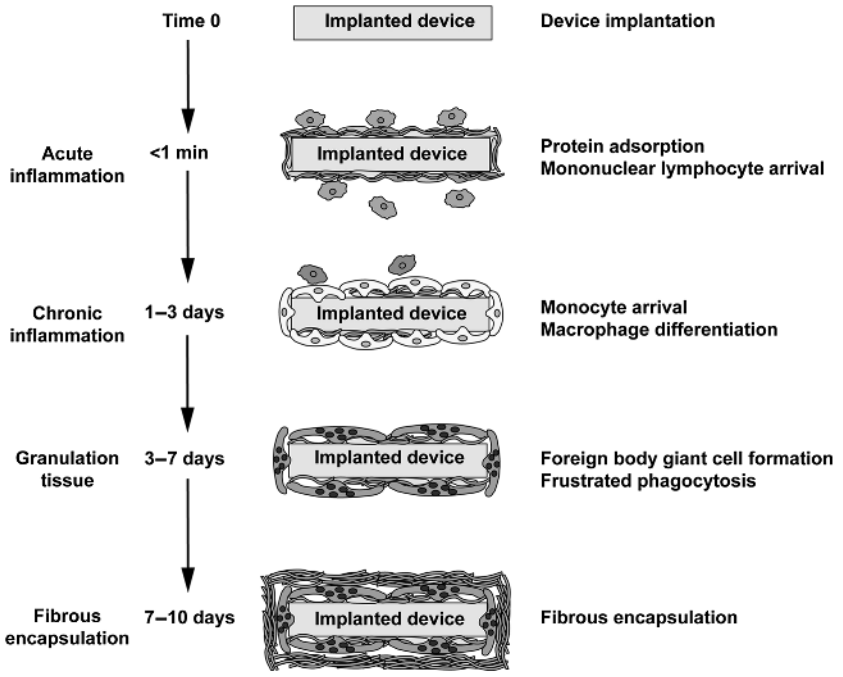

FIGURE 1.2 Illustration of the temporal series of host biological events during the host foreign body response following biomaterial implantation.

inflammatory cytokines such as IL-6, TNF-alpha, IL-4, and IL-13 (i.e., from mast cells) to accelerate recruitment of inflammatory and immune cells to the site of implant [15]. In normal wounds, these abate, but a foreign body provides continuous inflammatory stimulus for sustained, abnormal cell signaling. Fibroblasts then arrive at the implant site and mediate the formation of an avascular fibrous tissue via exuberant collagen production around the implant that can act as a physical barrier blocking access to essential components of the tissue surrounding the implants, an area of local hypoxia and poor perfusion to create an infection niche, and also a physical impediment of prosthetic motion if required (i.e., joint arthroplasty) or adjacent tissue-on-tissue motion (e.g., surgical adhesions) that are highly painful. Chronically, the excess connective tissue remodels into a dense fibrous capsule (fibrosis) that "walls off" the implant, separating the IMD from its physiological surroundings. This foreign body capsule is the hallmark of the FBR, and adversely affects the general performance of IMDs, limiting their reliability and long-term success. Reactions of both the host on the implant and the implant on the host/blood/tissue need to be understood to enhance IMD performance. Figure 1.2 illustrates the sequence of host-materials events following the implantation of a biomaterial/medical device into host tissue.

While some implants remain unaffected functionally by the FBR, certain types of IMDs are highly compromised. In particular, sensor implants such as continuous

glucose monitoring (CGM) sensors [20–22], pacemaker electrical leads [23], and neural deep brain stimulation arrays [24] undergo fibrosis that hinders function. The avascular fibrous tissue surrounding the implant impedes the implant's electrical [25] and chemical contact with the surrounding tissue while also depriving it of essential analytes [26–28] and nutrients, rendering implants less efficient. Pacemaker leads underwent early drug modification, with steroid reservoirs and elution from their porous electrode tips enhancing their impedance and conductance properties with tissue and their functioning lifetime, enhancing battery life and reducing fibrous tissue encapsulation [29,30]. Many CGM sensors are placed subcutaneously where normal sensor fouling, including protein adsorption on or infiltrated into the implanted sensors, as well as inflammatory wound site cellular reactions eventually limit analyte diffusion (mostly glucose and oxygen) into the sensing element, and contribute to the observed continual decreased analyte sensitivity with prolonged implantation [14,21,31]. In addition to ubiquitous sensor fouling and encapsulation, the host's acute inflammatory response to the implanted foreign body produces an immediate, sustained cascade of local tissue cellular reactions that alter the local environment around the implant, substantially modifying local metabolism and homeostasis. This triggers a departure from normal tissue analyte levels and causes the sensors to produce highly altered analyte levels from acute inflammation—an acute reporting phenomenon called "break-in" [32].

As the host foreign body response in soft and hard tissue sites typically produces device-based challenges associated with excess or unresolved inflammation, fibrosis, and infection, combination device strategies seeking to address this issue have used drugs with known pharmacological actions against these specific problems.

1.2.1 Anti-Inflammatory Drug Candidates to Inhibit the Foreign Body Response

Anti-inflammatory steroidal drugs (e.g., dexamethasone) are clinically familiar and used to reduce inflammation and the host FBR in tissues surrounding implant sites [33,34]. Dexamethasone, a glucocorticoid agonist, crosses cell membranes and binds to glucocorticoid receptors controlling different inflammatory pathways with high affinity by inhibiting leukocyte infiltration at sites of inflammation, suppressing humoral immune responses, and reducing edema and scar tissue. Molecular basis for dexamethasone's anti-inflammatory actions are thought to involve the inhibition of cyclooxygenase enzyme [35] that regulates arachidonic acid metabolism responsible for production of inflammatory prostaglandins.

Local controlled release systems containing the steroid, dexamethasone, have been used in intraocular application postsurgery in cataract treatments [36–40]. Local dexamethasone release [41] has also been used to reduce neointimal formation in the arterial wall after balloon angioplasty [42,43] and to prevent restenosis in intravascular drug-eluting stents [44]. Dexamethasone has also been used to improve the performance of pacemaker leads [45]. Dexamethasone release from PLGA microspheres coated onto a cotton suture implant has shown to decrease the acute inflammatory reaction around the implanted suture material [46]. Dexamethasone

has also been used in combination with angiogenesis factors such as vascular endothelial growth factor (VEGF) to promote new blood vessel growth while reducing inflammation in the tissue surrounding a hydrogel (PVA) scaffold implant [47]. Sequential or simultaneous release of dexamethasone and VEGF has been shown to improve the performance of implanted biosensors [47–51].

1.2.2 Antiproliferative Drug Candidates to Inhibit the Foreign Body Response

Sirolimus, also called rapamycin, is a potent immunosuppressive drug used in combination with medical devices. As a potent inhibitor of cytokine and growth factor-mediated cell proliferation, sirolimus acts by inhibiting activation of the intracellular protein enzyme, mTOR (mammalian target of rapamycin) [52], a downstream mediator of the PI3K/Akt phosphorylation signaling pathway regulating several key cell functions. Receptor-based inhibition of mTOR results in the blockage of cell cycle proliferation in the late G1 to S phase, causing antiproliferative and antihyperplastic actions [53,54]. Over 70 related "limus" derivatives are known drug candidates. Everolimus, temsirolimus, deforolimus, tacrolimus, and ABT-578 are also used as potent antiproliferative drugs. Paclitaxel is another commonly used antiproliferative drug used with medical devices such as drug-eluting stents. Paclitaxel inhibits cell proliferation, cell motility, shape, and transport between organelles [55]. Both rapamycin and paclitaxel have substantial clinical records as approved therapeutics for a number of indications independent of devices.

1.3 DEVICE-BASED THROMBOSIS

Under normal, steady-state circulation conditions (hemostasis), blood continuously contacts host endothelium with an intrinsic, active anticoagulant and antithrombotic system. Injury to blood vessels exposes subendothelial components, releases procoagulant stimulants, and disrupts hemostasis. Natural host response to this disruption involves blood platelet adhesion, activation, and aggregation in combination with activation of intrinsic and extrinsic coagulation cascades terminating in the formation of a crosslinked fibrin clot. These natural coagulation cascades are depicted in Figure 1.2. The combination of platelet and procoagulant cascade activation rapidly produces a thrombus/clot that stabilizes the injury and prevents further blood loss. Thrombus formation plays an important role in the maintenance of hemostasis. Thrombin-mediated fibrin polymer traps and stabilizes clusters of activated platelets to yield a stable thrombus critical for survival and also contribute powerfully to local wound healing.

Endothelial cells (ECs) lining the walls of the endothelium continuously synthesize and regulate several key molecules necessary for the maintenance of host hemostasis and the intrinsic blood compatibility of vasculature. The EC surface is a dense, brush-like layer of hydrated proteoglycans, called the glycocalyx. Glycocalyx glycoproteins enzyme-grafted with glycosaminoglycans (GAG) side chains [56], including heparan,

dextran, and chondroitin sulfate proteoglycans and hyaluronic acid, are negatively charged and highly hydrated, acting as a barrier and a lubricant between the ECs and blood components [57]. ECs also actively produce and release nitric oxide and prostacyclin (PGI_2) that actively prevent platelet adhesion and activation [58,59]. Heparan sulfate proteoglycan synthesized by the ECs inhibits platelet adhesion and activation [60] while also functioning as a catalytic cofactor for binding antithrombin-III and thrombin together to facilitate thrombin inhibition and anticoagulation [61,62]. ECs also produce tissue-type plasminogen activator (t-PA) and urokinase that act to initiate fibrin degradation and aid in clot dissolution [63,64]. This t-PA activity is tightly regulated by the EC-produced plasminogen activator inhibitor type-I [65–67].

Cardiovascular medical devices are placed into contact with patient's blood for varying periods of time, ranging from minutes (e.g., vascular access devices) to many hours (blood pumps, dialysis filters, and central lines), to years (e.g., stents, heart valves, vascular grafts, and pacemaker leads). The blood-contacting surfaces on these devices are critical to their performance, seeking to minimize activation of both platelets and the coagulation cascades. However, no materials chemistry or coatings used on these devices have proven clinically reliable in limiting risks of device-based thrombosis to date. Some blood-contacting biomaterials are grafted with heparin-like coatings, or polymers mimicking the EC glycocalyx [68]. Figure 1.5 shows one example of this device-based surface modification approach using heparin. Other approaches are designed to release anticoagulant and antiplatelet drugs for short durations [69]. No materials yet provide all the passive, active, and functional aspects of ECs in maintaining hemostasis, and, therefore, all induce thrombosis in contact with blood to varying degrees. Device-induced thrombosis is a major cause of failure in blood-contacting biomaterials, mainly cardiovascular implants, which constitute a major class of chronic disease-related IMDs. Implantation of a medical device lacking the properties of a healthy endothelium constitutes the introduction of a foreign object into circulation. Blood–material interactions after implantation spontaneously and immediately trigger a series of complex reactions involving protein and platelet absorption on the biomaterial surface, formation of clots and emboli, and activation of the host's immune system.

1.3.1 Platelet Activation in Device-Based Thrombosis

Platelets are anuclear cytoplasmic fragments present in blood essential for rapid, reliable blood clotting and wound healing [70]. Platelets play an essential role in controlling blood loss and maintaining hemostasis. One common platelet mode of action is the formation of a stable platelet plug when the blood vessel wall is damaged and the endothelial cell layer is disrupted, exposing the underlying basement membrane and extracellular matrix. With every surgical device implantation, blood vessels in the tissue surrounding an implant are injured, exposing collagen IV in the subendothelial layers to blood that results in the activation of circulating platelets. Additionally, platelets also get activated when they undergo shear stress caused by flow disturbances common to implanted devices. Platelet activation is followed by platelet degranulation and then by aggregation and adhesion to each other and to the

implanted material. Degranulation serves to release a broad array of potent platelet-derived biochemicals that potentiate local thrombosis by accelerating both local coagulation cascade reactions and platelet activation by release of highly procoagulant stimulants, enzyme substrates, and cofactors. The aggregated platelets are stabilized into a thrombus/clot by the newly formed fibrin polymer. Circulating platelets get activated under three major circumstances: (a) by contacting the basal lamina of the endothelial vessel wall, (b) by contacting with a biomaterial surface, and (c) due to flow disturbances caused in the presence of a biomaterial. Platelet adhesion, activation, and aggregation are combined with simultaneous thrombin-mediated fibrin polymerization that together result in thrombus formation.

1.3.2 Extrinsic and Intrinsic Coagulation Cascades

A biomaterial surface exposed to blood is coated with thousands of plasma proteins within seconds [71]. This adsorption activates some plasma proteins by inducing conformational changes or cleaving small fragments that trigger coagulation and inflammatory responses to the implanted device [72–74]. The coagulation cascade comprises two main branches: the intrinsic pathway (activated by contact with a biomaterial surface) and the extrinsic pathway (induced by EC injury). Both pathways converge at the proteolytic formation of thrombin from its prothrombin zymogen, the penultimate cascade step to converting soluble plasma- and platelet-derived fibrinogen to fibrin polymer. Fibrin polymer is a major protein component of the natural clot. Activation of intrinsic and extrinsic proteolytic reactions following blood contact with biomaterials actively and consistently produces thrombin-mediated fibrin clots unless pharmacological treatments attenuate these natural responses, typically by inhibiting key enzymes. The series of coagulant events triggered by the activation of intrinsic or extrinsic pathways following the implantation of a medical device into blood are shown in Figure 1.3. Adherent platelets—both on the biomaterial and trapped by the clot—activate to release numerous potent thrombotic promoters and catalysts by degranulation. They also recruit more circulating platelets to the device surface. Subsequent device-based thrombosis and thromboemboli formations produce many clinical complications, causing failure in small-diameter grafts, stents, valves, pumps, catheters, and other cardiovascular implants. Furthermore, causal links between device thrombosis and device-centered infection are increasing.

1.4 BIOMATERIALS-ASSOCIATED INFECTION

All implantable devices—from short-term devices, such as contact lens, glucose sensors, urinary catheters, and endotracheal tubes, to long-term surgically implanted devices, such as pacemakers, cardiac valves, endothelial grafts, and orthopedic implants, suffer commonly from varying risks of biomaterials-associated infections (BAIs) or implant-associated infections [41]. BAIs remain a major cause of IMD failure despite years of device innovation, improved quality of care, and surgical techniques [75]. In the United States, approximately 2 million nosocomial infections

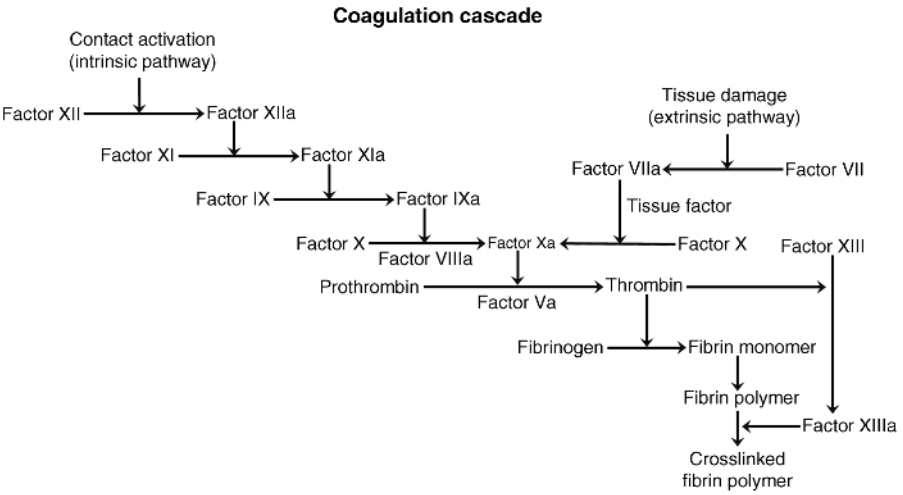

FIGURE 1.3 Extrinsic and intrinsic cascades for the zymogens, active proteins, and clotting factors mediating clot formation after procoagulant stimulus.

costing $11 billion occur annually [76]. A majority of nosocomial infections (60–70%) are biomaterial-associated infections caused from the increasing use of urinary and venous catheters, orthopedic implants, shunts, and other implants [77], and involving significant mortality and economic costs. Infection mitigation is a common problem with IMDs and a primary focus of surgical antibiotic prophylaxis in device placement. BAIs most often result from bacterial contamination of implants intraoperatively during the implantation procedure. They are able to colonize implants using the implant-adherent protein layer and thrombus, proliferating at rates that outpace host wound healing. Bacterial adhesion leading to the formation of mature biofilms on the surface of a biomaterial is shown in Figure 1.4. Bacteria and other pathogens have multiple sources during surgery: no surgical suites, surgical personnel, or patients are sterile, Pathogen seeding of implants and surgical sites is likely, although only small fractions of implants actually colonize and lead to clinically symptomatic infections as BAIs. Nonetheless, BAIs can result in difficult-to-treat systemic infections with costly adverse complications and mortality. BAIs are most prevalent in orthopedic [78,79], dental [80], cardiovascular [81–83], neural, and ophthalmological implants [84,85] and involve a broad spectrum of pathogens, many in polymicrobial implant infections. Rates of infection at the site of implantation postsurgery increase with the severity of the vascular and tissue injury [86]. Upon detection, BAIs often fail systemic administration of antibiotics. Therefore, common treatment most often involves immediate implant removal followed by long-term parenteral administration of antibiotics and then replacement with a second new implant. This often comes with associated morbidity and high treatment costs. Little change in BAI incidence has resulted from changes in surgical practice, device design, or antibiotic usage, prompting re-examination of the entire medical device infection scenario [87]. Since systemic antibiotic therapies have failed to bring down implant

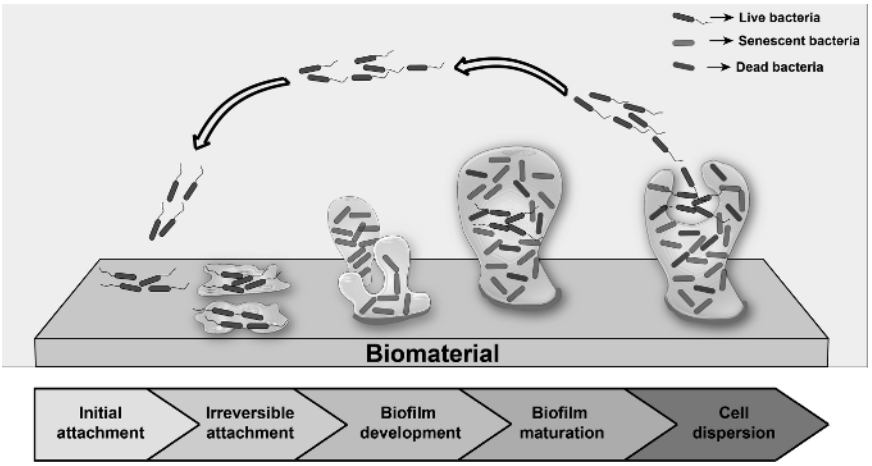

FIGURE 1.4 Bacterial seeding, colonization, biofilm transformation, differentiation, maturation, and further dissemination producing following biomaterial-associated contamination and infection. (See colour plate section.)

infection rates, local release of antiseptics and antibiotics has been sought in combination device form.

1.5 COMBINATION MEDICAL DEVICES

1.5.1 Drug-Eluting Stents

Coronary stent restenosis has been a major challenge since the introduction of percutaneous coronary intervention (PCI) for coronary artery disease [88]. Use of rigid but flexible endovascular scaffolds such as stents prevents the recoil and collapse of the vessel while also mitigating the vessel restenosis experienced after balloon angioplasty [89,90]. Although the development and use of stents in PCIs has demonstrated improvements over balloon angioplasty, vessel restenosis or in-stent restenosis after bare metal stent deployment also poses challenges to successful PCIs, resulting in past patient reinterventions in up to 50% in several patient classes depending on stent placement and patient pathophysiology [91,92]. Systemic administration of drugs to reduce in-stent restenosis is ineffective [93–95] mainly due to poor drug bioavailability, toxicity, and insufficient drug dosing to the implant site. Popularity of drug-eluting stent (DES) is due to proven success in mitigating the effects of tissue hyperplasia-caused vessel occlusion [9,96,97]. DES use has reduced the occurrence of repeated PCIs and surgical revascularization procedures to treat restenosis by 40–70% [8–10]. Emerging classes of DES coated with bioactive agents (DNA, proteins, and viral vectors) and biopharmaceuticals provide improved safety and efficacy in certain cases, but also pose challenges during their fabrication and require specific formulations and delivery mechanisms for reliability and efficacy [98].

In coronary applications, DES devices are typically localized expandable, slotted metal tubes (~4 mm long) coated with a polymer carrying a small dose (micrograms) of pharmacological agent. DES is collapsed around a deployment catheter and installed at a coronary lesion vessel by catheter-initiated intraluminal expansion. This provides structural support to the vessel while releasing drug locally to the vessel wall at the stent implant site [99]. The DES provides the advantage of effective localized drug delivery and therapeutic efficacy at the lesion site while avoiding excessive dose exposures through systemic delivery [100,101]. Other advantages include directional delivery of drug to the vessel wall tissue and only small fractions entering the bloodstream. Additional new stent designs can build drug depots in spatially designated locations on-stent [102], with versatility to carry multiple drugs, releasing with different release kinetics, and also two distinct therapeutic functions: antithrombosis on the blood side and antiproliferatives on the tissue side [103].

Sirolimus-eluting stents originally were the pioneer DES, showing noticeable improvements over early bare metal stent designs in PCI procedures, reducing cell proliferation, migration, and restenosis from the vessel bed at the stenting site. The sirolimus-eluting stent (Cordis CYPHER) was the first DES to receive clinical approval [104,105] in Europe, and the first "official" combination device approved by the FDA in 2003. Sirolimus is now the most extensively studied drug to reduce in-stent neo-intimal hyperplasia following coronary stent deployment [106]. Sirolimus- and paclitaxel-eluting stents (TAXUS®, Boston Scientific, USA) are the two commercially available, first-generation DES. These are coated with a very thin (~μm) nondegradable polymer layer (e.g., polyisobutylene or polymethacrylate copolymers) containing very little drug within the coated polymer (~μg/mm length of stent), released with an early significant burst (up to 50%) within the first 24–36 h postimplantation followed by slower release lasting more than 6 weeks in some cases [6].

After initial enthusiasm with the first-generation DES, controversial debate has ensued over long-term DES safety, with a shift in clinical focus to increased risks of late stent thrombosis [107,108]. Although both CYPHER and TAXUS effectively achieved primary goals of reducing cellular restenosis across almost all lesion and patient subsets over bare metal stents, their safety has been limited by suboptimal polymer biocompatibility, delayed stent endothelialization leading to late stent thrombosis, and local drug toxicity [109–113]. The permanent presence of the noneroding polymer covering the stent struts and wires has been correlated with tissue inflammatory response and local toxicity in preclinical studies [114,115]. Stent thrombosis risk gained primary focus after the dominant restenosis issue had been resolved using drug-eluting stents: DES devices are comparable to bare metal stents in occurrence of stent-associated thrombosis [116]. This has prompted new technologies and designs to overcome the thrombosis problem using new stent designs, stents with multiple drug reservoirs containing both antithrombotics and antiproliferatives, absorbable or biodegradable polymers, nonpolymer drug-loaded surfaces, and changes in the types and doses of currently used antiproliferative drugs placed on-stent.

Recent clinical introduction of the biodegradable polymer-coated DES [117] seeks to overcome stent thrombosis attributed to the permanent polymer layer on first-generation DES. Biodegradable stent coatings have been designed to release loaded drug for an intended amount of time before completely degrading. Clinically familiar poly(L-lactic acid) (PLA), poly(lactic-*co*-glycolic acid) (PLGA), and poly(D,L-lactide) (PDLLA) remain popular choices for biodegradable polymer DES coatings. BioMatrix (Biosensors Inc., USA) is a stainless steel stent containing Biolimus A9 (a derivative of sirolimus) as drug on the abluminal surface facing the vessel wall targeting the mTOR protein, loaded in a PLA coating. The drug is released to the vessel wall over 2–4 weeks and the PLA coating is gradually absorbed between 6 and 9 months. Several other novel DES devices with biodegradable coatings are in development. Cardiomind (Cardiomind Inc., USA), ELIXIR-DES (Elixir Medical Corporation, USA), JACTAX (Boston Scientific Corporation, USA), and NEVO (Cordis, USA) are example stents in development and clinical trials with degradable coatings used to deliver antiproliferative drugs to mitigate neointimal tissue hyperplasia in PCI procedures.

As the model and precedent combination product approved by the FDA, DES is an excellent example of combining a drug with a device to target and address a specific problem unsolved by either component alone or used together but separately. Despite improvements in early prototypes and first-generation stents using new designs, materials, drugs, drug loading methods, drug release kinetics, and release duration and improved understanding of local pharmacology and complications arising several months to years after DES placement, new technology should better address newer DES problems associated with late stent thrombosis, endothelialization, and local drug toxicity. Additionally, expansion of DES use to other challenging luminal lesions, both in vasculature, gut/digestive, and reproductive tissues, will require further innovation of drugs on devices.

1.5.2 Antimicrobial Central Venous Catheters

Central venous catheters are a critical component for fluid delivery and retrieval and parenteral drug and nutritional fluid administration in a variety of clinical settings for critically ill patients. In the United States, physicians insert more than 5 million central venous catheters every year [118]. The two major complications associated with catheters are bacteremia (infection) and thrombosis [119]. Catheters coated with both antimicrobial and antithrombotic agents have been developed and commercialized. Antimicrobial-coated catheter use and efficacy have been studied for more than a decade [120].

Infections associated with catheters are classified as catheter-related bloodstream infections (CRBSI). CRBSI can occur in 3–10% of all patients using central venous catheters [121], affecting over 300,000 patients in the United States annually [122] and causing more than 25,000 patient deaths [123,124]. Systemic administration of antibiotics to treat CRBSI either prophylactically or therapeutically is neither a clinically preferred nor a reliably efficacious route. Local administration of antimicrobial agents from properly designed combination devices seeks to provide small

efficacious doses of therapeutics released into local tissue sites without requiring high systemic drug dosing.

Techniques developed to reduce CRBSI incidence include modified catheter designs, use of antimicrobial impregnated catheters, use of cuffed tunneled catheters, local topical treatments, and use of antimicrobial lock solutions [125]. Coating or impregnating the surface of central venous catheters with antimicrobial agents helped to markedly reduce the risk of CRBSI, and their use has now become the standard of care [126,127]. Antimicrobial-coated catheters employ different methods to immobilize the antimicrobial agents onto catheter surfaces–both luminal and external. One method is to simply add the antimicrobial agent to the precursor polymer granules used to fabricate the catheter, similar to adding other constituents such as pigmentation or stabilization compounds prior to injection molding [128]. Another procedure involves electrostatically coating catheter surfaces layer-by-layer with antimicrobial agents and a binding material with opposite electrostatic charge. Hydrophobic alkylated regions of cationic surfactants such as tridodecylmethylammonium chloride (TDMAC) have been adsorbed on catheter surfaces, presenting a cationic surface to anionic drug molecules binding to the surfactant-coated surface [129,130]. Recently, a zwitterionic polymer brush-grafted layer has shown preclinical efficacy as an antimicrobial coating [131,132]. Addition of active drug release capability to this layer would provide enhanced bioactivity.

These strategies facilitate incorporation of different antimicrobials onto catheter surfaces to reduce CRBSI. Multiple antimicrobial agents are preferred (typically combinations of an antiseptic and antibiotic agent) to reduce the development of antimicrobial resistance to any single agent [133]. According to Centers for Disease Control and Prevention (CDC) guidelines, catheters containing combinations of minocycline/rifampin (MR) antibiotics and combinations of chlorhexidine/silver sulfadiazine (CS) antiseptics are the two most effective antimicrobial catheters to treat CRBSI [126,127]. Catheters coated with both antibiotics and antiseptics are FDA and CE approved and commercialized (e.g., CS: ARROWgard®, Arrow international, USA; MR: Cook Specturm® series catheters, Cook Critical Care, USA). Both ARROWgard and Spectrum series catheters have antimicrobial agents impregnated on internal and external surfaces using TDMAC adlayers [134]. Both MR and CS have shown broad-spectrum antimicrobial activity to both Gram-negative and Gram-positive organisms and fungi. Several randomized trials [135,136] conducted with MR and CS showed superior performance from MR-impregnated catheters versus CS-impregnated catheters in preventing CRBSI, especially in patients needing catheter-based access for more than 7–50 days *in situ* [137]. Catheters impregnated with MR have been shown to exhibit higher antiadherence activity and prolonged antimicrobial durability compared to catheters with CS against vancomycin-resistant *Staphylococcus aureus* and multidrug-resistant (MDR) Gram-negative organisms other than *Pseudomonas* [138]. Although MR shows high antimicrobial activity against *Staphylococci* and most of the Gram-negative bacilli [138], they are less effective against *Pseudomonas aeruginosa* (contributing 3–5% of CRBSI) and *Candida* species (contributing about 12% of CRBSI) [138]. *In vitro* studies using catheters coated with a combination of MR and CS have shown to be effective against

vancomycin-resistant *S. aureus*, Gram-negative bacilli, *P. aeruginosa*, and *Candida* species [139].

Silver nanoparticle-impregnated catheters (SNPs) (Medex Logicath AgTive®, Smith Medical International Ltd., UK) are CE approved and commercially available in Europe. Catheters coated with silver-based zeolite (SZ) on blood-contacting surfaces (e.g., Lifecath PICC Expert with AgION™ from Vygon International in Europe) use controlled release of silver nanoparticles from the coating to provide antimicrobial properties to the catheter. In a recent study [140] conducted over 14 months involving 246 central venous catheter insertions (122 silver zeolite-impregnated and 124 nonimpregnated catheters), the AgION catheters showed reduced CRBSI compared to uncoated catheters. In silver nanoparticle-impregnated catheters, a recent study has shown that platelets colliding with silver nanoparticles exposed on the coating surface accelerate the process of catheter-related thrombosis while simultaneously exhibiting strong antimicrobial properties [141].

Catheters with antithrombotic coatings are used to reduce the incidence of coagulation. The Carmeda® BioActive Surface (CBAS) on Spire Biomedical® catheter products (Spire Biomedical, Inc., Bedford, MA) and the Trillium® Biosurface developed by BioInteractions Ltd. (UK) are two commercially available antithrombotic-coated catheters. Both catheters use heparin-bonded polymer surfaces as an anticoagulant interface. Heparin is a polysaccharide with anticoagulant properties and has been used as an antithrombotic agent for clinical applications [142]. The CBAS treatment consists of heparin molecules covalently bonded to the catheter surface, exposing active heparin sequences to bind ATIII and thrombin from the bloodstream while shedding other protein components. Schematic representation of thrombin inhibition on a bioactive heparin-coated surface to limit device-based thrombosis is presented in Figure 1.5. The Trillium Biosurface treatment combines a hydrophilic polyethylene oxide layer with negatively charged sulfate polymers to retain hydration at the catheter surface and reduce blood adsorption. In addition, it has heparin covalently bonded to the polyethylene oxide layer for anticoagulation [143]. Although catheters coated with active antithrombotic layers are clinically used, the effects of these coatings on catheter complications are yet to be evaluated in the hemodialysis population where these complications also exist. Importantly, many such technologies have not been shown to produce significant cost-benefit using placebo-controlled blinded prospective studies.

Catheter lock solution (CLS) is another strategy used to reduce CRBSI incidence from central venous catheters. A biocompatible solution containing a combination of antimicrobial and anticoagulant agents constitutes the CLS. The CLS is injected into the lumen of the catheter after a hemodialysis session and retained there to reduce incidence of thrombus and associated biofilm formation. Catheter thrombosis can be limited using heparin solutions or treated by infusing a thrombolytic agent such as urokinase or tissue plasminogen activator (tPA) into the lumen of the catheter [144,145]. In a recent study, athrombogenic Camouflage™-coated (artificial glycocalyx) catheters have exhibited reduced need for urokinase injections for successful catheter tap and blood drawing over uncoated catheters in cancer patients with long-term catheters [68].

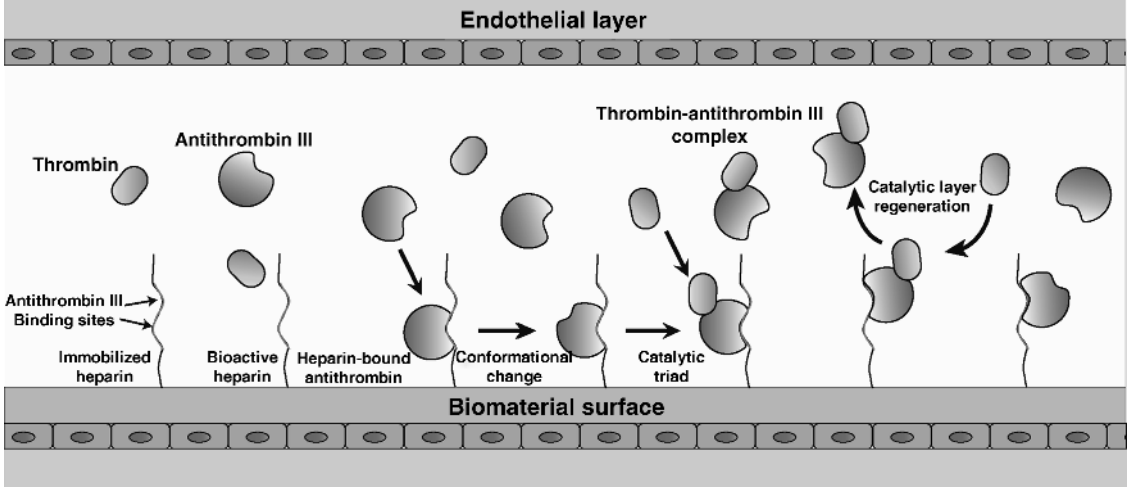

FIGURE 1.5 Bioactive heparin-immobilized surface capable of inhibiting thrombin activation, a key mediator in clot formation. The strategy is used for blood-contacting devices to limit complications from device-based thrombosis. (Reproduced with Permission from W. L. Gore.)

1.5.3 Antimicrobial Urinary Catheters

Urinary catheters allow passage of urine for treatment for patients with urinary retention complications, general surgery recovery, bladder obstruction, paralysis, or loss of sensation in the perineal area [6]. Urinary catheters are generally used to manage urinary incontinence in elderly patients or in patients with long-term spinal cord injuries. More than 30 million urinary catheters are employed in patients annually [146]. Unfortunately, catheter-associated urinary tract infections (CUTI) remain the most common nosocomial infection [147]. Catheter surfaces in contact with the urethral epithelia facilitate bacterial contamination, adhesion, retention, and biofilm formation on both the abluminal and luminal surfaces, eventually leading to infection of the urethra, then the bladder, and ascending into the ureters unless the catheter is exchanged frequently [148]. Microbes in the catheter mediate the breakdown of urea, resulting in an increase in the urine pH [149], inducing formation of mineral crystals on the catheter surface, leading to the formation of urinary infection stones [149] and blockage of the lumen by encrustation, which can produce kidney and bloodstream infections.

Systemic antibiotic therapies, antimicrobial topical ointments, and the use of antimicrobial agents in collection bags are commonly used to treat CUTIs. Silver-impregnated urinary catheters claim 30% reduction in the incidence of CUTI in some studies, although this is not a consensus [150]. Several catheters based on silver and silver oxide coatings are commercially available in the United States (SilvaGard® (I-Flow/Acrymed), KENDALL DOVER® series catheters (Tyco Healthcare), BACTI-GUARD® silver (C.R. Bard)) [75]. A recent UK study involving patients with urethral catheterization for up to 14 days found that silver-coated catheters were ineffective against infection; the incidence of infection is comparable to uncoated PTFE catheters [151].

Ciprofloxacin, gentamicin, norflaxin, nitrofurazone, and combinations of compounds, such as chlorhexidine and protamine sulfate, have been successfully incorporated into catheter coatings [152]. Nitrofurazone-coated catheters (Rochester Medical, MN) are an emerging class of antimicrobial urinary catheters shown to be efficacious against *Escherichia coli* [153] and have exhibited better antimicrobial properties than silver-treated catheters [154] in *in vitro* studies. However, further prospective double-blind powered two-arm clinical studies are required to validate claims for the efficacy of silver- and nitrofurazone-coated catheters in CUTIs.

1.5.4 Orthopedic Drug-Eluting Implants

Bone defects from trauma, disease, surgical intervention, and congenital deficiencies are among the most challenging orthopedic repair problems faced worldwide. Autologous bone grafts are the gold standard to treat bone defects, but are limited, not always appropriate, with harvesting complications, including infection susceptibility. Bone fractures and joint deficiencies are increasingly treated using a variety of implanted biomaterial stabilization devices, including bone cement, hip, knee, shoulder and elbow prosthesis, plates, nails, rods, wires, pins, and screws. Projected market revenues for such orthopedic implants are estimated at $23 billion in 2012 [155]. Bone-implant bonding [156] and long-term stabilization pose significant

clinical challenges, including implant infection, bone resorption, and implant loosening [157–159]. Despite the use of advanced stabilization mechanisms and implant instrumentation, some fractures are slow healing or nonunions, requiring revision surgeries at significant expense and patient morbidity. Recent advances in drug delivery are increasingly used with orthopedic implants as combination devices [160]. Increasing reports document effects from delivery of small-molecule osteoinductive agents, drug [161], scaffold [162], gene and cellular delivery [163,164], biologically derived growth factors, antiosteoporotic agents, and osteosynthetic genetic materials such as DNA transgenes and siRNA to bone defects from a variety of implant devices and vehicles [165–172].

BAI remains a major concern in orthopedic implants [173]. Rates of infection are estimated to be 1% for primary hip implants, 4% for knee implants (higher for secondary revisions), and more than 15% for some trauma-associated open fracture implants [155]. Orthopedic implants carry a lifetime risk of infection (acute and hematogenous sources) and are clinically addressed in most cases by revision surgery involving a further substantial risk of infection [155]. A commonly used clinical approach to manage orthopedic implant infection is the use of antibiotics in bone cement, polymethylmethacrylate (PMMA) or PMMA beads. These nondegradable polymer cements have been used to prevent osteomyelitis for four decades [174–176] using either bulk impregnation by the aminoglycoside antibiotics, gentamicin or tobramycin [6,177], or vancomycin (Europe only). The first antibiotic-blended bone cement to be approved in the United States was Simplex P (Stryker Howmedica Osteonics) containing tobramycin [6]. The Palacos^{TM} series of bone cements from Biomet, Inc. (Warsaw, USA) contain gentamycin and have been approved shortly after Simplex P. Recently, Depuy 1 gentamycin-releasing bone cement (Depuy Orthopaedics) has been approved by FDA. *In vivo* studies have demonstrated the efficacy of antibiotic-loaded cements in reducing orthopedic implant infections within a short time after implantation [178–180]. However, despite wide enthusiasm, drawbacks limit clinical applications of antibiotic-loaded bone cements. Pharmacokinetics studies show the inefficiencies of gentamicin release from antibiotic-loaded PMMA bone cements or PMMA beads, with less than 50% of the antibiotic release by 4 weeks [181–184]. The primary concerns with the use of antibiotic-loaded bone cements are possible allergic reactions to the antibiotic used, and the development of drug resistance to the antibiotic at the implant site.

An antimicrobial tibial internal fixation nail coated with a degradable polymer containing gentamicin is marketed in Europe. The polymer coated over the metal nail covers the cannulation, enabling antibiotic delivery to the intramedullary canal and releasing antibiotic for ~2 weeks [185,186]. The FDA recently approved a polyurethane sleeve coated with gentamicin (OrthoGuard AB, Smith & Nephew, UK) that can be used for coating pins and wires used for external fixation devices [187].

1.5.5 Antimicrobial Sutures

According to the CDC, the overall incidence of surgical site infection is estimated to be 2.8% in the United States [188]. Surgical sutures allow microbial adherence and

colonization similar to other biomaterials [189] and contribute to surgical site infection incidence. Microbial colonization to suture materials is highly variable, depending on specific microbial species, suture structure, and chemical composition [190]. Braided sutures have been shown to have higher microbial colonization compared to nylon-based monofilament sutures [191]. Triclosan-coated braided polyglactin 910 suture (Vicryl Plus Ethicon, USA) has been developed to mitigate suture-induced surgical site infections. Several *in vitro* and *in vivo* studies [192,193] have shown that the triclosan-coated Vicryl Plus sutures effectively inhibit growth of normal and methicillin-resistant strains of *S. aureus* and *Staphylococcus epidermidis* [192] while showing no difference in physical (strength, breaking force, etc.) and degradation characteristics compared to uncoated polyglactin 910 sutures [193]. Recent clinical trials have shown that use of triclosan-coated Vicryl Plus sutures in a diverse group of 450 patients resulted in a statistically significant reduction in the incidence of surgical site infection [194]. However, some studies advise caution and the need for larger scale studies [195]. Silver-containing sutures are being developed by X-Static. Another antimicrobial suture being developed by Polymedix (PolyCide^{TM}) contains the antibiotic polycide that disrupts microbial cell [75]. New antimicrobial strategies should be developed to overcome the limitations of current technologies.

1.5.6 Vascular Grafts with Antithrombotic Coatings

Synthetic vascular grafts have been used to treat vessel occlusion caused by vascular disease for over four decades. Large-diameter grafts have substantially better success rates clinically than those below 5 mm diameter, regardless of biomaterials used. Small-diameter vascular graft failure generally occurs as a consequence of acute thrombus formation on the graft luminal surface, anastomotic intimal hyperplasia, or progression of vascular disease [196]. Although anastomotic hyperplasia and disease progression are important factors for failure, reducing the propensity for acute thrombotic failure by improving graft surface blood compatibility has significant potential for improving clinical performance of small-diameter vascular grafts. Small-diameter expanded polytetrafluoroethylene (ePTFE) vascular grafts containing surface-immobilized heparin are FDA approved for treating vascular occlusion. CBAS-coated vascular grafts (e.g., Gore® PROPATEN® Vascular Graft, Gore® VIABAHN® Endoprosthesis, W.L. Gore, USA) containing immobilized heparin on the graft luminal surface are commercialized. Studies have shown reduction in thrombogenicity for small-diameter ePTFE vascular grafts containing immobilized heparin compared to uncoated ePTFE grafts [197].

1.5.7 Cerebrospinal Shunts

Hydrocephalus is treated using biomaterials-based cerebral shunt implants that drain excess cerebrospinal fluid (CSF) from the cranium to abdomen to relieve intracranial pressure [198]. Infections remain a major clinical complication in using CSF shunt implants and usually require frequent replacement of the shunt system at substantial

cost and morbidity (usually in infants and children) [199]. Antibiotic-impregnated CSF shunts demonstrate clinical efficacy in reducing implant infections [200,201]. BACTISEAL® from Depuy and ARES® from Medtronic are two antibiotic-impregnated CSF shunts that contain both clindamycin and rifampicin, released from the shunt surface. Both products demonstrate reduced infection against Gram-positive bacteria for at least 31 days after implantation [202,203]. This area, however, still faces numerous challenges in producing a long-duration product that performs reliably and reduces shunt replacement frequency.

1.6 FUTURE DIRECTIONS

1.6.1 Orthopedic Fixation Plate Sleeves

New biodegradable polymer sleeves formulated with various therapeutics and readily mounted onto orthopedic plates and screw fixation implants intraoperatively prior to implantation provide a patient- and implant-specific customizable therapeutics approach to IMD drug delivery. Sleeves must not interfere with device fixation mechanics and healing (typically on periosteum or in bone) and degrade without adverse incident. Biodegradable sleeves have been prepared using copolymers of glycolide, caprolactone, trimethylene carbonate, and lactide, containing the antimicrobial agents gentamicin sulfate and triclosan (highly potent bactericidal agents against *S. aureus* [204]). These sleeves slip over metallic internal fixation plates (e.g., limited contact dynamic compression plates) and implanted in sheep tibia with induced bone defects. Local release of antimicrobials to mitigate implant-associated bone infection was shown to kill microbes *in vitro* and produce no observed bone irritation or significant FBR in sheep *in vivo* [205]. A sleeve to deliver bone morphogenetic protein-2 (rhBMP-2) within PLGA microparticles through a porous sleeve made of resorbable polypropylene fumarate has also been tested [206]. The porous sleeve is loaded with desired amounts of drug-loaded microspheres prior to implantation, with possibilities to select from a variety of preloaded, preformulated PLGA microsphere/drug combinations. This strategy provides a case-dependent customized solution to surgeons using these implants. However, this intraoperative microsphere loading technique may produce inconsistent results. Multiple variants of sleeves supplied by manufacturers with standardized drug loading and drug delivery mechanisms may result in more standardized results while still allowing surgeons to choose a precise location on the implant to apply it for release.

1.6.2 Customizable Drug-Releasing Adhesive Patches and Intraoperative Custom Coatings

Unless performing drug formulation tasks for device addition off-label, surgeons are currently limited to using drug precoated and preloaded implants as received from a device manufacturer. These types of implants have predetermined amounts of drug, a fixed drug type, and the location of the drug distributed over the implant surface cannot be changed or modified. Such implants are manufactured as “one-size-fits-all”

and generally not customizable to any particular patient or condition, or surgeon preference. Increasingly, combinations of multiple drugs are proving more effective than single drugs in a given application. Flexibility for manipulating the drug type, drug loading, and its location over the implant surface can be beneficial to patients receiving certain implant types. New implant coating technologies to address these limitations with the flexibility in design and feasible intraoperative production to be readily customized to patients' needs are desirable. Customizable drug-containing "paints" and patches loaded with desired drugs with a controlled, custom dosing and flexible application locations on a desired implant intraoperatively have been recently proposed [207] to provide a possible solution to such needs. Adhesive drug patches fabricated from resorbable biomaterial laminates or composites in an aseptic environment would be loaded with drugs or drug-loaded degradable microparticles before or during surgery and cut into desired shapes to match the implant, dosing, and intended application. Drug-containing polymer coatings could also be sprayed onto implant surfaces directly using computer-controlled calibrated equipment preprogrammed to match the implant specifications with patient needs and surgeon preferences and applied either pre- or intraoperatively as a validated process. Custom drug-release patches and drug "paintable coatings" would be adhered as thin films to implant sites with surgical glues at desired locations before or during implant surgery.

1.6.3 Shape-Memory Polymeric Biomaterials

Many biomedical implants are polymer based and often require complex surgeries for device implantation and host integration due to their size and shape. Minimally invasive surgeries enable implantations of certain smaller implants with laparoscopes that limit patient risk, procedure cost, and morbidity. Use of biocompatible shape-memory polymers further provides new opportunities for improved implantation of certain medical devices with relative ease and less patient discomfort. Shape-memory processing enables specific material chemistries to "remember" a permanent shape while predeformed into metastable temporary shapes that trigger to the permanent shape with a stimulus (mechanical stress, heat, and light). This property allows modification of the device shape and size to conform to a catheter or a smaller implant readily inserted through smaller incisions using catheters or laproscopes than required for normal surgery. Nitinol is a shape-memory metal commonly used in cardiovascular stent applications due to its ability to be deformed to a small compressed conformation allowing easy insertion in a catheter with minimal implantation trauma and to regain its intended final shape after mechanical balloon-based deployment. Nickel allergy and final metal mechanical properties limit their utility. As an alternative, thermally induced shape-memory polymers can be used in polymer-based suture applications, especially those requiring complex knots, curve shapes, and conformations [208]. Shape-memory polymers have gained increased attention as a proposed biomaterial for minimally invasive surgical devices [208,209]. Medshape (Atlanta, USA) manufactures FDA-approved polymer-based shape-memory implants for suture anchors and soft tissue fasteners. Polymer-based shape-memory implants can also be used for drug delivery to

implant locations via impregnation of desired drugs into the material and release upon triggering to final shape after deployment [210].

1.6.4 See-and-Treat Combination Imaging/Drug Delivery Theranostic Agents

Some creative, new medical nanotechnology enables the possibility to combine the imaging, monitoring, and treating of disease condition onto a single platform. Nanoparticles engineered with imaging agents and also containing therapeutic agents permit simultaneous diagnostic and therapeutic functions when circulating *in vivo*. These so-called theranostic agents/devices often incorporate drug conjugates and complexes, dendrimers, liposomes, micelles, core–shell particles, microbubbles, and carbon nanotubes as carriers of either drugs or contrast agents, including optically active small molecules, paramagnetic metals and metal oxides, ultrasonic contrast agents, and radionuclides. This is an emerging area of combination devices that could significantly contribute to improved disease detection and targeted therapy as well as to personalized medicine [211].

Molecular imaging techniques such as magnetic resonance imaging (MRI), radionuclide-based imaging using computed tomography (CT) or positron emission tomography (PET), and high intensity focused ultrasound allow visualization and distinction of tissue, cellular, and subcellular biological processes with the help of contrast agents [211]. These imaging agents, combined into carriers capable of effectively delivering drugs to a biological target, will enable a "see and treat" modality to image the disease condition simultaneously with triggers to delivery therapy from the agent, constituting a theranostic device.

Drug conjugates or complexes with soluble polymers such as poly[*N*-(2-hydroxyl propyl) methacrylamide] (polyHPMA) have been well studied [212]. A contrasting agent visualized by MRI, such as radioactive I-131, conjugated with the doxorubicin-HPMA polymer anticancer prodrug conjugate already synthesized, would enable the complex to be used as a tumor theranostic agent [213]. Dendrimers have been extensively studied and are attractive drug delivery and contrast agent vehicles due to their large number of functional surface chemistry sites on them. Photoactivated drug release using dendrimers with doxorubicin conjugated to a photosensitive compound has been accomplished to target cancer [214]. Other researchers have successfully combined dendrimers with various MRI contrast agents such as high-spin gadolinium and paramagnetic iron oxide [215]. Combination of both of these chemistries onto a common platform constitutes a theranostic agent. Liposomes are another class of carriers recently studied as theranostic agents encapsulating various drugs and conjugated contrast agents [211]. Multiple studies have been performed with liposomal formulations with targeting, therapeutic, and imaging functionalities [216,217].

Several other colloidal and nanoparticulate carriers such as polymersomes, micelles, quantum dots, and carbon nanotubes can be conjugated with drugs and imaging agents for treating a condition simultaneously with detection and diagnosis [211]. While the dual conjugation chemistry is fairly straightforward in many cases, the challenge remains to produce long circulating times to allow these

particulate systems to achieve disease site accumulation. The concept of targeting these particles has proven very challenging to date, with very low levels of systemically administered dose (i.e., generally less than 5% of the injected dose) actually reaching the disease site from the bloodstream, with the majority of the dose targeting the liver, spleen, kidney, and lung in most cases. Imaging requires sensitivity, selectivity, and specificity *in vivo* [218]. Therapy requires effective dose delivery without toxic side effects. Building both critical properties onto a single nanoparticle platform is challenging: These two properties are not yet reliably achieved from these nanoparticle systems.

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