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(71) Applicants: **CLEMSON UNIVERSITY RESEARCH FOUNDATION** [US/US]; P.O. Box 946, Clemson, SC 29633-0946 (US). **MUSC FOUNDATION FOR RESEARCH DEVELOPMENT** [US/US]; 19 Hagood Avenue, Suite 909, Charleston, SC 29425 (US).

(72) Inventors: **VERTEGEL, Alexy, A.**; 391 College Avenue, Suite 401, Clemson, SC 29631 (US). **LUZINOV, Igor, A.**; 391 College Avenue, Suite 401, Clemson, SC 29631 (US). **CROSS, Christopher, E.**; 68 President Street, BED101A, MSC 501, Charleston, SC 29403 (US). **GIL, Dmitry**; 391 College Avenue, Suite 401, Clemson, SC 29631 (US). **BORODINOV, Nikolay**; 391 College Avenue, Suite 401, Clemson, SC 29631 (US).

(74) Agent: **GUY, Joseph, T.** et al.; Patent Filing Specialist Inc., 16 Wellington Avenue, Suite B, Greenville, SC 29609 (US).

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(54) Title: HIGHLY ADHERENT POLYMERS FOR ORTHOPEDIC DEVICE COATINGS

(57) Abstract: Provided is an orthopedic implant comprising a surface with a coating on the surface wherein the coating comprises a copolymer defined by Formula I: A_w-B_x-C_y-D_z wherein: A comprises an epoxy group; B comprises a hydrophobic group; C is an optional cross-linker; D of Formula I comprises a hydrophilic group; w is at least 0.1 to no more than 0.9 with the proviso that at least one of x or z is not zero; x is up to 0.9; y is up to 0.3; and z is up to 0.9.

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HIGHLY ADHERENT POLYMERS FOR ORTHOPEDIC DEVICE COATINGS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present invention claims priority to pending U.S. Provisional Patent Application No. 62/613,830 filed January 5, 2018 which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention is related to a coating for medical implants, particularly orthopedic devices, wherein the coating has superior adhesion to the medical implant and the coating is capable of slow release of antimicrobials thereby mitigating infection rates.

BACKGROUND

[0003] Orthopedic implants are available for many applications including joint replacements, bone repair fixtures and the like without limit thereto. For the purposes of the instant invention there are two general classes of orthopedic implants with one class being exclusively internal and typically permanent, such as a hip joint or shoulder joint, and the other being partially internal and temporary, such as Kirshner wires. All orthopedic implants are capable of housing bacteria and other undesirable materials and therefore infection due to an orthopedic implant is a particularly severe problem.

[0004] Pin site infections arise from the use of percutaneous pinning techniques such as those employed in skeletal traction, percutaneous fracture pinning, external fixation for fracture stabilization or complex deformation reconstruction. These sites are niduses for infection because the skin barrier is disrupted which allows for bacteria to enter at the junction of the skin and pin. After external fixation the rate of

pin site infections is usually high and, in some circumstances and techniques, approaches 100%. Following pin site infection the pin may become loose which causes increased pain and the integrity of the fracture fixation may be compromised resulting in structural deformity and inferior clinical results. The excessive pain is also related to increased narcotic usage which is a critical secondary consideration. While many of the pin site infections are treatable with adequate wound care and oral antibiotics, osteomyelitis and deep soft tissue infections may occur with evidence of up to 4% of the cases escalating to a requirement for a more complex care plan. Due to the morbidity and costs associated with its sequelae, strategies to reduce pin site infections are vital.

[0005] Patients with Kirshner wires are particularly vulnerable to infection. Kirshner wires, often referred to as K-wires in the art, are sharpened pins, typically of stainless steel or titanium, which are inserted into the body for holding or positioning bones or for immobilization of a joint. K-wires typically extend outside the body thereby creating an air interface where the orthopedic device and surgical site meet and provide a potential site for infection. Therefore, even if the surgical procedure is accomplished without introduction of infection, the surgical site is subject to post-surgical infection. The infection rate following a K-wire procedure ranges from 11% to 100% depending on the procedure, facility and other parameters. Infection can result in sepsis, osteomyelitis and mortality if not treated properly. It has been estimated that the economic burden of infections following K-wire procedures will exceed one billion dollars by 2020 in the U.S. alone.

[0006] Staphylococcal infections account for about 80% of the infections observed after K-pin procedures. Mitigating this infection alone would have a significant impact on the number and severity of post-surgical infections observed in

K-wire recipients. There have been many efforts associated with the formation of coatings, particularly on K-wires, to form a surface which is less susceptible to absorption of bacteria or capable of being impregnated with antimicrobials. Unfortunately, it is difficult to achieve adequate adhesion to metals and the coatings typically either delaminate or, if they survive simulated implant, the anti-microbial release is uncontrolled.

[0007] There has been a significant need for mitigating of the infection rate associated with orthopedic implants, in general, and K-wires specifically. Provided herein is a coating which is particularly suitable for orthopedic inserts wherein the coating has sufficient adhesion to survive implant and the coating provides for a slow release of antimicrobials.

SUMMARY OF THE INVENTION

[0008] The present invention is related to a coating for orthopedic implants wherein the coating has superior adhesion and provides for a slow release of antimicrobials.

[0009] More specifically, the present invention is related to a coating for orthopedic implants, and improved orthopedic implants comprising a coating, wherein the coating has sufficient adhesion to the orthopedic implant to survive surgical implant and the coating comprises antimicrobials which are released at a controlled rate.

[0010] A particular feature of the invention is the ability to adjust the release rate of a specific antimicrobial by alteration of the coating.

[0011] These and other embodiments, as will be realized, are provided in an orthopedic implant comprising a surface with a coating on the surface wherein the coating comprises a copolymer defined by Formula I:

A_w-B_x-C_y-D_z

Formula I

wherein:

A comprises an epoxy group or alkoxy silyl group;

B comprises a hydrophobic group;

C is an optional cross-linker;

D comprises a hydrophilic group;

w is at least 0.1 to no more than 0.9 with the proviso that at least one of x or z is not zero;

x is up to 0.9;

y is up to 0.3; and

z is up to 0.9.

[0012] Yet another embodiment is provided in a copolymer defined by Formula I:

A_w-B_x-C_y-D_z

Formula I

wherein:

A comprises an epoxy or alkoxy silyl group and

B comprises a hydrophobic group;

C is an optional cross-linker;

D of Formula I comprises a hydrophilic group;

w is at least 0.1 to no more than 0.9 with the proviso that at least one of x or z is not zero;

x is up to 0.9;

y is up to 0.3; and

z is up to 0.9.

BRIEF DESCRIPTION OF DRAWINGS

[0013] Fig. 1 is a graphical representation of an embodiment of the invention.

[0014] Fig. 2 is a graphical representation of an embodiment of the invention.

[0015] Fig. 3 is a graphical representation of an embodiment of the invention.

[0016] Fig. 4 is a graphical representation of an embodiment of the invention.

DESCRIPTION

[0017] The present invention is related to improved orthopedic devices comprising a coating with superior adhesion to the orthopedic device wherein the coating is strongly adherent to the metal surface, remains intact upon application of shear and bending forces typically associated with an orthopedic surgery and maintains structural integrity during placement of the implant. A particular feature is the coating is capable of slow release of a loaded drug. Particularly preferred are drugs selected from the group consisting of anti-inflammatory drugs, antimicrobial drugs, anticancer drugs, antioxidant drugs or growth factor drugs with any other compatible drug being suitable for use.

[0018] The present invention is specific to a polymeric coating comprising a copolymer formed by the polymerization of a monomer comprising an epoxy terminal group with a mixture of monomers comprising hydrophobic groups and hydrophilic groups. The epoxy termination crosslinks with hydroxyl groups on the metal thereby providing adhesion of the polymeric matrix to the metal. The hydrophobic and hydrophilic components of the co-polymer allow for control of antimicrobial release rate and drug affinity.

[0019] The coating on the implant surface will be fabricated using a grafting method supplemented with cross-linking of the coating. The grafting method

includes reaction of functionalized polymers with complimentary functional groups located on the substrate surface. One of the advantages of the grafting method is that the reaction does not require elaborate synthetic procedures. The synthesis and modification are sequential and therefore the conditions of the synthesis are not complicated by the presence of the substrate being coated which increases flexibility with regards to the materials which can be easily coated.

[0020] The surface modification process is preferably accomplished by dissolving previously prepared copolymers in a solvent, preferably water. The copolymer is then deposited as a film on the surface being modified by any suitable technique preferably selected from dip-coating, spray-coating or drop-casting. The coating thickness can be easily controlled by copolymer concentration and other processing parameters such as residence time in solution or deposition amount.

[0021] While not limited thereto, the polymer is preferable formed by radical polymerization which is well known to those of skill in the art and further detail thereof is not necessary.

[0022] A particularly preferred polymer is defined by Formula I:

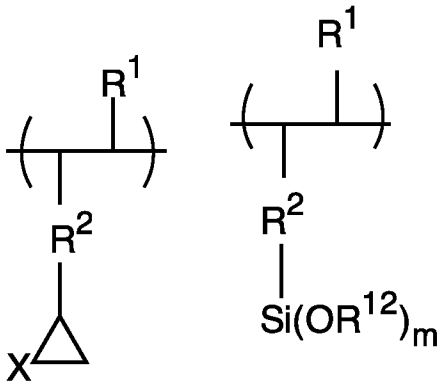
$$A_w\text{-}B_x\text{-}C_y\text{-}D_z$$

Formula I

wherein the formula represents a copolymer of monomers chosen from A, B, C and D, as will be more fully described herein, and the subscripts represent the mole fraction of each monomer in the copolymer and therefore the sum of w, x, y and z is unity. The copolymer can be a random copolymer wherein A, B, C and D are randomly distributed, a block co-polymer comprising discrete blocks of each monomer, periodic copolymers wherein the monomers are arranged in a repeating

sequence, statistical copolymers wherein the sequence follows a statistical rule or combinations thereof throughout the polymer chain.

[0023] Component A of Formula I comprises an epoxy group and is represented in the copolymer by the formula:



or

wherein:

X is O or N and preferably O;

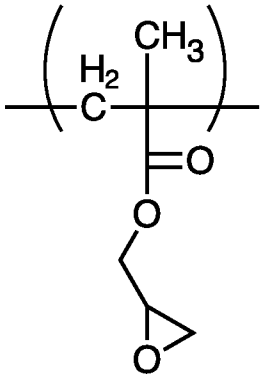
R^1 is a hydrogen or alkyl of up to 4 carbons;

R^2 is a linking group preferably selected from alkyl of 2 to 5 carbons and –C(O)-O-CH_2-;

R^{12} is an alkyl of up to 10 carbons which may be substituted.

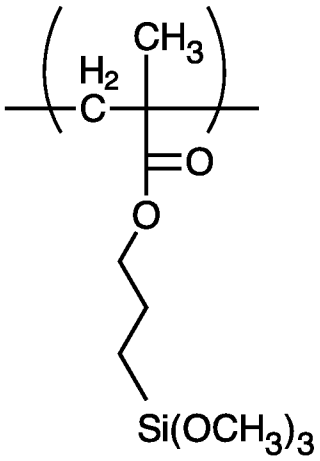
[0024] The epoxy or alkoxy silyl group reacts with the metal surface and provides for strong adhesion of the coating to the metal surface. Epoxy groups also provide excellent storage properties and can remain stable for as much as six months in water. Under acid or base conditions the ring opens and is reactive with any nucleophilic group such as the hydroxyl groups on the surface of a metal.

[0025] A particularly preferred component A is a glycidyl methacrylate (PGMA) moiety represented in the polymer by:

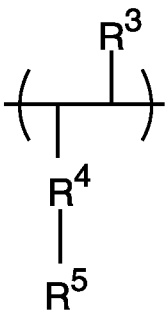


Another particularly preferred group for component A is an alkoxy silyl. Alkoxy silyls provide strong adhesion of the coating to the metal surface and ensures structural integrity of the coating during the application of shear and bending forces.

A particularly preferred alkoxy silyl group is 3-(trimethoxysilyl) methacrylate represented by the following structure:



[0026] Component B of Formula I comprises a hydrophobic group represented in the copolymer by the formula:



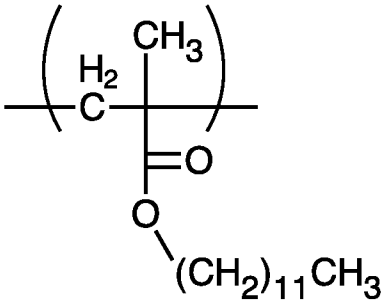
wherein:

R^3 is a hydrogen or alkyl of up to 4 carbons;

R^4 is a linking group preferably selected from alkyl of 2 to 5 carbons and –C(O)-O-CH_2-; and

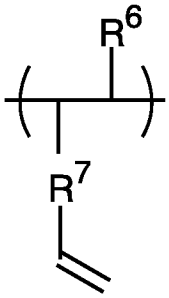
R^5 is an alkyl of 6 to 100 carbons and more preferably 10 to 100 carbons.

[0027] A particularly preferred component B is lauryl methacrylate (LMA) represented by the polymerized monomer:



.

[0028] Component C of Formula I is an optional cross-linker, and preferably a UV cross-linker, capable of crosslinking with other groups within the copolymer thereby providing additional adhesion or polymeric strength. Component C of Formula I is represented in the polymer by the formula:

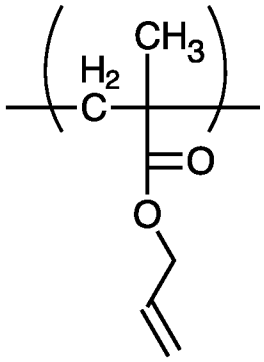


wherein:

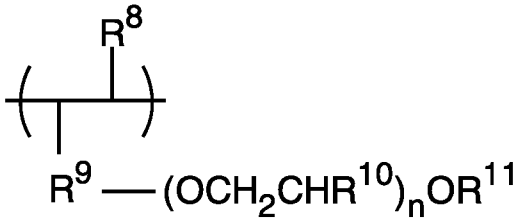
R^6 is a hydrogen or alkyl of up to 4 carbons; and

R^7 is a linking group preferably selected from alkyl of 2 to 5 carbons and –C(O)-O-CH_2-.

[0029] A particularly preferred component C is allyl methacrylate (AMA) represented by the polymerized monomer:



[0030] Component D of Formula I comprises a hydrophilic group providing water solubility, swellability, protein repellency and a matrix. Compound D is represented in the polymer by the formula:



wherein:

R^8 is a hydrogen or alkyl of up to 4 carbons;

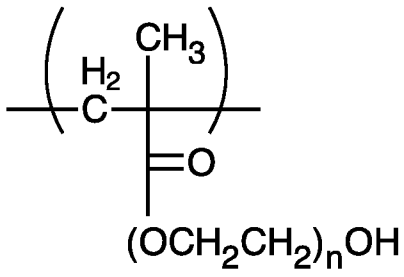
R^9 is a linking group selected from alkyl of 2 to 5 carbons and –C(O)-;

R^{10} is a hydrogen or alkyl of up to 4 carbons;

R^{11} is a hydrogen or alkyl of up to 4 carbons; and

n is at least 2 to no more than 25.

[0031] Poly (oligo(ethylene glycol) methyl ether methacrylate) (POEGMA) as component D has particularly desirable protein/cell repellency properties and the ability to compatibilize materials with water. The reactive methacrylate moiety is capable of undergoing polymerization while quite long poly ethylene glycol moieties provide water compatibility to the copolymer. The poly ethylene glycol moieties are known to have low toxicity and do not trigger immune system responses. A particularly preferred component D is polymerized ethylene glycol methacrylate (OEGMA) represented by the polymerized monomer:



wherein n is preferably an integer sufficient to achieve a molecular weight of 300 to 2000 and preferably 800 to 1200. Particularly preferred component D is OEGMA wherein n is selected from the integers 2-9, or combinations thereof, wherein the hydrophilicity increases with increasing n.

[0032] In Formula I the subscripts are defined by molar ratio such that after polymerization the copolymer is represented as one mole. In Formula I, w is at least 0.1 to no more than 0.9 with at least one of x or z is not zero. Below about 0.1 mole fraction the number of epoxy groups is insufficient to form an adhesive bond to the metal. Above a mole fraction of about 0.9 there is insufficient hydrophobic or hydrophilic moieties to absorb a sufficient amount of antimicrobial to be beneficial. More preferably, w is at least 0.1 to no more than 0.85, even more preferably at least

0.1 to no more than 0.73, even more preferably at least 0.1 to no more than 0.6 and most preferably at least 0.1 to no more than 0.3.

[0033] In Formula I, x is up to 0.9 and preferably at least 0.01 up to 0.9. The molar ratio of component B is determined based on the degree of hydrophobicity required to achieve the release rate. A higher portion of the hydrophobic moiety will slow water absorption and therefore decrease the release rate of hydrophilic antimicrobials. If the hydrophobic moiety is too high the antimicrobials cannot be absorbed in the copolymer. More preferably, x is at least 0.2 to no more than 0.8 and even more preferably at least 0.5 to no more than 0.7.

[0034] In Formula I, y is up to 0.3 and preferably 0.001 up to 0.3. The optional cross-linker provides additional intra-polymer cross-linking which increases the mechanical robustness of the polymer. If the degree of cross-linking is excessive the microbacterial is unable to be absorbed and released from the copolymer matrix. More preferably, y is no more than 0.05. The optional cross-linker allows for secondary cross-linking if necessary such as by UV activation.

[0035] In Formula I, z is up to 0.9 and preferably 0.01 up to 0.9. The molar ratio of component D is determined based on the degree of hydrophilicity required to achieve the release rate. A higher portion of the hydrophilic moiety will increase water absorption and therefore increase the release rate of hydrophilic antimicrobials. More preferably, z is at least 0.1 to no more than 0.5 and even more preferably at least 0.1 to no more than 0.3.

[0036] The copolymer is formed on the surface of the metal to form an adequate coating which preferably does not exceed about 0.1 wt% of the mass of the K-wire or about 100 μM thickness. Above a thickness of about 100 μm the coating becomes less robust and deterioration is observed upon insertion through a Septa™ used to

simulate surgical insertion. More preferably, the thickness of the coating is about 0.1 to 5 μm and even more preferably about 0.5 to 1 μm.

[0037] The surface of the metal can be used as is or treated to increase the number of surface hydroxyl groups thereby increasing the bonding sites available for reaction with the epoxy or alkoxy silyl group. The surface may be on an exclusively internal orthopedic device, such as a replacement joint, or a partially external orthopedic device such as a Kirshner wire. The surface is not particularly limited herein with the proviso that the surface have cross-linkable groups on the surface such as hydroxyl groups. Titanium, stainless steel and ceramic surfaces are particularly preferred.

EXPERIMENTAL

EXAMPLE 1

[0038] Control K-wires were coated with monolaurin (ML), a natural antimicrobial agent active against *S. aureus*. Sample K-wires were coated with a copolymer formed from 20 mole percent glycidyl methacrylate, 60 mole percent ethylene glycol methacrylate and 20 mole percent ethylene glycol methacrylate available as OEGMA 950 from Sigma Aldrich. Some of the K-wires were pulled through Septa™, to simulate surgical insertion, and the antimicrobial activity was measured. Each example was replicated nine times. The results are provided in Table 1:

Table 1

Concentration of ML mg/ml	Maximum concentration of bacteria inactivated in the presence of 1 cm pieced of K-wires		
	No Polymer, no Septa	No Polymer after Septa	With Polymer after Septa
1	~$6x10^6$	0	~$6x10^6$

3	~$7x10^6$	0	~$8x10^7$
5	~$6x10^6$	0	~$7x10^8$
10	~$8x10^6$	0	~$2x10^9$

[0039] Based on the results of Table 1 subsequent experiments reported herein utilized a coating solution comprising 10 wt% ML and 5 wt% polymer unless otherwise stated.

[0040] Additional tests were done wherein bacterial count was monitored versus time for different bacteria. In Fig. 1 the bacteria count was measured for *S. aureus* versus time. The K-wire alone as a control was ineffective as expected. Samples coated with ML only demonstrated an immediate decrease in bacteria due to essentially immediate release of ML, however, the activity was not sustained. The sample prepared with ML in polymer demonstrated a steady decrease in bacteria to a plateau of about 100 CFU/ml which represents negligible bacterial concentration. The test was repeated with Methicillin-Resistant Staphylococcus Aureus (MRSA) as the bacteria with results similar to those observed for *S. aureus* as illustrated graphically in Fig. 2.

[0041] The storage stability of monolaurin in the polymer layer on a K-wire was compared to monolaurin on a K-wire without the polymer layer. The antibacterial activity of the monolaurin coating after 5 days at 50°C, corresponding to about 45 days at room temperature, was measured against 10^5 CFU of planktonic *S. aureus*. The results are presented graphically in Fig. 3. The wires were not passed through a Septa™ for these test. The results demonstrate an improved storage stability for the inventive examples.

[0042] Effectiveness of the inventive examples against biofilms was determined. Samples were prepared including a control K-wire (Control), a K-wire coated with ML only but not passed through a Septa™ (ML Coated), a sample treated with ML and passed through a Septa™ (ML Coated Septa), and inventive examples comprising ML with polymer, using OEGMA as the hydrophilic moiety (ML/P0EGMA). Some of the inventive samples were passed through a Septa™ (ML/P0EGMA Septa).The samples were all incubated in *S. aureus* for 48 hours. The results are provided graphically in Fig. 4. As realized from the results presented in Fig. 4 the ML coated sample demonstrates effective resistance unless passed through a Septa™ suggesting the ML coating is removed or otherwise rendered ineffective. The inventive examples are not negatively impacted by passing through the Septa™ which indicates a robust coating on the surface.

EXAMPLE 2

[0043] An 0.062" stainless steel Kirscher wire was dip-coated with Copolymer A comprising a 15/66/19 molar ratio of GMA, OEGMA and LMA. Copolymer A was deposited from a methylether ketone (MEK) solvent with a 2.5 wt% polymer concentration. The coating was thermally treated at 80°C for 5 hours to crosslink the reactive groups. The polymer thickness was about 900 nm as determined by atomic force microscopy. The polymer layer was loaded with monolaurin, as a water insoluble antimicrobial, and vancomycin, as a water-soluble anti-microbial to test release rate. The antimicrobials were added by introducing the coated polymer to an MEK solution comprising the antimicrobial. Wires dip-coated in polyactide (PLA) from acetone solution were used as controls. The inventive coating remained virtually intact after pulling the coated wire through a Septa™ cap. In the case of the PLA coated wire, further studies using scanning electron microscopy showed

evidence of deterioration of the polymer layer whereas the inventive coating showed no signs of mechanical or structural deterioration.

EXAMPLE 3

[0044] The performance of Copolymer A was compared to poly(lactide-co-glycolide) PLGA) with monolaurin as a model antimicrobial additive. *S. aureus* biofilms were grown by statically incubating a *S. Aureus* suspension with 1 cm K-wire pieces for 48 hours. Monolaurin incorporated into both coatings, and a coating of monolaurin with no polymer layer were all efficient in preventing biofilm formation. However, after pulling the wires through silicon rubber Septa™ caps both the monolaurin, with no polymer coating, and the PLGA based coating lost the antimicrobial activity while the sample utilizing Copolymer A remained efficient against biofilm formation.

EXAMPLE 4

[0045] K-wires were prepared as in Example 3 with vancomycin as the antimicrobial. The K-wires were drilled into a mechanically equivalent femoral bone construct available from Sawbones USA as Model #3414. The wires were then removed from the drill, rinsed by deionized water and cut into pieces. The pieces that were exposed to the bone were placed into test tubes containing 10^7 colony forming units (CFU) if *S. aureus*. Only the K-wires with a Copolymer A coating containing vancomycin showed antimicrobial activity. Control samples comprising a K-wires with a Copolymer A coating but no vancomycin where not efficient confirming that Copolymer A does not provide antimicrobial activity.

EXAMPLE 5

[0046] The cytotoxicity of CoPolymer A was evaluated. A coating was applied as discussed above and the effects on cell proliferation were evaluated in a pilot cell

culture experiment with murine 7F2 osteoblasts (ATCC® CRL-12557) in a protocol adapted from open literature. Osteoblasts were passaged after reaching confluency and aliquots containing about 40,000 cells were transferred into a sterile 24-well plate containing uncoated wires, as a control, Copolymer A as an inventive example and PGMA homopolymer. The samples were incubated in the presence of the cells for 2, 4 and 8 days at 37°C in 5%W CO_2. Following the incubation the wires were removed from the wells and osteoblasts were exposed to 5 mg/ml MTT reagent (3-[4,5-dimethylthiazol-2yl]-2,5-diphenyl-tetrazolium bromide) for 4 hours followed by dissolution in dimethyl sulfoxide and measurement of optical density at 570 nm. Six replicates were performed for each of the time periods. Neither the inventive sample nor the PGMA coated wires had an effect on cell proliferation rate. The OD_{570}, which corresponds to the number of living cells, was not significantly different for coated and uncoated wires at different time points.

[0047] The invention has been described with reference to the preferred embodiments without limit thereto. Additional embodiments and improvements may be realized which are not specifically set forth herein but which are within the scope of the invention as more specifically set forth in the claims appended hereto.

Claimed is:

1. An orthopedic device comprising:

a surface;

a coating on said surface wherein said coating comprises a copolymer defined by Formula I:

$$A_w\text{-}B_x\text{-}C_y\text{-}D_z$$

Formula I

wherein:

A comprises an epoxy or alkoxy silyl group and

B comprises a hydrophobic group;

C is an optional cross-linker;

D of Formula I comprises a hydrophilic group;

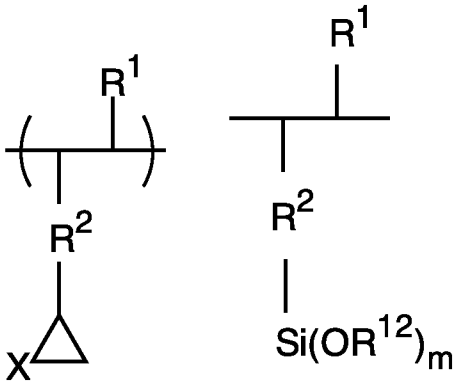
w is at least 0.1 to no more than 0.9 with the proviso that at least one of x or z is not zero;

x is up to 0.9;

y is up to 0.3; and

z is up to 0.9.

2. The orthopedic device of claim 1 wherein said A is represented in the copolymer by the formula:



or

wherein:

X is O or N;

R^1 is a hydrogen or alkyl of up to 4 carbons;

R^2 is a linking group; and

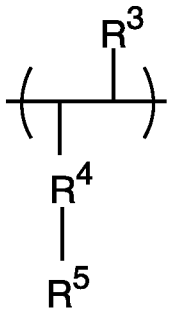
R^{12} is an alkyl of up to 10 carbons which may be substituted.

3. The orthopedic device of claim 2 wherein said X is O.

4. The orthopedic device of claim 2 wherein said R^2 is selected from alkyl of 2 to 5 carbons and –C(O)-O-CH_2-.

5. The orthopedic device of claim 2 wherein said A is polymerized glycidyl methacrylate or polymerized 3-(trimethoxysilyl) methacrylate.

6. The orthopedic device of claim 1 wherein said B is represented in the copolymer by the formula:



wherein:

R^3 is a hydrogen or alkyl of up to 4 carbons;

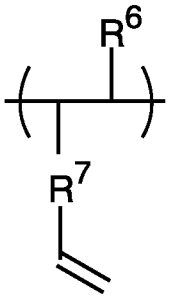
R^4 is a linking group; and

R^5 is an alkyl of 10 to 100 carbons.

7. The orthopedic device of claim 6 wherein R^4 is selected from alkyl of 2 to 5 carbons and –C(O)-O-CH_2-.

8. The orthopedic device of claim 6 wherein said B is polymerized lauryl methacrylate.

9. The orthopedic device of claim 1 wherein said C is represented in the polymer by the formula:



wherein:

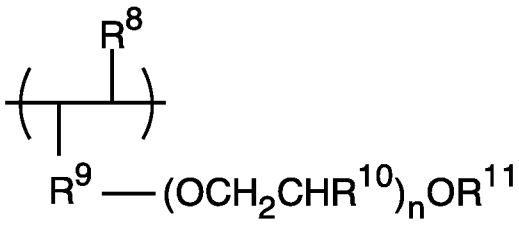
R^6 is a hydrogen or alkyl of up to 4 carbons; and

R^7 is a linking group.

10. The orthopedic device of claim 9 wherein said R^7 selected from alkyl of 2 to 5 carbons and $–C(O)-O-CH_2-$.

11. The orthopedic device of claim 9 wherein said C is polymerized allyl methacrylate.

12. The orthopedic device of claim 1 wherein said D is represented in the polymer by the formula:



wherein:

R^8 is a hydrogen or alkyl of up to 4 carbons;

R^9 is a linking group;

R^{10} is a hydrogen or alkyl of up to 4 carbons;

R^{11} is a hydrogen or alkyl of up to 4 carbons; and

n is at least 6 to no more than 25.

13. The orthopedic device of claim 12 wherein R^9 is selected from alkyl of 2 to 5 carbons and –C(O)-.

14. The orthopedic device of claim 13 wherein said n is selected from the integers 2-9.

15. The orthopedic device of claim 1 wherein said w is at least 0.1 to no more than 0.3.

16. The orthopedic device of claim 1 wherein said x is at least 0.2 to no more than 0.8.

17. The orthopedic device of claim 16 wherein said x is at least 0.5 to no more than 0.7.

18. The orthopedic device of claim 1 wherein said y is no more than 0.05.

19. The orthopedic device of claim 1 wherein said z is at least 0.1 to no more than 0.5.

20. The orthopedic device of claim 19 wherein said z is at least 0.1 to no more than 0.3.

21. The orthopedic device of claim 1 wherein said surface comprises a material selected from titanium, stainless steel and ceramic.

22. The orthopedic device of claim 1 wherein said surface is on an internal device or a device which extends external to the patient.

23. The orthopedic device of claim 2 wherein said device is a Kirshner wire.

24. The orthopedic device of claim 1 wherein said Formula I is selected from a random copolymer, a block co-polymer, a periodic copolymer, a statistical copolymer and combinations thereof.

24. The orthopedic device of claim 1 wherein said coating is no more than 100 μm thick.

25. The orthopedic device of claim 24 wherein said coating is at least 0.1 to 5 μm thick.

26. The orthopedic device of claim 25 wherein said coating is at least 0.5 to no more than 1 μm thick.

27. The orthopedic device of claim 1 further comprising a drug incorporated into said coating.

28. A copolymer defined by Formula I:

$$A_w\text{-}B_x\text{-}C_y\text{-}D_z$$

Formula I

wherein:

A comprises an epoxy or alkoxy silyl group and

B comprises a hydrophobic group;

C is an optional cross-linker;

D of Formula I comprises a hydrophilic group;

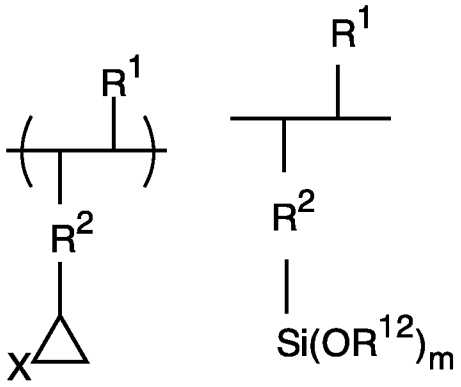
w is at least 0.1 to no more than 0.9 with the proviso that at least one of x or z is not zero;

x is up to 0.9;

y is up to 0.3; and

z is up to 0.9.

29. The copolymer of claim 28 wherein said A is represented in the copolymer by the formula:



or

wherein:

X is O or N;

R^1 is a hydrogen or alkyl of up to 4 carbons;

R^2 is a linking group; and

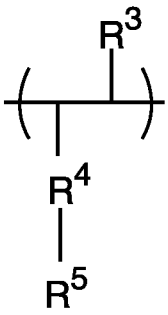
R^{12} is an alkyl of up to 10 carbons which may be substituted.

30. The copolymer of claim 29 wherein said X is O.

31. The copolymer of claim 29 wherein said R^2 is selected from alkyl of 2 to 5 carbons and $–C(O)-O-CH_2-$.

32. The copolymer of claim 29 wherein said A is polymerized glycidyl methacrylate or polymerized 3-(trimethoxysilyl) methacrylate.

33. The copolymer of claim 28 wherein said B is represented in the copolymer by the formula:



wherein:

R^3 is a hydrogen or alkyl of up to 4 carbons;

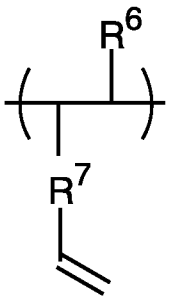
R^4 is a linking group; and

R^5 is an alkyl of 10 to 100 carbons.

34. The copolymer of claim 33 wherein R^4 is selected from alkyl of 2 to 5 carbons and –C(O)-O-CH_2-.

35. The copolymer of claim 33 wherein said B is polymerized lauryl methacrylate.

36. The copolymer of claim 28 wherein said C is represented in the polymer by the formula:



wherein:

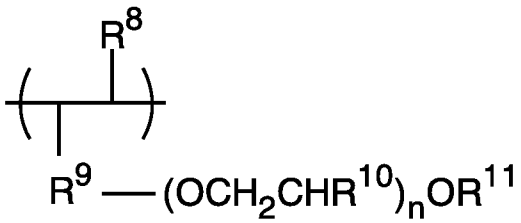
R^6 is a hydrogen or alkyl of up to 4 carbons; and

R^7 is a linking group.

37. The copolymer of claim 36 wherein said R^7 selected from alkyl of 2 to 5 carbons and –C(O)-O-CH_2-.

38. The copolymer of claim 36 wherein said C is polymerized allyl methacrylate.

39. The copolymer of claim 28 wherein said D is represented in the polymer by the formula:



wherein:

R^8 is a hydrogen or alkyl of up to 4 carbons;

R^9 is a linking group;

R^{10} is a hydrogen or alkyl of up to 4 carbons;

R^{11} is a hydrogen or alkyl of up to 4 carbons; and

n is at least 6 to no more than 25.

40. The copolymer of claim 39 wherein R^9 is selected from alkyl of 2 to 5 carbons and –C(O)-.

41. The copolymer of claim 40 wherein said n is selected from the integers 2-9.

42. The copolymer of claim 28 wherein said w is at least 0.1 to no more than 0.3.

43. The copolymer of claim 28 wherein said x is at least 0.2 to no more than 0.8.

44. The copolymer of claim 43 wherein said x is at least 0.5 to no more than 0.7.

45. The copolymer of claim 28 wherein said y is no more than 0.05.

46. The copolymer of claim 28 wherein said z is at least 0.1 to no more than 0.5.

47. The copolymer of claim 46 wherein said z is at least 0.1 to no more than 0.3.

48. The copolymer of claim 28 wherein said Formula I is selected from a random copolymer, a block co-polymer, a periodic copolymer, a statistical copolymer and combinations thereof.

49. The copolymer of claim 29 further comprising a drug incorporated into said copolymer.

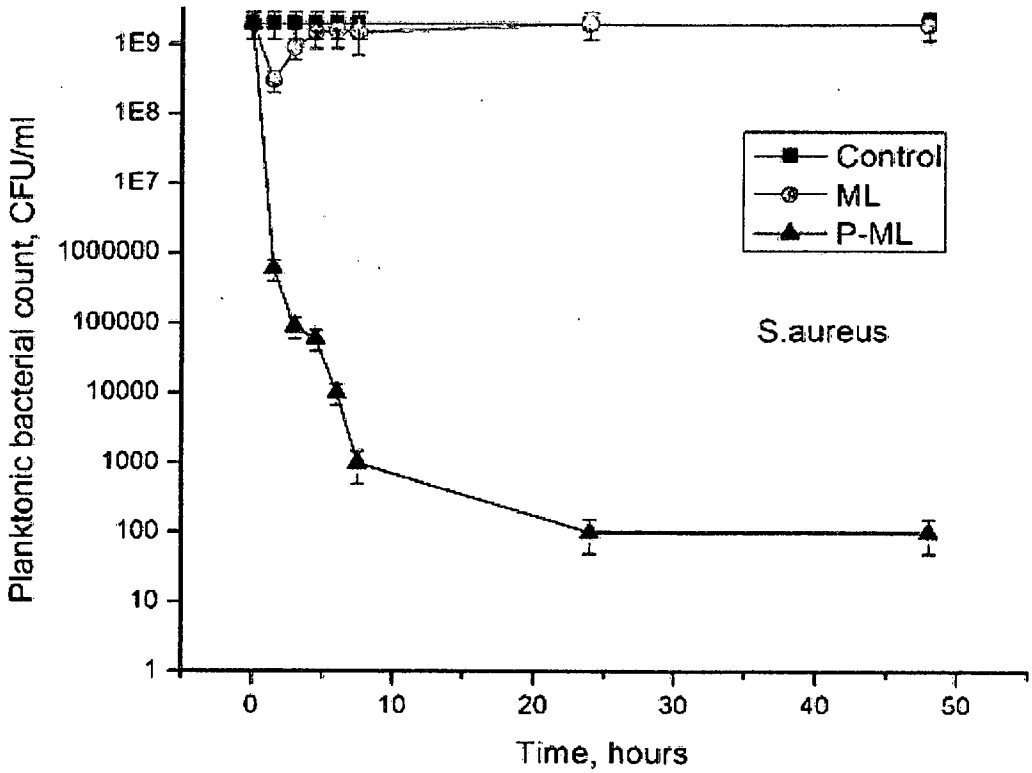

Planktonic bacterial count, CFU/ml
1E9
1E8
1E7
1000000
100000
10000
1000
100
10
1
0
10
20
30
40
50
Time, hours
Control
ML
P-ML
S.aureus

Fig. 1

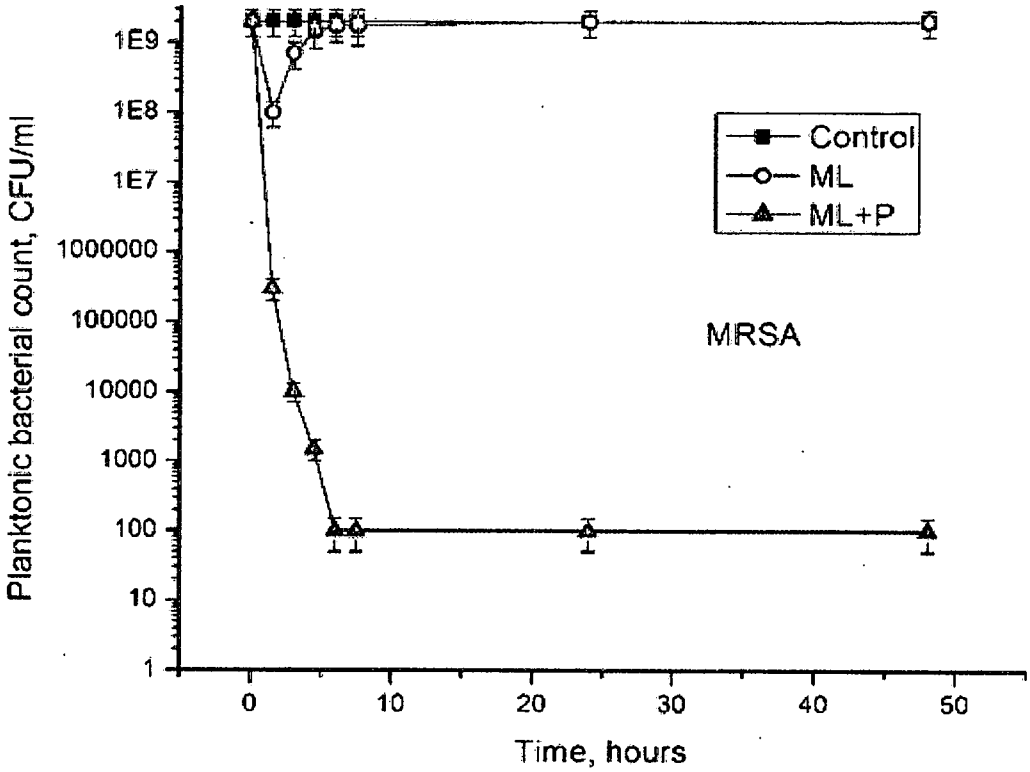

Planktonic bacterial count, CFU/ml
1E9
1E8
1E7
1000000
100000
10000
1000
100
10
1
0
10
20
30
40
50
Time, hours
Control
ML
ML+P
MRSA

Fig. 2

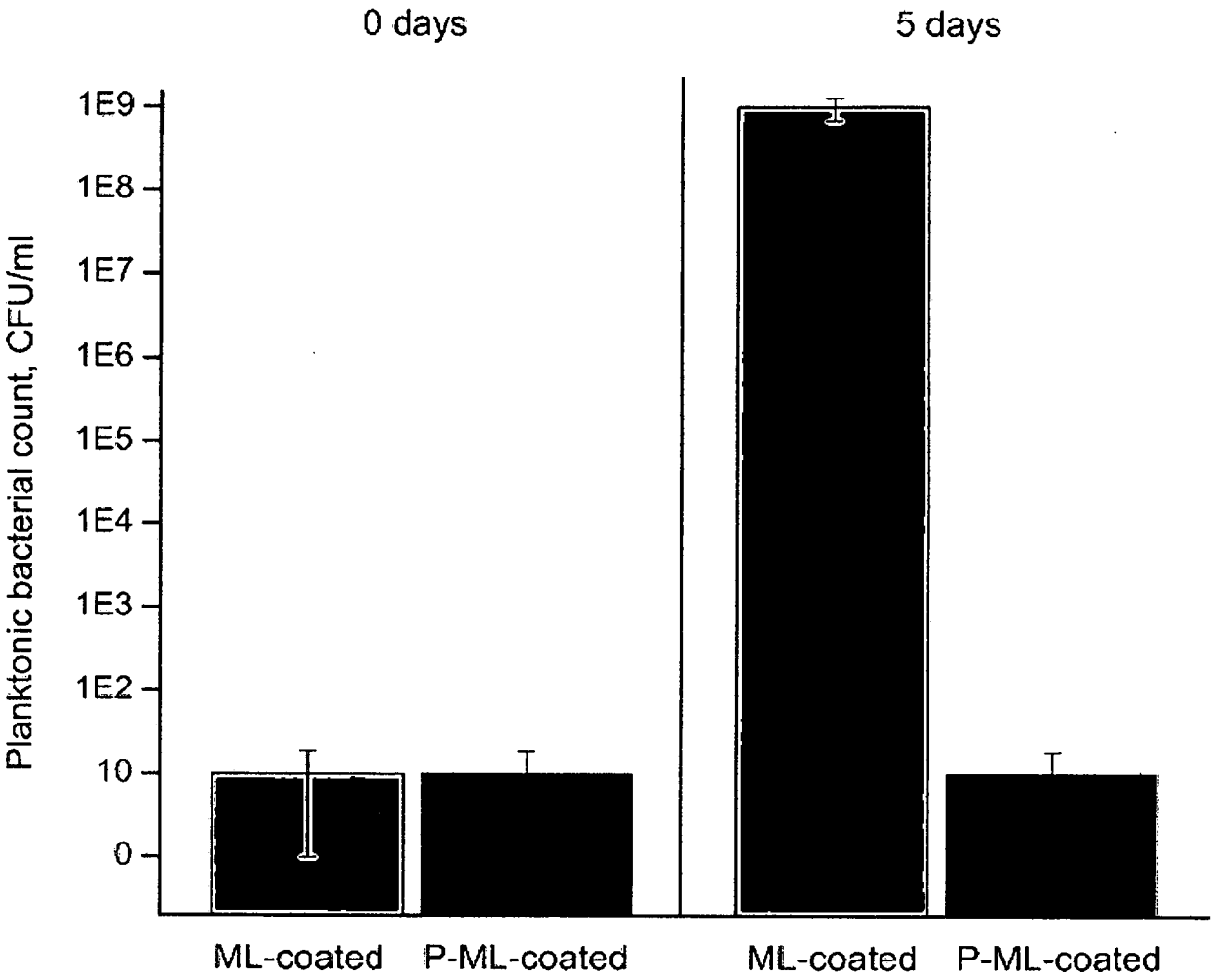

0 days
5 days
Planktonic bacterial count, CFU/ml
1E9
1E8
1E7
1E6
1E5
1E4
1E3
1E2
10
0
ML-coated
P-ML-coated
ML-coated
P-ML-coated

Fig. 3

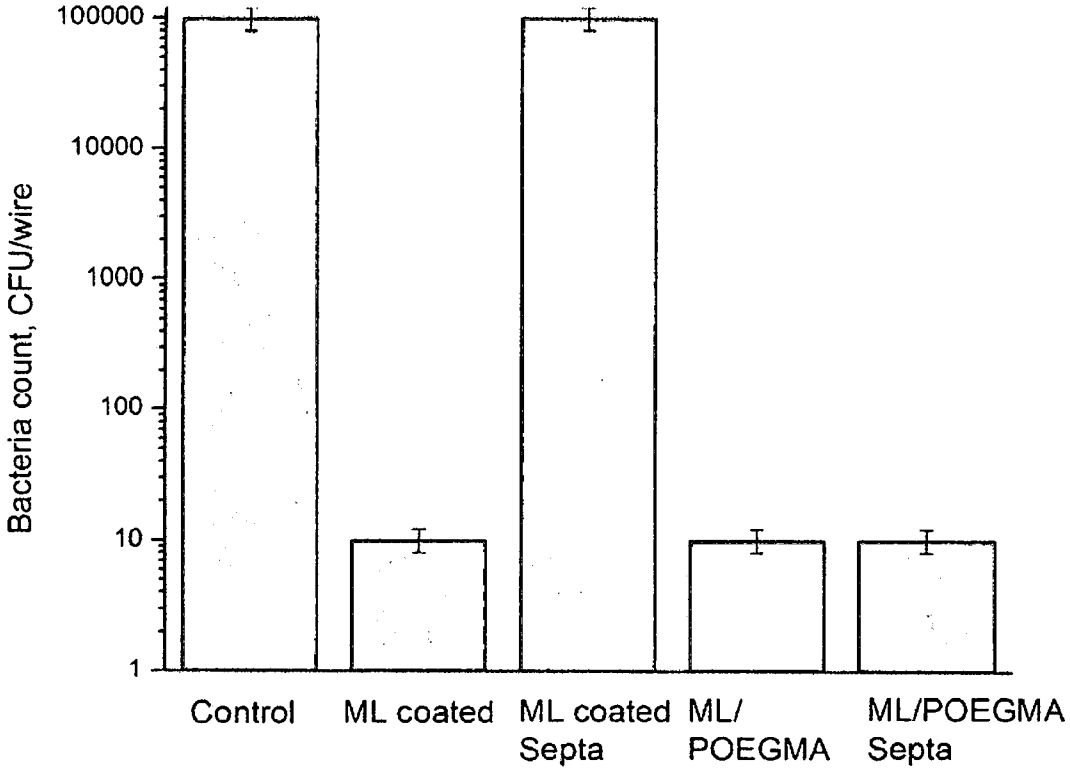

100000
10000
1000
100
10
1
Bacteria count, CFU/wire
Control
ML coated
ML coated Septa
ML/ POEGMA
ML/POEGMA Septa

Fig. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/12346

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 25/10; A01N 25/16; A01N 33/12 (2019.01)
CPC - A01N 25/10; A01N 25/16; A01N 33/12; A01N 41/04; A01N 41/12; A01N 43/40; A01N 59/00; A01N 59/16; A61H 19/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	1st elected invention:	1st elected invention:
X -- Y	US 7,270,678 B2 (Valint, Jr. et al.) 18 September 2007 (18.09.2007); col 2, ln 5, 40, col 6, ln 3-5, 25-35, col 9, ln 20-60	28-32, 39-42, 45, 48 ---------- 1-5, 12-15, 18, 21-23, 24a, 24b, 25-27, 49
Y	US 2007/0166344 A1 (Qu et al.) 19 July 2007 (19.07.2007); abstract, para [0029], [0038], [0056], [0078]-[0079], [0083]-[0084]	1-5, 12-15, 18, 21-23, 24a, 24b, 25-27, 49
A	US 8,308,699 B2 (Zhang et al.) 13 November 2012 (13.11.2012); entire document	1-5, 12-15, 18, 21-23, 24a, 24b, 25-32, 39-42, 45, 48-49
A	Wei et al. "Multifunctional copolymer coating of polyethylene glycol, glycidyl methacrylate, and REDV to enhance the selectivity of endothelial cells" Journal of Biomaterials Science, Polymer Edition. 08 October 2015 (08.10.2015) vol 26, pg. 1357-1371; entire document	1-5, 12-15, 18, 21-23, 24a, 24b, 25-32, 39-42, 45, 48-49
	2nd elected invention:	2nd elected invention:
X	US 8,308,699 B2 (Zhang et al.) 13 November 2012 (13.11.2012); col 2, ln 26-27, col 3, ln 1, col 5, ln 1, col 11, ln 42, col 12, ln 26, 32, 35-36, col 14, ln 61 - col 15, ln 6, col 15, ln 8, 24-28, col 20, ln 14, col 28, ln 1-2	1-2, 4-16, 19-23, 24a, 24b, 25-29, 31-43, 46-49

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 May 2019	28 MAY 2019
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/12346

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 7,270,678 B2 (Valint, Jr. et al.) 18 September 2007 (18.09.2007); entire document	1-2, 4-16, 19-23, 24a, 24b, 25-29, 31-43, 46-49
A	US 2007/0166344 A1 (Qu et al.) 19 July 2007 (19.07.2007); entire document	1-2, 4-16, 19-23, 24a, 24b, 25-29, 31-43, 46-49
A	Wei et al. "Multifunctional copolymer coating of polyethylene glycol, glycidyl methacrylate, and REDV to enhance the selectivity of endothelial cells" Journal of Biomaterials Science, Polymer Edition. 08 October 2015 (08.10.2015) vol 26, pg. 1357-1371; entire document	1-2, 4-16, 19-23, 24a, 24b, 25-29, 31-43, 46-49

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/12346

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
(see supplemental page)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-16, 18-23, 24a, 24b, 25-49

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

--continued from Box No. III--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-49, directed to a copolymer of claim 28, formula I and compositions comprising the same. The copolymer of claim 28 will be searched to the extent that it encompasses the first species of claim 28, represented by a copolymer of formula I wherein A comprises an epoxy; B comprises a hydrophobic group; C is an optional cross-linker; D of Formula I comprises a hydrophilic group; w is 0.1 with the proviso that at least one of x or z is not zero; x is 0; y is 0; z is 0.9. It is believed that claims 1-5, 12-15, 18, 21-32, 39-42, 45 and 48-49 reads on this first named invention, and thus these claims will be searched without fee. Applicant is invited to elect additional compounds of claim 1 wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be copolymer of formula I wherein A comprises an epoxy; B comprises a hydrophobic group; C is an optional cross-linker; D of Formula I comprises a hydrophilic group; w is 0.7 with the proviso that at least one of x or z is not zero; x is 0; y is 0; z is 0.3 (i.e., claims 1-5, 12-14, 18-32, 39-41 and 45-49)

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique copolymer of formula I, which is not required by any other invention of Group I+.

Common technical features:

The inventions of Groups I+ share the technical feature of a copolymer of formula I.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by a document entitled "Multifunctional Copolymer Coating of Polyethylene Glycol, Glycidyl Methacrylate, and REDV to Enhance the Selectivity of Endothelial Cells" to Wei et al. (hereinafter Wei). Wei discloses a copolymer of formula I wherein A comprises an epoxy; B comprises a hydrophobic group; C is an optional cross-linker; D of Formula I comprises a hydrophilic group; w is 0.45 with the proviso that at least one of x or z is not zero; x is 0; y is 0; z is 0.55 (pg. 1362, right col, para 3: PG polymer composed of PEGMA and GMA; Scheme 2: polymer listed; pg. 1363, Table 1: PG-1; 55% PEGMA; 45% GMA).

As said compound was known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+. The inventions of Group I+ thus lack unity under PCT Rule 13.

Note: Claims 1 and 28 lack clarity for ranges of x, y and z; for the purpose of this ISR, ranges for x, y and z are assumed to be x is 0 to 0.9; y is 0 to 0.3 and z is 0 to 0.9.

Note: Applicant's 2nd elected species is suggested to read of claims 1-16, 19-44 and 47-50 (see attached response); however, claims 3 and 30 are incompatible with the elected species wherein A is alkoxyl silyl as they define a moiety X, wherein A is therefor an epoxy. Claim 44 is incompatible as x is defined in range greater than 0.3. Claim 46 does read on the elected species and is included as dependent claim 47 is included. Additionally, Claim 50 is missing. For the purpose of this ISR, the 2nd elected species is assumed to read on claims 1-2, 4-16, 19-23, 24a, 24b, 25-29, 31-43 and 46-49.