Biocompatibility: A Key Functional Requirement of Next-Generation Medical and Combination Devices

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ABSTRACT

The array of polymeric, biologic, metallic, and ceramic biomaterials will be reviewed with respect to their biocompatibility, which has traditionally been viewed as a requirement to develop a safe medical device. With the emergence of drug and biologic combination products, tissue engineered scaffolds and new fabrication methodologies such as 3D printing, the paradigm shift continues that requires biocompatibility to be designed into the device. In fact, next-generation medical devices will require enhanced biocompatibility by using pharmacologic and biologic agents, bioactive coatings, nano-textures and particles, or hybrid systems containing cells that control biologic interactions to have desirable biologic outcomes. The concept of biocompatibility has moved from a "do no harm" mission (i.e., nontoxic, nonantigenic, nonmutagenic, etc.) to one of doing "good," that is, encouraging positive healing responses. These new devices will promote the formation of normal healthy tissue as well as the integration of the device into adjacent tissue. In these contexts, biocompatibility has become a disruptive technology that can change therapeutic paradigms. Database tools to access biocompatibility data of the materials of construction in existing medical devices, alongside regulatory data for these devices, will facilitate the use of existing and new biomaterials for new medical device designs.

Keywords: Biomaterial; biocompatibility; bioactive; biostable; biodegradable; drug eluting; implant; tissue engineering; regenerative medicine; 3D printing; additive manufacturing; database.

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Abbreviations: Co-Cr-Mo, cobalt-chrome-molybdenum; ISO, International Standards Organization; OCP, FDA's Office of Combination Products; PMMA, polymethylmethacrylate; PTFE, poly(tetrafluoroethylene); PVC, poly(vinyl chlo- ride); SIBS, styrene-isobutylene-styrene triblock copolymer or Poly(Styrene- b-isobutylene-b-styrene); ULTI, ultra-low temperature isotropic carbon.

INTRODUCTION

Materials used in medical devices, particularly in those applications in which the device either contacts or is temporarily inserted or permanently implanted in the body, are typically described as biomaterials and have unique design requirements. The National Institute of Health Consensus Development Conference of November 1982 defined a biomaterial as "any substance (other than a drug) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments, or replaces any tissue, organ, or function of the body" (Boretos and Eden, 1984, pp. 27-88, 128-132, 193-253). Over the past 10 years there have been a number of technological and competitive changes that have significantly pushed biomaterial use in not just interventional and implantable medical devices, but into micro/nano-particle device and drug delivery applications, drug delivery excipients (e.g., synthetic and biopolymer biodegradables for medtech, drug delivery and cell delivery excipients), and scaffolds for tissue engineering.

The required material properties are determined by the specific device application and the functional life of the device, which ranges from temporary use to permanent implant. Devices can be used in (1) blood-contacting applications, such as extracorporeal devices that remove and return blood from the body, devices that are inserted into a blood vessel, or devices that are permanently implanted; (2) soft-tissue device applications, such as soft-tissue augmentation; (3) orthopedic and dental applications for joint, bone, and tooth replacement and repair; (4) specific organ applications (e.g., neural); (5) carriers/excipients for drug delivery and combination device applications; and (6) scaffolds for tissue engineering for tissue and organ replacement.

Materials for medical devices can be characterized as synthetic polymers, biodegradable polymers, bioactive materials, natural macromolecules (i.e., biopolymers), metals, carbons, ceramics, and nano-enabled materials and particles (Boretos and Eden, 1984; Helmus and Tweden, 1995; Helmus, 2003: Helmus et al, 2009). They can be implanted for permanent replacement, as in an artificial heart valve or hip prosthesis, or for temporary use, such as an intravenous catheter or bone plates and rods. The sterilized device, and by default, the materials of which it is constructed, need to meet basic biocompatibility requirements, generally as defined by the ISO 10993 standards, to be nontoxic, nonthrombogenic, noncarcinogenic, nonantigenic, and nonmutagenic (Helmus, 2003). ISO 10993-1 has moved to "Evaluation and testing within a risk management process"[1] [2] . This process should generally begin with assessing materials, the manufacturing processes, the clinical use, and the frequency and duration of exposure. This assessment may identify biomaterial-based risks, e.g., chemical toxicity, biological response – including manufacturing and processing – that could alter the

[1] ISO 10993 Biological evaluation of medical devices —Part 1: Evaluation and testing within a risk management process; Use of International Standard ISO 10993-1, FDA, Guidance for Industry and Food and Drug Administration Staff "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" June 16, 2016

[2] Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" Guidance for Industry and Food and Drug Administration Staff June 16, 2016

physicochemical characteristics of the device. Potential risks should be addressed and include knowledge gaps to be evaluated by testing. A context is given for interpretation in the appropriate benefit-risk context. In blood-contacting applications, it must be nonthrombogenic to mitigate complications from thrombi and emboli. Potential complications will vary with a device and its application. Biodegradation and infection become increasingly important in longer term applications such as central venous catheters and permanently implanted devices. Because of the large surface area in extra-corporeal circuits, activation of biologic pathways, such as the coagulation, fibrinolytic, and complement pathways, may be magnified. Patients who are treated by extracorporeal methods (e.g., hemodialysis) are repeatedly exposed to leachable plasticizers and sterilant residuals.

Many devices, such as heart valves, artificial hearts, and hip implants are constructed of multiple materials. Joining methods can affect material properties that can reduce strength, fatigue life, and biostability. The material's form and size, how it interfaces with the body, and its required duration of use will determine its required properties. One material property alone is unlikely to lead to a successful and durable device, whereas a lack of a single key property can lead to failure.

There are and will continue to be controversies concerning biostability of the starting materials, and as fabricated. One contemporary controversy concerns the biostability of polypropylene meshes, e.g., https://www.consumersafety.org/legal/hernia-mesh-lawsuit/. In this specific case, there is confusion between the device, quality systems, and correct clinical use with a biomaterial. This presentation ignores that properly qualified polypropylene has extensive literature on biocompatibility and biostability. Polypropylene, as used in sutures and implants, has decades of clinical use. The data summary of Polypropylene in the database shows that if properly compounded with antioxidants, degradation is negligible in vitro and clinical explants! However, the device and material qualification used here needs to be confirmed.

There are new processing techniques that have become or are becoming important methodology for producing biomaterials products, including electro-spinning and 3D Printing/Additive Manufacturing. It is important to remember that these are processing methods that have their own processing aids and additives. The biomaterials are a tool in the production of these products. As with any manufacturing process, all products need to be evaluated for biocompatibility and durability, which can be profoundly affected by processing. It is also important to note that there are significant differences in the Additive Manufacturing process for the class of material: polymeric/plastic, biopolymer, metals, and ceramics. The recent article comparing spinal interbody fusion devices is a good example comparing 3D printed PEEK, Titanium plasma sprayed PEEK, and 3D printed Titanium (McGilvray et al). It is interesting to note that in the Materials for Medical Devices Database that there are 44 approved orthopedic devices citing use of 3D printed materials: from Titanium and its alloys (spinal, joint and fixation devices); 3 PEEK devices (spine, skull plate, and surgical devices); and 1 Dimethacrylate-based resin dental device (Materials for Medical Devices Database). As described by Ventola, 2014, "The three most commonly used 3D printer technologies in medical applications are: selective laser sintering (SLS), thermal inkjet (TIJ) printing, and fused deposition modeling (FDM)". Additionally, Bioprinting deposits "bioink", i.e., biologically derived molecules suitable for processing that contain living cells or tissue. These

printed structures can be further differentiated into the desired tissue or organ by direct implantation or by further cell growth in a bioreactor.

Coatings for improved biocompatibility, scaffolds for tissue engineering and as carriers for drug and cell delivery have an increasingly important role. Bioactive materials, which tend to use the nature of natural material or mimic natural materials, have applications in orthopedic implants to enhance bone attachment, antimicrobials to mitigate infection, and antithrombotics to mitigate thrombus. Drug–polymer combinations have been used in drug-eluting stents, heparin-release coatings for catheters, and steroid-releasing electrodes for pace-makers (Helmus and Tweden, 1995; Ranade et al., 2004; Ranade et al., 2005; Stokes, 1987). These drug-eluting devices are representative of combination devices that have the potential to create potent new therapies by using the best properties of drug-device, biologic-device, or drug-biologic combinations. The Food and Drug Administration's Office of Combination Products (OCP) has broad responsibilities covering the regulatory lifecycle of these combination products and will determine which Center has primary regulatory responsibility (Helmus, 2007; https://www.fda.gov/combinationproducts/default.htm). For example, the drug-eluting stent is primarily regulated by Center for Devices and Radiological Health, but Center for Drug Evaluation and Research has secondary responsibility for the analysis of drug content and compounding and manufacturing requirements.

Drug-eluting stents have been a common therapy in coronary artery disease and are being evaluated in peripheral and specific organ applications. The field has moved to biostable coatings, biodegradable coatings, biodegradable stents, coating-free stents, and bare metal stents (Chandrasekhar 2016). Newer therapies for drug-coated balloons for peripheral and coronary applications are just moving into the clinic. The drug may be coated directly on the surface of the balloon with a carrier or the drug can be placed in an excipient/carrier coated on the angioplasty balloon. Many use carriers (known as excipients) which are soluble agents and macromolecules such as polysorbate, sorbitol, hydrophilic urea and polyethylene glycol 8000 (Materials for Medical Devices Database).

The phenomena controlling the bio response are basically wound healing in the presence of a sterile medical device. The outcome of this healing process can have profound implications on the success of a device and can depend on material properties such as texture, crystallinity, wettability, surface chemistry, cytotoxic leachables, and degradation products (Andrade et al., 1987; Brash, 2000; Helmus and Tweden, 1995). These properties determine primarily the interaction between the materials and proteins in the biological environment, and, subsequently, the interactions with the cells and tissues. The biologic response to materials, e.g., inflammation and thromboresistance, is an important consideration in the design of medical devices.

Chronic inflammatory responses resulting in a thick fibrous capsule and the persistence of white cells, is undesirable and can lead to damage to surrounding tissue and to failure of the device. Leachables can cause local cytotoxicity and result in inflammation. Hypersensitivity reactions can occur to corrosion products and residual monomers, plasticizers, additives such as antioxidants, and degradation products. Cytotoxic leachables and degradation products, which may exhibit systemic effects if the dose is high, may result from the fabrication and sterilization methods used as well as ambient degradation by processes such as hydrolysis and

oxidation over time (Coury et al., 1988; Stokes, 1987; Takahara et al., 1992). Contamination by bacteria, endotoxins (the breakdown products of gram-negative bacteria), and particulate debris can have profound effects on inflammatory responses (Helmus et al., 1986). These responses are generally a matter of handling, processing, and minimizing wear and corrosion in vivo. The lack of bacteriological contamination can be designated as an incoming requirement on materials from a vendor; however, wear and corrosion debris are inherent properties of materials and are a matter for appropriate materials selection.

Biostability refers to the ability of a material to resist biodegradation mechanisms and maintain its properties in situ. Degradation may result from hydrolysis, oxidation, enzyme catalyzed enhancement of hydrolysis, oxidation, lipid absorption, swelling, and calcification. Biomaterials with enhanced compatibility will combine new materials that have negligible leachables and exceptional biostability to mitigate adverse biologic responses to leaching of additives and breakdown products. Styrene-isobutylene-styrene triblock elastomer, used as the carrier for paclitaxel in the drug-eluting stents (Ranade et al., 2004; Ranade et al., 2005), is an example of this type of new-generation materials. Other exceptionally biostable carriers include the PVDF-HFP (vinylidene fluoride and hexafluoropropylene copolymer) used in the Xience stent (MMD).

Biomaterials for use as scaffolds for tissue engineering and carriers (excipients) for pluripotential cells like mesenchymal stem cells have become critically important for bioreactor grown tissue and in situ repair (Mao 2015). Scaffolds can be synthetic polymers with a strong interest in biodegradables and in extracellular matrix materials that have a strong capability to adhere cells via cell adhesion peptides like RGD. The ASTM standards for scaffolds are listed in Table 1.

An emerging biocompatibility issue is the formation, in some clinical cases, of lymphoma in textured mammary implants (Clemmens et al 2017). The investigations into etiology are still ongoing. However, a focus has been on double capsule formation which might result in delayed seroma, capsular contracture. There may also be an association of bacteria and biofilm. The double capsule formation may result if the initial tissue (capsule) that forms around the textured implant pulls away from the surface and allows new tissue capsule to form. This is an example of how a process to reduce capsular contracture, that is a porous texture (Pollock, H. 1992), can potentially result in an unintended consequence of lymphoma. The FDA recently released a statement that it now considers association between all breast implants, regardless of filling or texture, and Breast Implant Associated- Anaplastic Large Cell Lymphoma (BIA-ALCL with the risk of developing this disease within the scar capsule adjacent to the implant[3].

[3] https://www.fda.gov/MedicalDevices/Safety/LetterstoHealthCareProviders/ucm630863.htm

TABLE 1.—International standards for biological evaluation of medical devices[4].

ASTM Standards Tissue Engineering

ISO 10993-1	Biological evaluation of medical devices; Evaluation and testing within a risk management process
ISO 10993-2	Animal welfare requirements
ISO 10993-3	Tests for genotoxicity, carcinogenicity, and reproductive toxicity
ISO 10993-4	Selection of tests for interactions with blood
ISO 10993-5	Tests for cytotoxicity: In vitro methods
ISO 10993-6	Tests for local effects after implantation
ISO 10993-7	Ethylene oxide sterilization residuals
ISO 10993-8	Withdrawn: Clinical investigation of medical devices
ISO 10993-9	Framework for identification and quantification of potential degradation products
ISO 10993-10	Tests for irritation and skin sensitization
ISO 10993-11	Tests for systemic toxicity
ISO 10993-12	Sample preparation and reference materials
ISO 10993-13	Identification and quantification of degradation products from polymeric medical devices
ISO 10993-14	Identification and quantification of degradation products from ceramics
ISO 10993-15	Identification and quantification of degradation products from metals and alloys
ISO 10993-16	Toxicokinetic study design for degradation products and leachables
ISO 10993-17	Establishment of allowable limits for leachable substances
ISO 10993-18	Chemical Characterization of materials
ISO 10993-19	Physico-chemical, morphological, and topographical characterization of materials
ISO 10993-20	Principles and methods for immunotoxicology testing of medical devices

ASTM[5]

F2150-13	Standard Guide for Characterization and Testing of Biomaterial Scaffolds Used in Tissue-Engineered Medical Products
F2027-16	Standard Guide for Characterization and Testing of Raw or Starting Materials for Tissue-Engineered Medical Products
F2450-10	Standard Guide for Assessing Microstructure of Polymeric Scaffolds for Use in Tissue Engineered Medical Products
F2103-11	Standard Guide for Characterization and Testing of Chitosan Salts as Starting Materials Intended for Use in Biomedical and Tissue-Engineered Medical Product Applications
F2903-11	Standard Guide for Tissue Engineered Medical Products (TEMPs) for Reinforcement of Tendon and Ligament Surgical Repair
F2883-11	Standard Guide for Characterization of Ceramic and Mineral Based Scaffolds used for Tissue-Engineered Medical Products (TEMPs) and as Device for Surgical Implant Applications
F3142-16	Standard Guide for Evaluation of in vitro Release of Biomolecules from Biomaterials Scaffolds for TEMPs

[a]Helmus (2003);

[4] https://webstore.ansi.org/RecordDetail.aspx?sku=ISO+10993+-+Biological+Evaluation+of+Medical+Devices+Package&gclid=CjwKCAjwhLHaBRAGEiwAHCgG3tYeXtEzOpvkEK3to1z5SVgxygsqsb_vu6sp_tweWOcK8vnhYIWh2RoC3CsQAvD_BwE

[5] https://www.astm.org/search/fullsite-search.html?query=tissue%20engineering%20scaffolds&

Thromboresistance relates to the tendency of a material to reduce thrombus or emboli formation by formation of platelet-based and/or fibrin-based clots. Thrombi can form a nidus for coagulation, and they can also form a site that is prone to bacterial colonization and infection. Consumption of blood elements may be an indication of microemboli and activation of thrombotic mechanisms, and is undesirable. Many bioprostheses, such as the bioprosthetic pericardial heart valve, are considered thromboresistant, whereas mechanical heart valves made from a variety of materials require permanent anticoagulation therapy. The effect of design and materials on thrombosis is difficult to separate in these cases. Materials such as poly(ester) fabrics are moderately thromboresistant but are suitable for their application as vascular grafts larger than 6 mm in diameter. Intimal hyperplastic responses resulting in the excess thickening of vascular tissue limit the use of synthetic small-diameter vascular grafts (Boretos and Eden, 1984) and result in the chronic closure of vessels after angioplasty.

Basic schemes for testing the acceptability of materials in terms of cytotoxicity, hemolysis, and mutagenicity can be found in these standards and guidelines: American Society for Testing and Materials (ASTM) F-748, the International Standards Organization 10993 standards; Table 1. These provide a method of testing by device application (Helmus, 2003).

MEDICAL MATERIALS INFORMATION

Materials can be classified in a variety of different ways. The following, which is suitable for medical devices, sorts by type and application: synthetic polymer, biodegradable materials, tissue-derived materials, bioderived macromolecules, passive surface coatings, bioactive and tissue-adhesive materials, metals, ceramics and glassy carbons, composites, and nano materials. Table 2 gives examples of materials in each category, a medical device in which it is used, a list of ISO 10993 tests that it passed when fabricated as part of that medical device, and literature citations on its blood and soft-tissue compatibility. These data were extracted from ASM International's Materials for Medical Devices Database, Cardiovascular Implant Materials Module (ASM International and Granta Design, 2007).

The database is an extensive resource, containing the engineering and biological performance of materials used in surgical and implantable devices as well as information about compatible coatings and drugs, manufacturing processes, and an extensive database of relevant published literature. The data are comprehensively cross-linked and fully traceable to original sources. The database can be used for selection of materials, drugs, and coatings for medical devices, including finding information on current applications of materials, biocompatibility issues, and data on medical device recalls where material-related issues may be a contributing factor.

BIOCOMPABILITLITY

Table 3 summarizes biocompatibility issues that might be a consideration in each category of biomaterials described below. These considerations are general and are influenced by the nature of the material (e.g., biostable vs. biodegradable) and application (e.g., soft-tissue, blood, or hard-tissue applications). The issues highlighted are the ones of particular importance to that category. The physical integrity and failure of devices have profound influence on the safety and efficacy of the device and are therefore categorized in this table.

TABLE 2.—Selected examples of materials from Materials for Medical Devices database.[a]

Material examples	Device examples	ISO 10993 tests	Biocompatibility citations for soft tissue response and blood comp
Synthetic plastic - Ultra high molecular weight polyethylene	Annuloplasty rings	3, 4, 6, 10, 11	Chowdhury et al. (2004), Takami et al. (1997), Hunter et al. (1995), Richardson et al. (1975)
Synthetic elastomer – Silicone rubber	Sewing ring component pericardial heart valve	3, 5, 6, 10, 11	Belanger et al. (2000), Harmand and Briquet (1999), Iomhair and Lavelle (1996), McCoy et al. (1989), Mirzadeh et al. (2003), Ertel et al. (1994), Bordenave et al. (1992), Ammar (1984), Van der Giessen et al. (1996), Spilizewski et al. (1987)
Synthetic textile - Polyethylene terphthalate	Mechanical heart valve	3, 4, 5, 6, 10, 11	Toes (1999), Bonchek et al. (1969), Radomski et al. (1987), Marois knitted/woven et al. (1999), Marois et al. (1996), Urayama et al. (1996), Granström et al. (1986)
Biodegradable - Polylactic acid	Biodegradable pericardial replacement	3, 4, 5, 6, 10, 11	Nguyen et al. (2003), (Tamai et al. (2000), Kohn et al. (2004), Cutright and Hunsuck (1971), Su et al. (2003)
Tissue-derived - Bovine pericardium	Heart valve	3, 4, 5, 6, 10, 11	Fürst and Banerjee (2005), Chang et al. (2001), Chang et al. (2002), Neuhauser and Oldenburg (2003)
Tissue-derived – Porcine SIS (small intestine submucosa)	Dura tissue substitutes, nerve cuffs, patches, surgical mesh, wound and burn dressings, wound and tissue closure	3, 4, 5, 6, 7, 10, 11	Badylak et al. (1989), Mostow et al. 2005, Niezgoda et al. (2005), Oelschlager et al. (2006), Helton et al. (2005), Franklin et al. (2008), Ansaloni et al. (2003), Chaliha et al. (2006), Bejjani and Zabramski (2007), Champagne et al. (2006), Wiedemann and Otto (2004), Knol (l2007).
Tissue-derived - Porcine urinary bladder matrix	Surgical mesh, wound and burn dressings	3, 4, 5, 6, 7, 10, 11	Parcells et al. (2014)
Bio-derived - 2-methacryloyloxyethyl phosphorylcholine	Stent coating	3, 4, 5, 6, 7, 10, 11	De et al. (2002), Galli et al. (2001), Rose et al. (2004), Malik et al. (2001), Goreish et al. (2004)
Passive coating - Butyl methacrylate	Carrier for drug-eluting stent	3, 4, 5, 6, 10, 11	Sousa et al. (2001), Suzuki et al. (2001)
Bioactive - Surfactant heparin	Annuloplasty rings	3, 4, 5, 6, 7, 10, 11	Tonda et al. (2005), Lazar et al. (1999), Novello et al. (2000), Yang et al. (2005), De Scheerder et al. (1997)
Tissue adhesive – Albumin	Tissue sealant	3, 5, 6, 10, 11	Skarja et al. (1997), Werthén et al. (2001), Marois et al. (1996)
Metal – Stainless steel	Endovascular stent	3, 4, 5, 6, 7, 10, 11	Selvaduray and Bueno (2004), Hao et al. (2005b), Wever et al. (1997), Indolfi et al. (2000)
Metal – Platinum chromium alloy	Stents (Synergy, Zenith and Rebel)	3, 4, 5, 6, 7, 10, 11	Kereiakes et al. 2010 and Stone et al. (2011)

Metal – Bioabsorbable magnesium alloy	Stents	(CE Marked device)	
Ceramics and carbon – Pyrolytic carbon (LTI)	Mechanical heart valve	3, 4, 5, 6, 10, 11	Yannas (2004), Feng and Andrade (1994), Mantero et al. (2002), Yang et al. (1996), Maropis et al. (1977), Antoniucci et al. (2000)
Composites – silicone imprecgnated with barium sulfate	Annuloplasty ring	3, 4, 5, 6, 7, 10, 11	See silicone rubber above
Nantotechnology – Nanostructured copolymer Styrene-isobutylenestyrene (SIBS)	Carrier for drug-eluting stent	3, 4, 5, 6, 10, 11	Gallocher et al. (2006), Silber (2003), Ranade et al. (2004)

Iso = International Standards Organization. a. ASM International (2006).

TABLE 3.—Biocompatibility issues.

	Synthetic	Biodgradable	Tissue	Bioderived	Passive coatings	Bioactive coatings	Metals & alloys	Ceramics & carbons	Comopsites	Nano-materials
Biocompatability										
ADME, biodegradation, byproducts, biodeposition		+	+	+		+		+		+
Bioactivity assay			+	+		+	+	+		+
Biodegradation particulates		+		+		+				
Biodegradation: Effect of infection, acid pH		+	+	+		+				
Biodegradation: Effect of hematoma, basic pH		+	+	+		+				
Calcification	+		+	+		+				
Cell membrane and blood-brain barrier passage										+
Cells viability (cryopreserved allografts, tissue engineered constructs, bioprinting, magnetic nanoparticle delivery)			+							
Corrosion byproducts							+			
Cytotoxic preservatives			+							
Decellularization process			+							
Extractables	+	+	+	+	+	+			+	
Hypersensitivity reactions	+		+	+		+			+	
Immune responses			+	+		+				
Infections contamination: Bacterial, viral, fungal, prion			+	+		+				
Lipid uptake	+		+	+					+	
Matching biomechanics of original tissue			+				+	+	+	
Necrotic cell death/apoptosis										+
Purity				+		+				
Protein adsorption: Hydrophilic	+				+					

	Synthetic	Biodgradable	Tissue	Bioderived	Passive coatings	Bioactive coatings	Metals & alloys	Ceramics & carbons	Comopsites	Nano-materials
Protein adsorption: Hydrophobic	+				+					
Sterilization residuals	+	+	+	+	+	+				
Surface exposure of compound particles									+	
Uptake in the reticuloendothelial system										+
Thromboresistance			+		+	+		+		
Physical integrity										
Biostability	+		+	+	+	+	+	+	+	
Coating adherence					+	+				
Corrosion: Pitting, fretting, stress							+			
Cross-linking effects on properties			+	+						
Durability/ fatigue life	+		+		+	+		+	+	
Fatigue life	+	+	+				+	+	+	
Fracture toughness	+					+		+	+	
In situ cure time: Bone cements, tissue adhesives	+					+		+	+	
Rate of biodegradation: Surface								+		
Rate of biodegradation: Bulk		+	+	+						
Wear	+				+		+	+		

ADME = adsorption, deposition, excretion, and metabolism

SYNTHETICS

Commonly available synthetic polymers are used in applications such as sutures, housings for extracorporeal devices (e.g., blood oxygenators, hemodialysis, and plasmapheresis devices), vascular grafts, heart-valve stents, abdominal patches, periodontal patches, and low-cost, high-volume tubing, connectors, and bags.

Examples include poly(amides), used as suture materials; poly(vinyl chloride) (PVC),[1] used as tubing and bags for the storage of blood and pharmaceutical products; poly(ethylene terephthalate) textiles, used as large-diameter vascular graft materials and as sewing cuffs on mechanical and biological heart valves; polymethylmethacrylate (PMMA), used as a fixation cement for the orthopedic prosthetics and for housings for extra-corporeal devices; and poly(tetrafluoroethylene) (PTFE), used extensively as an expanded membrane material for medium-diameter vascular grafts, abdominal patches, periodontal membranes, and as anterior-cruciate-ligament prostheses (Helmus, 2003). These materials tend to exhibit structural stability, relative biocompatibility, and low cost. Some vendors supply specifically designated biomedical grades. Master files are kept on the material production, and the vendors usually certify the materials' biocompatibility based on standardized testing that shows the materials as supplied are noncytotoxic and stable in the biological environment for certain periods of time and under certain conditions. Because of ongoing concerns with medical liability, some materials suppliers have limited the availability of their materials for use in permanent medical devices.

Some of the unique properties of synthetic materials are being used in new-generation devices. Hydrogel coatings, such as poly(ethylene oxide), are used for blood contact because of low levels of protein adsorption and their exceptional lubricity (Helmus and Hubbell, 1993). Poly(ether urea urethanes) are an example of a thermoplastic elastomer with excellent fatigue resistance. This material is used in the pumping bladder of the artificial heart. Highly oriented and highly crystalline poly(eth-ylene terephthalate) film is used as a balloon in certain angioplasty catheters because of its extraordinary bursting strength (Helmus and Hubbell, 1993). Table 3 summarizes the issues related to synthetic polymers.

BIODEGRADABLES

Biodegradable biomaterials are of high interest because of their ability to be absorbed gradually by the body (Kohn et al., 2004). The property of biodegradation in the biological environment makes these materials particularly appropriate for applications that are temporary in nature. These applications would normally require surgical removal.

Biodegradable products must have breakdown products that are nontoxic and eliminated by the body's metabolic pathways. The most widely used biodegradable materials are homopolymers or copolymers of alpha-hydroxy acids, such as lactic and/or glycolic acids (Williams, 1981). These materials can be formulated to degrade with a half-life for mass loss ranging from a few months to a few years. They are widely used as bioresorbable sutures and carriers for drug-eluting stents.

Surface-erodible polymers are hydrophobic and are used to maintain the device's physical strength for longer periods of time or to approach a zero-order release rate of pharmaceutical agents formulated into these surface-erodible polymers (Kohn et al., 2004). Examples include the polyanhydrides and polyorthoesters. Table 3 summarizes the issues related to biodegradables.

TISSUE-DERIVED MATERIALS

Processed tissues of human or nonhuman origin are used for ligaments, arteries, veins, and heart valves. Biodegradation and calcification during a period of 10 to 15 years has been an ongoing issue. Biologically derived materials are particularly susceptible to biodegradation mediated by proteolytic enzymes from plasma or from adherent cells. Calcification, seen particularly in biologically derived materials such as the bioprosthetic heart valve, can lead to stiffening and tearing of the bioprosthetic heart valve cusps (Levy et al., 2003; Carpentier et al., 2007). Newer multiple-step processes entail treating the tissue to reduce antigenicity and to increase longevity in vivo by enzyme digestion, detergent extraction, and/or cross-linking with glutaraldehyde or other bifunctional agents. Significant efforts in reducing calcification have been demonstrated with ethanol and aluminum chloride treatments (Levy et al., 2003) as well as improvements in both calcification and thromboresistance with surfactant and alcohol treatment (Carpentier et al., 2007). More recently, animal-derived mucosal-like tissues which, e.g., Porcine Small Intestine Submucosal tissue (SIS) and bladder tissue, have regenerative capabilities (Londono and Badylak, 2016). These tissues have limited clinical use for tissue repair and are being evaluated in new applications such as heart valves. Devices fabricated from these materials that are based on predicate devices without claims will most likely be regulated as a 510K. However, if there is no predicate device or if claims are made these are almost certainly going to be regulated by the FDA's Division of Biologics. Table 3 summarizes the issues related to tissue-derived materials.

BIODERIVED MACROMOLECULES

Purified macromolecules are used for cardiovascular and soft-tissue applications. Collagen, both from human and nonhuman sources, is used as a space filler in cosmetic surgery, as a coagulation-inducing material, as a matrix to promote healing, and as a surface-treatment to make textile vascular grafts non-porous. Hyaluronic acid is being used as a coating to increase the lubricity of catheters and as an injectable into joints to reduce inflammation. Phosphorylcholine-derived polymers have been used to produce thromboresistant and biocompatible surfaces (De et al., 2002; Galli et al., 2001; Rose et al., 2004; Malik et al., 2001; Goreish et al., 2004). Human fibrin is used as a sealant and space filler in vascular and plastic surgery. Table 3 summarizes the issues related to bioderived macromolecules.

PASSIVE SURFACE MODIFICATIONS AND COATINGS

Specialized polymer coatings (e.g., silica-free silicones, hydrogels, and fluorocarbons), used to improve biocompatibility, and in many cases, to increase lubricity, have been in development for several cardiovascular applications (Hoffman, 1987). Plasma etching and plasma polymerization have also been used to modify surface properties. For example, the surface modification of vascular graft materials with nonpolymerizing gas plasmas (such as argon, oxygen, or nitrogen plasmas) has been observed to increase wettability and to generally increase the extent of cell attachment to materials. Treatment with a polymerizing gas plasma, such as tetrafluoroethylene, has been used to place a very thin, highly cross-linked polymer overlayer on a variety of base polymer substrates. These processes allow modification of

surface properties without changing the bulk physical properties of the materials. Ultra-low temperature isotropic (ULTI) carbon is used to modify Dacron polyester sewing cuffs and vascular grafts to improve their "blood compatibility" properties (Haubold et al., 1981). Table 3 summarizes the issues related to surface coatings.

BIOACTIVE COATINGS AND TISSUE ADHESIVES

Bioactivity refers to the inherent property of some materials to participate in specific biological reactions. Bioactive coatings may be formed from molecules that prevent blood clotting or initiate the enzymatic degradation of thrombus. Heparin coatings have been applied on cardiovascular implants, including stents, and annuloplasty rings. A heparin surfactant coating on polyester fabric of annuloplasty rings was shown in an arterio-venous shunt model to significantly reduce thrombus and platelet uptake (Helmus and Scott, 1999). Some negatively charged surfaces initiate the degradation of complement components with the potential for fewer side effects for extracorporeal treatments such as dialysis (Chenoweth, 1987). Cell-adhesion peptides and proteins are being investigated for enhancing endothelialization and soft-tissue adhesion (Tweden et al., 1995). Antimicrobial surfaces have been fabricated by immobilizing broad-spectrum antimicrobials such as silver, silver sulfadiazine, or specific antibiotics. (Russell et al)

Bioactive coatings for orthopedic and dental-implant applications consist of calcium phosphate ceramics. These materials promote biological fixation by direct bonding with bone because of their chemical similarity with bone mineral (Cook et al., 1991). Interactions with the glycosaminoglycan molecules allow cellular deposition of collagen, which functions as a scaffold for mineralization.

Tissue adhesives such as methyl cyanoacrylates were used before the 1960s in the United States, but the hydrolytic breakdown product was formaldehyde, which is cytotoxic. This resulted in a greatly restricted use of cyanoacrylate. Different cyanoacrylate analogues, such as octyl-2-cyanoacrylate, are currently being evaluated and do not appear to demonstrate cytotoxic responses (Nitsch et al., 2005).

Fibrin glue is being investigated for producing microvascular anastomoses (Amrani et al., 2001) and controlling excessive bleeding by acting as a hemostatic agent. Table 3 summarizes the issues related to bioactive coatings.

METALS AND METALLIC ALLOYS

Commonly used alloys include austenitic stainless steels, cobalt-chrome-molybdenum (Co-Cr-Mo), tantalum, and titanium. Austenitic stainless steels, Co-Cr-Mo alloys, titanium, and titanium alloys are the preferred metals for orthopedic and dental applications.

Although stainless steels are used for permanent implants, they have shown that nickel-ion release can result in nickel hypersensitivity. Austenitic stainless steel is widely used in guidewires for angioplasty and angiography catheters, endovascular stents, fracture plates, nails, screws, and joint replacement (Helmus, 2003).

Titanium alloys are used for heart-valve and artificial-heart structural components because of

their low density, high strength, low modulus (stiffness), low corrosion rate, and lack of cytotoxic effects. Titanium and its alloys are also used for pacemaker cases, fracture plates, nails and screws, and joint-replacement packaging for electrical stimulators because of these same properties (Helmus, 2003).

Endovascular stents can be fabricated from titanium, tantalum, nickel-titanium shape-memory alloys, austenitic stainless steel, and cobalt chrome. These devices can keep a vessel from rapidly closing after angioplasty if plaque rupture occurs. Anticoagulation and antiplatelet therapy is required for a few months with these devices. Most stents are crimped onto the end of an angioplasty catheter and expanded by the balloon at the site of the lesion to restore blood flow. Furthermore, the stent reduces but does not necessarily eliminate the restenosis that occurs because of the hyperplastic response of the lesion after injury caused by angioplasty. Other designs are self-expanding and use the spring-like property of the metallic alloy to be positioned. Nickel–titanium alloys are typically used in these devices. Recently, more radiopaque alloys have been utilized, e.g., PtCr alloys. Biodegradable magnesium alloys for stents and temporary devices such as bone plates and components are being evaluated with this alloy.

Co-Cr alloys are used for dental implants, bone plates, wires, screws, nails, joint-replacement parts, and self-expanding stents, and in heart valves and rings because of their corrosion resistance, fatigue resistance, and strength (Helmus, 2003). Table 3 summarizes the issues related to metal alloys.

CERAMICS AND GLASSY CARBONS

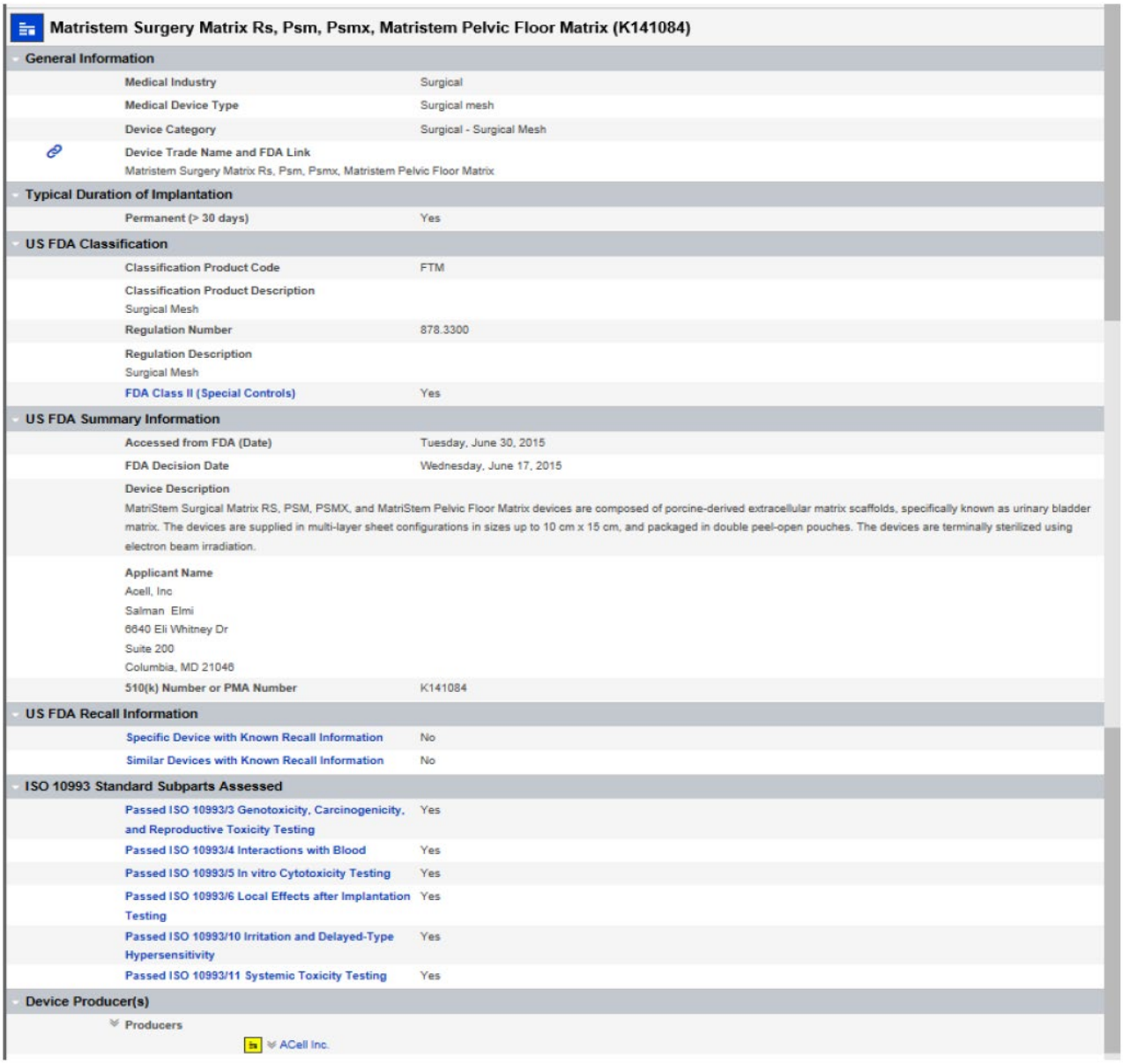
Ceramics have been used extensively in dental and orthopedic applications (Hench and Best, 2004). Specifically, dense, high-purity alumina has been used as the ball and socket of total-hip endoprostheses (Griss and Heimke, 1981). Alumina has also been used in dental implants. Dense hydroxylapatite ceramics have been used in jaw reconstruction for maintenance of the alveolar ridge (Swart and Groot, 1987). Granules of hydroxylapatite have been used to fill bony, periodontal, and alveolar ridge defects.

Carbons have been widely used as heart-valve components, particularly as leaflets in mechanical valves, because of their resistance to degradation and their very high resistance to wear (Barenberg et al., 1990; Williams 1981; Ritchie et al., 1990). In particular, pyrolytic carbons, produced by the pyrolysis (thermal decomposition) of hydrocarbon vapors, have been used extensively. Glassy and pyrolytic carbon have also been used as dental implants. Table 3 summarizes the issues related to ceramics and glassy carbons.

COMPOSITES

Composite structures are particularly useful for meeting unique combinations of design requirements such as high strength, low density, and anisotropic properties. Many cardiovascular catheters use coextruded tubes with wires in the wall for steering the catheters and increasing their torsional rigidity (Rashkind and Wagner, 1981; Vandomael et al., 1986). Textile vascular prostheses have been coated with proteins such as collagen, gelatin, and albumin to eliminate the need for pre-clotting (Snyder and Helmus, 1988). The newer carbon-

fiber composites based on engineering plastics are being investigated for orthopedic applications (Spector et al., 1990). They have the potential for use as structural components for the artificial heart and heart valves. Radio-opaque fillers such as barium sulfate are used to increase the visibility of polymers under X-ray. Table 3 summarizes the issues related to composites.



Matristem Surgery Matrix Rs, Psm, Psmx, Matristem Pelvic Floor Matrix (K141084)

General Information	
Medical Industry	Surgical
Medical Device Type	Surgical mesh
Device Category	Surgical - Surgical Mesh
Device Trade Name and FDA Link	Matristem Surgery Matrix Rs, Psm, Psmx, Matristem Pelvic Floor Matrix
Typical Duration of Implantation	
Permanent (> 30 days)	Yes
US FDA Classification	
Classification Product Code	FTM
Classification Product Description	Surgical Mesh
Regulation Number	878.3300
Regulation Description	Surgical Mesh
FDA Class II (Special Controls)	Yes
US FDA Summary Information	
Accessed from FDA (Date)	Tuesday, June 30, 2015
FDA Decision Date	Wednesday, June 17, 2015
Device Description	MatriStem Surgical Matrix RS, PSM, PSMX, and MatriStem Pelvic Floor Matrix devices are composed of porcine-derived extracellular matrix scaffolds, specifically known as urinary bladder matrix. The devices are supplied in multi-layer sheet configurations in sizes up to 10 cm x 15 cm, and packaged in double peel-open pouches. The devices are terminally sterilized using electron beam irradiation.
Applicant Name	Acell, Inc Salman Elmi 6640 Eli Whitney Dr Suite 200 Columbia, MD 21046
510(k) Number or PMA Number	K141084
US FDA Recall Information	
Specific Device with Known Recall Information	No
Similar Devices with Known Recall Information	No
ISO 10993 Standard Subparts Assessed	
Passed ISO 10993/3 Genotoxicity, Carcinogenicity, and Reproductive Toxicity Testing	Yes
Passed ISO 10993/4 Interactions with Blood	Yes
Passed ISO 10993/5 In vitro Cytotoxicity Testing	Yes
Passed ISO 10993/6 Local Effects after Implantation Testing	Yes
Passed ISO 10993/10 Irritation and Delayed-Type Hypersensitivity	Yes
Passed ISO 10993/11 Systemic Toxicity Testing	Yes
Device Producer(s)	
Producers	ACell Inc.

FIGURE 1.—Porcine Uninary Bladder Matrix, from the Materials for Medical Devices Database (ASM International, 2018). This selected example demonstrates some of the data available on this tissue derived material (e.g., tissue source, Device Applications ISO 10993 tests performed).

NANOMATERIALS

Nanomaterials are well suited for targeted drug delivery, molecular diagnostics, and imaging applications (both magnetic resonance imaging and X-ray imaging). Nanoporous materials will have applications in implants, as membranes (for example, for dialysis machines), and also in drug delivery. Nanostructured materials can enhance the biocompatibility and mechanical properties of medical devices, whereas drugs and nanostructured polymers can be combined to control the rate at which the drug is released in yet another drug-delivery application. The unique mechanical properties of nanostructured and nanocomposite materials (such as high strength and shape-memory properties) are also invaluable for implants and catheter devices (Helmus, 2007). The TAXUS drug-eluting stent was shown by atomic force microscopy to have nanostructured microphase separation of the styrene-isobutylene-styrene triblock copolymer. The drug, paclitaxel, forms 20- to 30-nm particles that were typically in the styrene phase (Ranade et al., 2004; Ranade et al., 2005).

Most of the applications for emergent nanoparticles have been for imaging and drug delivery (Anselmo and Mitragotri) and are regulated as a pharmaceutical. These particles can be fabricated from biodegradables like polylactide/gylactides or albumin, hydrogels like Polyethylene Glycol (PEG) and magnetic materials like magnetite. Pharmaceutical use of nanoparticles will be regulated as a pharmaceutic. These require not only the local and systemic toxicology to be evaluated but also ADME – Adsorption, Deposition, Metabolism and Excretion of the drug and nanoparticle (Brand et al 2016). There is a magnetic nanoparticle therapy by Pulse Therapeutics as a medical device to enhance delivery of thrombolytic drugs through clot[6].

Magnetic particle targeting methodology is evolving and allowing precise delivery within organs, e.g., the brain, for drug delivery and/or precise energy delivery by localized heat, electric or magnetic fields. Magnetite nanoparticles typically have demonstrated inherent biocompatibility. Translation into the clinic will dramatically increase over the next decade (Weinberg, IN, Mair LO, Jafari, S et al, in press).

There continue to be many unknowns about the potential safety effects of nanomaterials, particularly nanoparticulates. These effects relate to their uptake in the reticuloendothelial system (e.g., lung, spleen, liver), the ability to cross cell membranes, the potential to induce necrotic cell death or apoptosis, and the ability to interact at the level of cellular receptors (Helmus, 2007). Table 3 summarizes the issues related to nanomaterials.

CASE STUDY

This case study is of Tissue Engineered Muscle Repair Constructs (TEMR) created by seeding human derived muscle progenitor cells (MPCs) onto a bladder acellular matrix (BAM).

There is a significant need for muscle transplants for traumatic muscle injury and loss of large muscle mass. Tissue Engineered Muscle Repair Constructs (TEMR) were developed to allow the creation of human muscle by bioreactor growth of muscle from human muscle

[6] https://euphratesvascular.com/#pulse

progenitor cells. These constructs were created by seeding human-derived muscle progenitor cells (MPCs) onto a bladder acellular matrix (BAM) (porcine urinary bladder) and subjecting it to cyclic mechanical stretch in a custom-built bioreactor (i.e., preconditioning), which causes MPCs (myoblasts) to align forming a confluent monolayer of myoblasts and myotubes (Machingal, Corona et al. 2011, Corona, Machingal et al. 2012, Corona, Ward et al. 2014). Figure 2 shows a histopathological section of the BAM as prepared for seeding. The ASM datasheet on the Matristem Porcine Bladder Matrix is a similar material to that used here, Figure 1. Figure 3A shows the muscle nuclei in Blue (DAPI), Fig. 3B) shows Actin filaments in Red after ReadyProbe staining (Life Technology), and Fig. 3C) shows a merged image of nuclei and actin staining[7]. Clinical Trials a planned for the near future as an Biologic IND regulatory process.

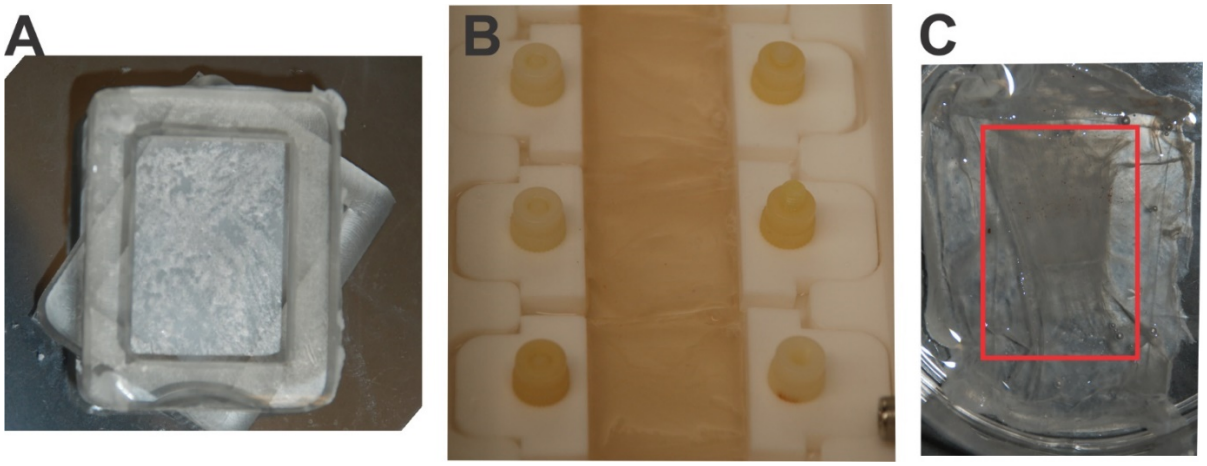


FIGURE 2 Preparation of Tissue Engineered Muscle Repair Constructs (TEMR) by University of VA. Muscle progenitor cells are seeded onto (A) porcine bladder acellular matrix (BAM), shown wrapped around a silicone frame for support. Cell seeded BAM scaffold is then removed from the silicone frame and placed in a (B) cyclic stretch bioreactor. End product, TEMR construct, is shown in (C). Red square marks the center of constructs, where there is a high cell density (i.e., a uniform monolayer of cells—myoblasts and myotubes).

[7] This work was supported in part by the US Army Medical Research Acquisition Activity under Contract No W81XWH-14-2-004 (G.J. Christ, PI). Image Credit: Juliana A. Passipieri, Senior Scientist, Laboratory of Regenerative Therapeutics, University of Virginia, Depts. Of Biomedical Engineering and Orthopaedic Surgery, GJ Christ, PI.

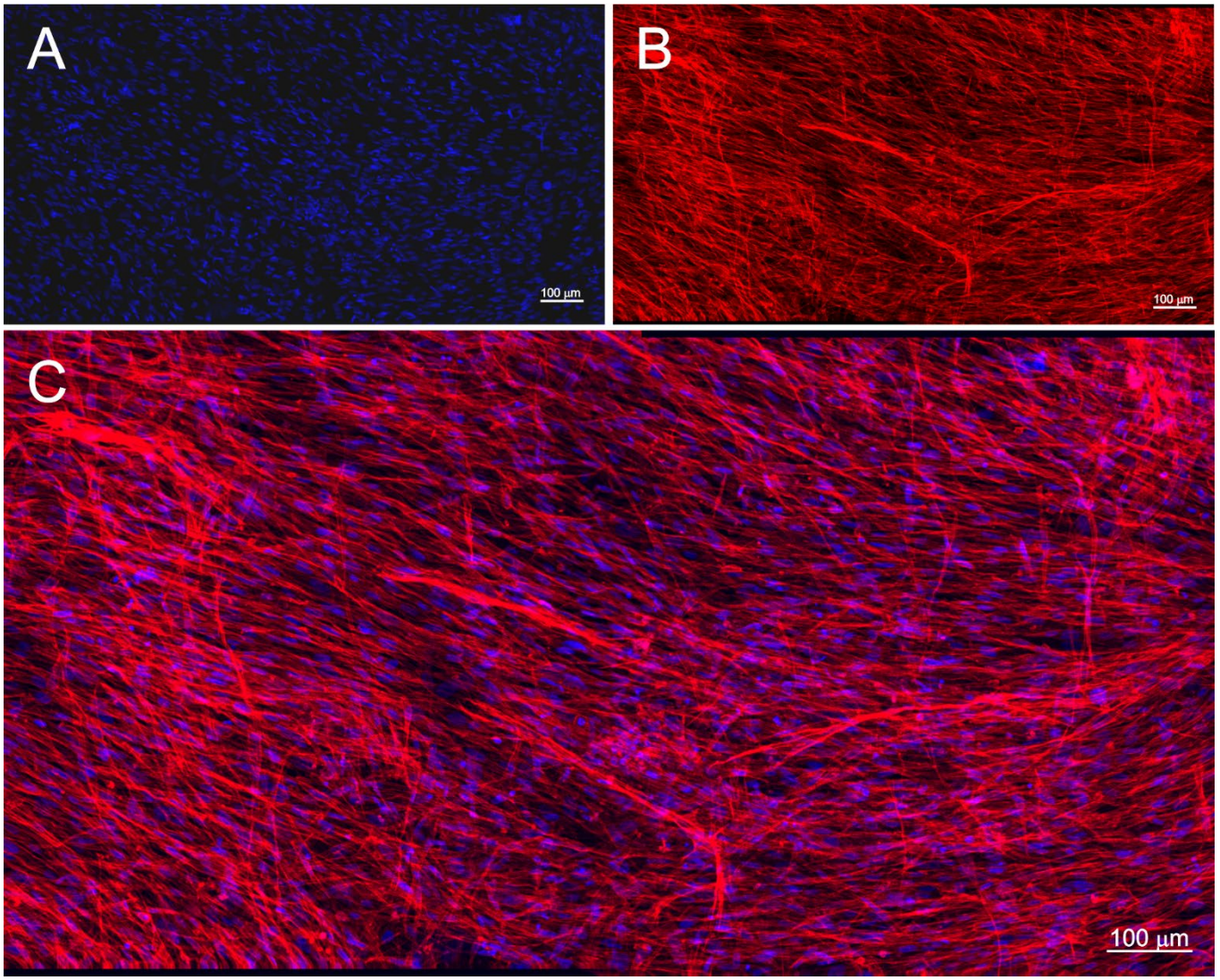


Figure 3. Tissue Engineered Muscle Repair Constructs (TEMR) A) Nuclei are shown in Blue (DAPI), B) Actin filaments are shown in Red after ReadyProbe staining (Life Technology), and C) shows a merge image of nuclei and actin staining.

CONCLUSION

The materials used in building a medical device must meet stringent functional requirements. Included in these requirements are biocompatibility concerns, a need to address what tissues the device interfaces within the body and the biologic response that can result from this interaction, engineering properties, and compatibility with suitable combinations of coatings and elutable drugs. Materials selection made within the context of functional requirements will dramatically increase the safety and effectiveness of the device. Understanding the historic context of materials used in medical-device design and the biocompatibility of these materials facilitates selection decisions in the design of new devices.

New database tools allow rapid review of the biocompatibility of materials used in existing medical devices and all other important associated information. Furthermore, the evolving technology of highly biostable, bioactive, and drug-eluting biomaterials allows control of the healing response to improve safety and efficacy of implantable medical devices.

NOTE

Plasticizer leaching is an ongoing concern with PVC materials; this problem has been addressed by developing plasticizers with low potential for leaching (Shimizu, 1989).

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