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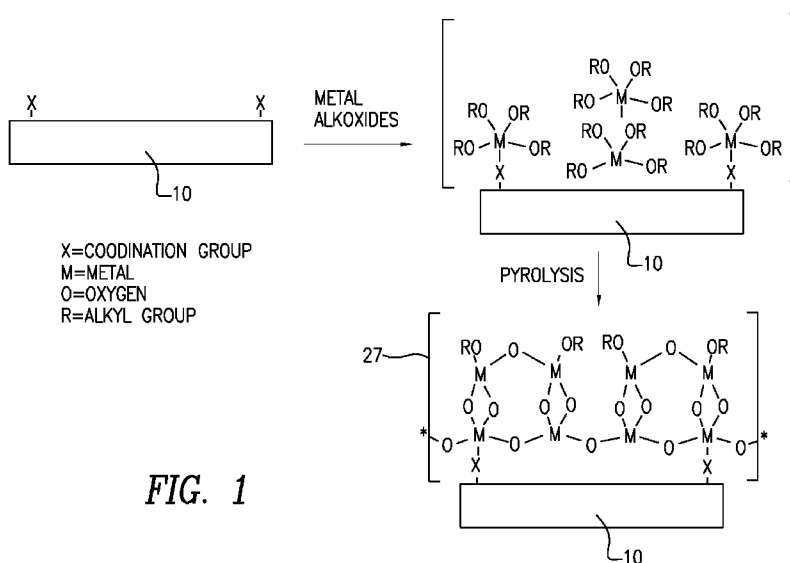


FIG. 1

(57) Abstract: Polymer substrates including adhesion layers for activating the surface of the substrate are provided, thereby allowing the substrate to react with organic, inorganic, metallic and/or organometallic materials. The surface of the polymer substrate is coated with a metal oxide layer that is subjected to conditions adequate to form an oxide adhesion layer. Combining deposition techniques for formation of functionalized polymer surfaces with photolithographic techniques enables spatial control of RGD presentation at the polymer surfaces are achieved with sub-cellular resolution. Surface patterning enables control of cell adhesion location at the surface of the polymer and influences cell shape. Metallization of polymers as described herein provides a means to prepare metal-based electrical circuitry on a variety of flexible substrates.

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FUNCTIONALIZED SUBSTRATES AND METHODS OF MAKING SAME**5 TECHICAL FIELD**

The present invention relates to substrates with activated surfaces. In particular, a thin layer of metal oxide on the surface of a polymer substrate forms an adhesion layer for activating the surface of the substrate.

10 BACKGROUND ART

An activated layer which is bonded to the surface of a substrate is useful in making devices for use as an interface between the substrate and other materials such as organic or metallic materials. This activated layer allows the substrate to react with and to bind to the organic or metallic material.

15 It is well known to develop an organic layer covering a substrate surface using polymerization methods to deposit a polymer layer on the surface. In general these layers do not display good surface conformation. That is, the growth of polymer overlayers tends to occur by surface attachment of monomer moieties at isolated locations across the surface ("islands") which are incorporated into a polymer as polymerization proceeds from these islands outward
20 until the polymeric mass eventually bridges over the surface between "islands", but without forming additional chemical bonds to the surface between the "islands". This growth and bonding pattern tends to form layers which have a thickness equal to many layers of the species comprising the layer (often hundreds of nanometers to microns thick) but which have relatively few bonds between the species comprising the coating layer and the substrate surface.

25 Organic layers comprising bulk polymers, applied for example, by "spin-on" techniques are also well known. These types of coatings also display the same sparse bonding pattern between the substrate surface and the coating. Coated substrates having a low number of bonds per unit area of surface between the coating and substrate surface exhibit poor mechanical attachment between the substrate and the coating and poor electronic communication between
30 the substrate surface and the coating. As a consequence they are not mechanically robust and do not in general display long term stability. Such coatings also may not display efficient charge carrying properties when used in electronic devices. An example of organic monolayers on inorganic substrates is found in U.S. Patent No. 6,146,767, the entirety of which is incorporated herein by reference.

In some applications, it may be necessary to activate the substrate surface before depositing subsequent layers on the surface. The present inventors have previously shown that it is possible to functionalize substrates that contain acidic protons, such as -OH or -NH groups, by their reaction with Group IV alkoxides. This procedure yields a molecular adhesion species that is bound to the surface of the bulk polymer, but is limited to materials that have acidic groups on their surface. See, Dennes, T. J.; Hunt, G. C.; Schwarzbauer, J. E.; Schwartz, J. High-Yield Activation of Scaffold Polymer Surfaces to Attach Cell Adhesion Molecules. *J. Am. Chem. Soc.* **2007**, *129*, 93-97 (p. 95, below Scheme 3, col. 2, lines 20 – 38; p. 96, below Figure 1, col. 1 lines 1 – 24 and col. 2 lines 1 - 6); and Dennes, T. J.; Schwartz, J. Controlling cell adhesion on polyurethanes. *Soft Matter* **2008**, *4*, 86-89 (pg.87, below Scheme 1, col. 1 lines 22 – 24 and col. 2 lines 1 – 19), incorporated herein by reference. Thus biomedically important polyesters and polyketones, which do not have readily acidifiable groups, cannot be employed. Additionally, the adhesion species are individual molecules attached to a polymer surface and do not form a continuous matrix that coats the surface. To that end, it is desirable to functionalize the surface of a polymer substrate with a continuous, thin alkoxide layer that does not require a proton transfer step.

SUMMARY OF THE INVENTION

The present invention provides a broadly applicable chemical process for activation not only of polyamides and polyurethanes, but also polyesters, polyketones, polyethers, polyimides, aramides, polyfluoroolefins, epoxies, or composites containing these polymers.

In one embodiment, the present invention provides activated, or functionalized, polymer surfaces that can be used to covalently bond subsequent material or layers thereof on the surface. The polymer is coated with a thin layer of metal oxide (oxide adhesion layer) in what may be termed a continuous layer. "Continuous layer" as used herein refers to a layer that is formed by a matrix of individual molecules that are chemically bonded and linked to each other, as opposed to individual molecules covering the surface. In the present case, metal alkoxide molecules are bonded together on at least a portion of a polymer surface to form a continuous layer. One major advantage of a continuous layer is that the entirety of the surface that is covered by the continuous metal oxide adhesion layer is activated. In the prior art, where individual molecules are laid on the surface, only the area of the surface where an acidic proton is available, *i.e.*, the area with acidic functionality, can be activated.

In accordance with one aspect of the present invention, a polymer surface may include acidic functionality regions as well as regions coated with a metal alkoxide functionalized layer.

In such embodiments the metal alkoxide functionalized layer may be viewed as filling in the spaces between the regions of acidic functionality.

In accordance with another embodiment metal alkoxide functionalized layers may be applied to regions of polymer having acidic functionality.

5 The metal oxide adhesion layer is thin, about 1nm-1 μ m, preferably about 2 nm, such that it is flexible. The thin layer allows the oxide adhesion layer to bend with the substrate material without cracking, peeling, or breaking.

The coating process involves depositing a metal alkoxide on the polymer, and heating the substrate, with or without partial hydrolysis, so that the metal alkoxide molecules form a
10 continuous metal oxide adhesion layer covalently attached to the polymer surface.

Various polymer surfaces, including surfaces of polyethylene terephthalate (PET) and polyetheretherketone (PEEK), can be functionalized via an alkoxide adhesion layer. By reaction with the adhesion layer RGD-terminated polymer surfaces were prepared and achieved the highest loadings yet reported on polymers (40-180 pmol/cm² or 10-40% spatial coverage) and
15 were successful for enabling attachment and spreading of fibroblasts or osteoblasts *in vitro*. When vapor-deposition techniques for formation of functionalized polymer surfaces are combined with known photolithographic techniques, spatial control of RGD presentation at the polymer surfaces are achieved with sub-cellular resolution. This surface patterning enables control of cell adhesion location at the surface of the polymer and influences cell shape.
20 Metallization of polymers in accordance with the present invention provides a means to prepare metal-based electrical circuitry on a variety of flexible substrates.

BRIEF DESCRIPTION OF THE DRAWINGS

A more complete understanding of the invention may be obtained by reading the
25 following description of specific illustrative embodiments of the invention in conjunction with the appended drawings in which:

FIGURE 1 depicts a schematic exemplary method for activating the surface of a polymer to achieve a composition in accordance with at least one aspect of the present invention;

FIGURE 2 depicts a schematic exemplary method for making a composition in
30 accordance with at least one aspect of the present invention;

FIGURE 3 depicts a schematic exemplary method for making a composition in accordance with at least one aspect of the present invention;

FIGURE 4 depicts a schematic exemplary method in accordance with at least one aspect of the present invention;

FIGURE 5 depicts a schematic exemplary method in accordance with at least one aspect of the present invention;

5 FIGURE 6 depicts a schematic exemplary method of formation of a metal oxide/alkoxide layer on a polymer surface in accordance with at least one aspect of the present invention;

FIGURE 7 depicts a schematic exemplary method of phosphonic acid deposition on an adhesion layer in accordance with at least one aspect of the present invention;

10 FIGURES 8A and 8B are graphical depictions of X-ray photoelectron spectra (XPS) of phosphorous (P) regions (FIGURE 8A) and zirconium (Zr) regions (FIGURE 8B) of an organophosphonate bound to the adhesion layer on PET in accordance with at least one aspect of the present invention;

15 FIGURES 9A and 9B depict atomic force micrograph (AFM) images of PET (FIGURE 9A) and phosphonic acid on PET (FIGURE 9B) in accordance with at least one aspect of the present invention;

FIGURE 10 depicts an exemplary schematic method of binding carboxylic acids and silanes to PET and PEEK via an adhesion layer in accordance with at least one aspect of the present invention;

20 FIGURES 11A-11D depict images of osteoblast cell attachment on derivatized PEEK in accordance with at least one aspect of the present invention. FIGURE 11A depicts cells on RGD-modified PEEK (**30a**), FIGURE 11B depicts C₁₂bisphosphonate (C12BP)-modified PEEK, and FIGURE 11C PEEK control surfaces after 3 h, fixed and stained with anti-vinculin antibodies and fluorescein-conjugated secondary antibodies. Scale bars are 50 μm. FIGURE
25 11D indicates then number of cells per 10x microscope field counted for untreated PEEK, RGD-derivatized, and C12BP-derivatized PEEK;

FIGURE 12 is a schematic depiction of a method of patterning fluorescein or RGD onto PET and PEEK in accordance with at least one aspect of the present invention;

30 FIGURES 12A and 12B are images of patterned fluorescein according to the method depicted in FIGURE 12 on PEEK (FIGURE 12A) and PET (FIGURE 12B) in accordance with at least one aspect of the present invention (scale bars are 50 μm);

FIGURE 13 is an image of patterned rhodamine (red-background) and fluorescein (green-circles) on PET in accordance with at least one aspect of the present invention (scale bar is 50 μm);

FIGURES 14A-14C are images of cells seeded on RGD islands on Nylon 6/6 (FIGURES 14A and 14B) and PET (FIGURE 14C) in accordance with at least one aspect of the present invention. Cells were stained for vinculin-containing focal adhesions in FIGURES 14A and 14B) and labeled with Cell Tracker Green® in FIGURE C. Red circles indicate pattern boundaries in FIGURE 14C (scale bars are 50 μm);

FIGURES 15A and 15B are graphical depictions of electron dispersive X-ray (EDX) analysis before (FIGURE 15A) and after (FIGURE 15B) reduction of a copper salt bound to the adhesion layer with dimethylamineborane (DMAB) in accordance with at least one aspect of the present invention;

FIGURES 16A and 16B are images of EDX maps of Zr (FIGURE 16A) and Cu (FIGURE 16B) features patterned on Kapton® polyimide film in accordance with at least one aspect of the present invention; and

FIGURES 17A and 17B are graphical representations of AFM of Cu “seed” patterned on Kapton® (a registered trademark of DuPont) polyimide film in 10 μm features by DMAB reduction (FIGURE 17A) and AFM of copper-filled “pits” formed by NaBH_4 reduction (FIGURE 17B) in accordance with at least one aspect of the present invention.

It should be noted that the appended drawings illustrate only typical embodiments of this invention and are therefore not to be construed as limiting of its scope, for the invention may admit to other equally effective embodiments. Where possible, identical reference numerals have been inserted in the figures to denote identical elements.

BEST MODE OF CARRYING OUT INVENTION

In the following description, for purposes of explanation, specific numbers, materials and configurations are set forth in order to provide a thorough understanding of the invention. It will be apparent, however, to one having ordinary skill in the art that the invention may be practiced without these specific details. In some instances, well-known features may be omitted or simplified so as not to obscure the present invention. Furthermore, reference in the specification to phrases such as “one embodiment” or “an embodiment” means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least

one embodiment of the invention. The appearances of phrases such as “in one embodiment” in various places in the specification are not necessarily all referring to the same embodiment.

Now referring to FIGURE 1 devices or compositions in accordance with the present invention include a surface activated polymer substrate **10** having coordination groups X, and an
5 oxide adhesion layer **27** bonded to a surface thereof via coordination groups X, wherein the oxide adhesion layer **27** is a metal alkoxide generally depicted as M-O-R. The oxide adhesion layer **27** is one that has been subjected to a process such as but not limited to pyrolysis, microwaving, complete hydrolysis and/or partial hydrolysis.

Polymeric substrate **10** is any polymer that can be functionalized, and may include any of
10 various substances comprising synthetic and/or natural polymer molecules having a surface coordinating group X capable of coordinating with the metal atom M of the metal alkoxide. Examples of suitable polymer substrates include, but are not limited to, polyamides (e.g., proteins), polyurethanes, polyureas, polyesters, polyketones, polyimides, polysulfides, polysulfoxides, polysulfones, polythiophenes, polypyridines, polypyrroles, polyethers, silicones
15 (polysiloxanes), polysaccharides, fluoropolymers, epoxies, aramides, amides, imides, polypeptides, polyethylene, polystyrene, polypropylene, glass reinforced epoxies, liquid crystal polymers, thermoplastics, bismaleimide-triazine (BT) resins, benzocyclobuteneABFGx13, low coefficient of thermal expansion (CTE) films of glass and epoxies, and composites including these polymers. Essentially, any donor-electron pair on the surface of the polymer capable of
20 coordinating with the metal alkoxide is suitable for use with the present invention. In preferred embodiments the polymer substrates are polyethylene terephthalate (PET), polyetheretherketone (PEEK), polyimides, aramides, epoxies, and nylon. The oxide adhesion layer **27** adheres to the surface of the polymer by the covalent bonding between the coordinating group on the surface of the polymer and the metal of the metal alkoxide.

25 Alkoxides of transitional metals are particularly useful for the present invention. Periodic Table Group 3-6 and 13-14 metals are desirable metals for compositions of the present invention. The preferred metals are Zr, Al, Ti, Hf, Ta, Nb, V and Sn, with the most preferred metals being Zr and Ta. Depending upon the position of the transition metal on the Periodic Table, the transition metal alkoxide will have from three to six alkoxide groups or a mixture of
30 oxo and alkoxide groups. Preferred alkoxide groups have from 2 to 4 carbon atoms, such as ethoxide, propoxide, iso-propoxide, butoxide, iso-butoxide, tert-butoxide and fluorinated alkoxide. The most preferred metal alkoxides are zirconium tetra(tert-butoxide) and tantalum pentaethoxide.

Compositions in accordance with the present invention may include additional material bound via the oxide adhesion layer 27 to the polymer substrate 10. Such additional material includes but is not limited to organic, metallic, organometallic or inorganic compounds. The usefulness of the additional material will be apparent to those skilled in the art. For example, further organic material can be used in making biosensors, gene chips and the like, while metals can be laid to make semiconductor chips, flexible electronic devices and circuits or the like. Further organometallic material can be used in making supported catalysts, synthetic reagents and the like, while inorganic materials can be laid down to make seed beds for electroless metal deposition, and antibacterial coatings or the like.

10 Suitable further organic materials, compounds or complexes include but are not limited to organic compound sufficiently acidic to react with a metal oxide or alkoxide; carboxylic, phosphonic, phosphoric, phosphinic, sulfinic, sulfonic and hydroxamic compounds, nucleic acids, polymers, proteins, organic acids, and the like. Now referring to FIGURE 2, for example, the additional material is an organic compound octadecylphosphonic acid (ODPA), which forms
15 a bond as octadecylphosphonate with oxide adhesion layer 27.

Suitable further metallic materials, compounds or complexes include but are not limited to copper, silver, gold, aluminum, nickel, palladium, rhodium and platinum and salts thereof. Now referring to FIGURE 3, copper is exemplified as an additional material.

20 Suitable further organometallic materials, compounds or complexes include but are not limited to organometallic compounds that can react with an oxide, alkoxide, hydroxide or hydroxyl. Examples include but are not limited to alkyls, alkoxides, amides, substituted amides, complexes containing ligands comprising acidic functional groups including phosphonic, carboxylic, phosphinic, hydroxamic, and sulfonic acids.

25 Suitable further inorganic materials, compounds or complexes include but are not limited to inorganic materials with a high dielectric constant, silanes, siloxanes, carboxylates, phosphonates, alkenes, alkynes, alkyl halides, epoxides, carboxylic esters, amides, phosphonate ester and imides.

30 The additional material may be introduced to the oxide adhesion layer by techniques know to those of skill in the art, including but not limited to evaporative, sputter, immersion or extractive deposition. In some embodiments it may be desirable to subject the oxide adhesion layer to complete or partial hydrolysis prior to deposition of the additional material. In some embodiments it may be desirable to subject the deposited additional material to heat or microwave treatment.

The adhesion layer may be functionalized to elicit a biological response, such as but not limited to cell attraction, cell non-adhesion, and cell death by selecting a material for use with a substrate in a biological application. Suitable materials include saccharides, oligosaccharides, polysaccharides, organic acids, nucleic acids, proteins, and peptides.

5 Compositions and devices in accordance with the present invention may form or be included in various devices, including but not limited to cardiovascular implant devices, such as but not limited to stents, replacement heart valves (leaflets, sewing cuffs, and orifice), annuloplasty rings, pacemakers, pacemaker polymer mesh bags, pacemaker leads, pacing wires, intracardiac patches/pledgets, vascular patches, vascular grafts, defibrillators, and intravascular
10 catheters; tissue scaffold devices including but not limited to non-woven meshes, woven meshes, and foams; stents; and bone, joint and spinal implants; bone fixation cerclage; dental and maxillofacial implants; and other devices that would benefit from increased osteoconductivity; neurosurgical devices and implants such as but not limited to shunts and coils; and general surgical devices and implants such as but not limited drainage catheters,
15 shunts, and vascular patches. Specifically, such devices may include an embodiment of the present invention whereby the adhesion layer is functionalized to increase osteoconductivity. Examples of suitable materials/functionalized regions include for example polyetheretherketone (“PEEK”), nylon, polyethylenes, PET, polyurethanes, and silk.

Other devices of the present invention include compositions and materials described
20 herein and further including at least some regions of in the oxide adhesion layer that are functionalized for bioresistance. In one embodiment the oxide adhesion layer is functionalized to include at least one polyethylene glycol bound (PEGylated) region, as is described in further detail hereinbelow in the Experiments.

Compositions and devices in accordance with this embodiment include but are not
25 limited to all devices specific to an application of use by an orthopedic, cardiovascular, plastic, dermatologic, general, maxillofacial or neuro surgeon or physician including, but not limited to, diagnostic implant devices, biosensors, stimulators, diabetic implants such as glucose monitoring devices, external fixation devices, external fixation implants, orthopedic trauma implants, implants for use in joint and spinal disorders/reconstruction such as plates, screws,
30 rods, plugs, cages, scaffolds, artificial joints (e.g., hand, wrist, elbow, shoulder, spine, hip, knee, ankle), wires and the like, oncology related bone and soft tissue replacement devices, dental and oral/maxillofacial devices, cardiovascular implants such as stents, catheters, valves, rings, implantable defibrillators, and the like, contact lenses, ocular implants, keratoprotheses, dermatologic implants, cosmetic implants, implantable medication delivery pumps; general

surgery devices and implants such as but not limited to drainage catheters, shunts, tapes, meshes, ropes, cables, wires, sutures, skin staples, burn sheets, and vascular patches; and temporary/non-permanent implants.

5 In accordance with another embodiment the adhesion layer may be disposed on the substrate in a pattern or micropattern as described in further detail hereinbelow.

In accordance with another embodiment the additional material may be disposed on the adhesion layer in a pattern or micropattern as described in further detail hereinbelow.

The adhesion layer and/or the additional material contain at least two different regions of functionalization.

10 Methods of making compositions and devices in accordance with the present invention include activating a polymer surface comprising the steps of a) contacting a metal alkoxide with the surface; and b) subjecting the metal alkoxide to conditions adequate to form an oxide adhesion layer on the surface. The contacting step may be achieved by any suitable technique known to those skilled in the art such as but not limited to vapor or immersion deposition. The
15 step of forming an oxide adhesion layer may be achieved by subjecting the metal alkoxide to conditions of pyrolysis, microwaving, complete hydrolysis or partial hydrolysis. When heating conditions are employed, it is preferred that the metal alkoxide is heated to between about 50°C and the melting point of the polymer.

Now referring to FIGURE 1, a schematic of one embodiment of the present invention for
20 activating the surface of a polymer is depicted. A polymeric substrate **10** is functionalized according to the method of the present invention by coating at least a surface of the substrate **10** with a thin, continuous layer of metal alkoxide. The molecules of metal alkoxide are first brought into reactive proximity to the polymer molecules such as by, but not limited to, vapor deposition or immersion deposition methods known in the art. If an ultrathin layer is desired,
25 vapor deposition is the preferred process. The deposited metal alkoxide molecules are then heated to between about 50°C and the melting point of the polymer (the heating should not be at or above the melting point of the polymer) to pyrolyze the metal alkoxides. During pyrolysis, the individual metal alkoxide molecules are covalently bonded together forming a continuous metal oxide adhesion layer. It should be appreciated that, although FIGURE 1 shows
30 tetraalkoxides, other metals form different alkoxides. For example, transition metals of Groups 3 and **13** form trialkoxides; transition metals of Group 5 form pentaalkoxides or mixed oxoalkoxides; and transition metals of Group 6 form hexaalkoxides or mixed oxoalkoxides.

In accordance with another embodiment of the present invention, a further step may include reacting the oxide adhesion layer with an additional material selected from an organic,

metallic, organometallic or inorganic compound to bind the additional material to the polymer surface via the oxide adhesion layer. The additional material may be added by reaction with the oxide adhesion layer by various methods available in the art, such as but not limited to evaporative, sputter, immersion or extractive deposition. In one embodiment of the present invention, the material may be added using lithography to lay a pattern of material on to the oxide adhesion layer. Now referring to FIGURES 4 and 5, a lithographic process is depicted for use with the present invention. The polymer surface is completely coated with a photoresist, and is then exposed to UV light through a mask. The areas that were exposed to the UV light can be developed and removed away, leaving openings in the photoresist and access to the polymer surface in small areas. These areas are functionalized with the metal oxide adhesion layer. The photoresist is then dissolved away in acetone leaving small patterned areas in the polymer surface that include the adhesion layer. The patterned areas are preferentially reactive toward organic compounds (FIGURE 4) and metallic species (FIGURE 5).

In accordance with one embodiment, the oxide adhesion layer may be subjected to complete or partial hydrolysis prior to deposition of the additional material to give the oxide adhesion layer with one or more alkoxide groups remaining on the metal atoms. In other embodiments, the deposited additional material is subjected to heat or microwave treatment to give the oxide adhesion layer with one or more alkoxide groups remaining on the metal atoms.

20 Examples

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds and articles of the present invention and practice the claimed methods. The following examples are given to illustrate the present invention. It should be understood that the invention is not to be limited to the specific conditions or details described in these examples.

Example 1 -Formation of a zirconia thin film on polymer substrate

All reagents were obtained from Aldrich and were used as received unless otherwise noted. PET, PEEK, and nylon 6/6 were obtained from Goodfellow, Inc. Acetonitrile was dried over CaH_2 ; and tetrahydrofuran (THF) was dried over KOH overnight. Both were distilled prior to use. Surface modified samples were analyzed using a Midac M25 10C interferometer equipped with a surface optics SOC4000 SH specular reflectance head attachment. Fluorimetry experiments utilized a Photon Technology International Fluorescence Spectrometer.

Polymer substrates (nylon 6/6, PET or PEEK) were placed in a deposition chamber equipped with two stopcocks for exposure either to vacuum or to the vapor of zirconium tetra(tert-butoxide). The chamber was evacuated at 10^{-3} torr for 1 hour and polymer slides were exposed to vapor of zirconium tetra(tert-butoxide) (with external evacuation) for 1 minute followed by 5 minutes exposure without external evacuation. This cycle was repeated twice, after which a heating tape was applied to the chamber, and the internal temperature of the chamber was raised to 60°C and kept at that temperature for 5 minutes (without external evacuation). The chamber was then allowed to cool and was then evacuated at 10^{-3} torr for 1 hour to ensure removal of excess zirconium tetra(tert-butoxide) and to give surface activated polymers (with reference to FIGURE 1, where M=Zr, and R=tert-butyl). AFM section analysis showed the zirconia film to be thin. IR analysis shows that some tert-butoxy groups remain in the deposited and pyrolyzed film.

Further experiments with zirconium tetra(tert-butoxide) employing the following polymers and resins were performed with good results: polyimide Kapton[®], polylactide-*co*-glycolate (PLGA), poly-3-hydroxybutyrate-*co*-valerate (PHBCV), Goretex, and Aramide. It is to be expected that similar treatment of other polymers will yield similar results.

Example 2 -Reaction of phosphonic acid with activated polymers

Activated polymers produced in Example 1 were placed in a 0.1 mM solution of octadecylphosphonic acid (ODPA) in THF for 1 hour, giving phosphonate-bound polymer surfaces (with reference to FIGURE 2, where M=Zr, and R=tert-butyl). Phosphonate-derivatized surfaces are effective at binding bio- or other classes of molecules.

Example 3 -Metallization of activated polymers

Activated polymers produced in Example 1 were treated with an aqueous solution of a copper salt, which was absorbed onto the zirconium oxide adhesion layer. Treatment with either sodium borohydride or an amine borane gave a copper-coated polymer (with reference to FIGURE 3, where M=Zr, and R=tert-butyl). Electron dispersive X-ray based analysis showed the presence of both copper and zirconium.

Example 2a-Reaction of carboxylic acid with activated polymers

Activated PLGA polymer produced in Example 1 was placed in a 0.1 mM solution of maleimidopropionic acid in ethanol for 30 min, giving the maleimidocarboxylate-bound

polymer surface (with reference to FIGURE 10, where M=Zr) to give **29**. This derivatized surface is effective at binding bio- or other classes of molecules (**30a** and **30b**).

Example 3 -Metallization of activated polymers

5 Activated polymers of polyimides, aramides and Goretex composites produced as in Example 1 were treated with an aqueous solution of a copper salt, which was absorbed onto the zirconium oxide adhesion layer. Treatment with either sodium borohydride or an amine borane gave a copper-coated polymer (with reference to FIGURE 3, where M=Zr, and R=tert-butyl). Electron dispersive X-ray based analysis showed the presence of both copper and zirconium.
10 Similarly, silver nitrate was used to deposit silver metal onto activated PET. It is to be expected that similar treatment of other polymers will yield similar results, as will the use of other metal salts using similar reducing agents.

Example 3a. Electroless plating of copper.

15 A sample of Kapton treated first with the zirconium based adhesion layer, then copper sulfate, and then diethylamineborane as described in Example 3 was placed in a copper plating bath at 60°C under nitrogen. The bath consisted of 0.1 M trisodium citrate dihydrate, 1.2 M ethylenediamine, 0.1 M copper sulfate hydrate, 0.03 M ferrous sulfate hydrate, 6.4×10^{-4} M 2,2-dipyridine, 1.2 M NaCl, and sufficient sulfuric acid to give pH = 6. A small amount of PEG 200
20 (2.5 mg) was added to a 50 ml bath.

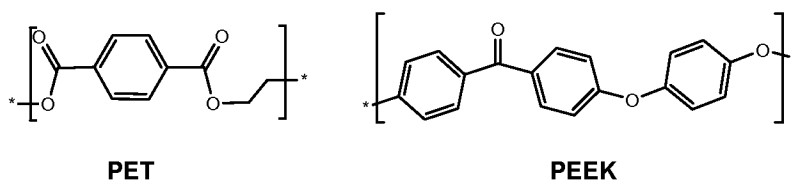
Experiments

Experiment 1

25 Details of the techniques and materials used herein are contained in the Experimental Section.

Formation of Metal Oxide/Alkoxide Adhesion Layers on Polymer Surfaces

Surface derivatization of solid polyethylene terephthalate (PET) and polyetheretherketone (PEEK) (shown below)



proceeded as follows. Polymer films (0.5 mm thick) were treated with vapor of zirconium tetra(*tert*-butoxide) (**1**) or titanium tetra(*tert*-butoxide) (**2**) and were then heated gently to 75 °C. After heating, samples were sonicated for 1 min in dry THF (for PET) or acetonitrile (for PEEK). IR spectra of polymer surface-bound alkoxide/oxide adhesion layers (**27**) showed $\nu_{\text{C-H}}$ = 2976 cm^{-1} , indicative of *tert*-butoxide groups, which initially gave a static water contact angle of 90° and which decreased to 35° by hydrolysis of *tert*-butoxy ligands when the samples were exposed to water overnight (FIGURE 6).

Now referring to FIGURE 7, the adhesion layer **27**-coated polymer films were treated with octadecylphosphonic acid (ODPA) via the tethering-by-aggregation-and-growth (T-BAG) method (see, Hanson, E.; Schwartz, J.; Nickel, B.; Koch, N.; Danisman, M. F. Bonding Self-Assembled, Compact Organophosphonate Monolayers to the Native Oxide Surface of Silicon. *J. Am. Chem. Soc.* **2003**, *125*, 16074-16080 (p. 16076, col. 1 lines 21 - 40), incorporated herein by reference) to yield surface **28**, which had a water contact angle of 95° (Scheme 5-2). IR analysis of **28** showed peaks in the aliphatic region ($\nu_{\text{CH}_2, \text{asym}} = 2920 \text{ cm}^{-1}$; $\nu_{\text{CH}_2, \text{sym}} = 2849 \text{ cm}^{-1}$) characteristic of disordered alkyl chains. See, Gawalt, E. S.; Koch, N.; Schwartz, J. Self-Assembly and Bonding of Alkanephosphonic Acids on the Native Oxide Surface of Titanium, *Langmuir* **2001**, *17*, 5736-5738 (p. 5736, col. 2 lines 1 - 23), incorporated herein by reference. After soaking in deionized water for 24 h and 30 min of sonication in ethanol, X-ray photoelectron spectroscopy of octadecylphosphonate-coated PET (**28**) showed characteristic Zr (3d) and P (2p) bands FIGURES 8A and 8B, which suggested an overall Zr:P ratio of $\geq 2:1$. This ratio is consistent with a model in which the Zr adhesion layer deposits as a bilayer (**27**), and only the topmost layer reacts with the octadecylphosphonate (**28**).

The coated PET was rigorously physically flexed and surface abraded with a Kimwipe®. Now referring to FIGURES 9A and 9B, AFM analysis of **28** showed a film depth of 3-4 nm, which is a reasonable height for the adhesion layer and ODPA; ODPA forms a ca. 2 nm thick film, which suggests a thickness of 1-2 nm for **27**, and is consistent with XPS results.

The relationship between deposition and heating times of **1** and adhesion layer thickness was probed via quartz crystal microgravimetry (QCM). A silicon QCM crystal was placed in the deposition chamber with samples of PET and PEEK. The change in crystal frequency after deposition and heating was related via the Sauerbrey equation (3) to the mass of the adhesion layer that had been deposited on the crystal. Here, μ_q is the shear modulus of quartz ($2.947 \times 10^{11} \text{ g/cm} \cdot \text{s}^2$) and ρ_q is the density of quartz (2.648 g/cm^3).

$$\Delta m = \frac{-\Delta f \sqrt{\mu_q \rho_q}}{4f_0^2} \quad (3)$$

It was observed that longer deposition and heating times (1 hr) produced a ca. 8 nm surface layer, while shorter exposures (5 min) generated a ca. 1 nm layer (ca. 2 monolayers). Layer thicknesses were estimated assuming that the adhesion layer packs similarly to zirconia. To that end, the thickness was calculated as the quotient of the measured aerial surface density of **27** on the QCM crystal (in ng/cm²) and the known density of zirconia (5.89x10⁹ ng/cm³) (Table 1).

Deposit Time (min)	Heat Time (min)	$\Delta f / \Delta m$ (Hz)/(ng/cm ²)	Thickness (nm)	Monolayers
5	10	289±14/594	1	2
10	10	587±11/1206	2	4
60	60	2295±17/4717	8	16

Table 1. Effect of deposition and heating time on adhesion layer thickness.

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Binding Organics to Polymers via the Adhesion Layer

Deposition of an adhesion layer **27** onto the surfaces of PET and PEEK activates them towards reaction with carboxylic acids, phosphonic acids, and silanes; this allows exquisite control of their surface wetting properties and enables the attachment of RGD or other cell-adhesive molecules in high yield. Now referring to FIG. 10, to efficiently tether RGD, polymers coated with **27** were immediately placed in a dry solution of 3-maleimidopropionic acid in acetonitrile to give **29**, which is active for Michael addition of RGDC.

Silanes bound efficiently to PEEK and PET surfaces were derivatized with **27**. The **27**-coated polymer films were soaked for 1 hr in deionized water (to hydrolyze any remaining *tert*-butoxy ligands), blown dry, and soaked for 1 hr in a 0.1 mM solution of octadecyltrichlorosilane (OTS) in acetonitrile. The deposited silane films were crosslinked by soaking in deionized water for 5 min, after which the samples were cleaned by sonication in ethanol for 15 min, to give **31**. Infrared spectra showed ($\nu_{\text{CH}_2, \text{asym}} = 2918 \text{ cm}^{-1}$; $\nu_{\text{CH}_2, \text{sym}} = 2848 \text{ cm}^{-1}$) indicative of disordered alkyl chains, and contact angle analysis indicated an increase in surface hydrophobicity ($\Theta = 95^\circ$ vs. 80° (PET) and 60° (PEEK)).

25

The relationship between the thickness of the adhesion layer **27** and the amount of ODP or OTS bound to a sample surface was probed via QCM. Layers of the adhesion layer **27** with 2-16 monolayers were deposited on silicon-coated QCM crystals. The layers were hydrolyzed and then reacted with ODP or OTS as described previously. The crystals were

rinsed vigorously with methanol, and their frequencies were noted. Interestingly, the coverage (corrected for crystal surface roughness; $R_f = 1.3$) (See, Carolus, M. D.; Bernasek, S. L.; Schwartz, J. Measuring the Surface Roughness of Sputtered Coatings by Microgravity. *Langmuir* **2005**, *21*, 4236-4239 (p. 4237, col. 1 lines 29 - 57), incorporated herein by reference) of OTS or ODPA appears to be independent of the thickness of **27** (Table 2). This indicates that only the topmost layer of **27** is reactive toward organic functionalization.

27 Thickness (nm)	ΔF OTS (Hz)	OTS Coverage (nmol/cm ²)	ΔF ODPA (Hz)	ODPA Coverage (nmol/cm ²)
1	303±3	1.33	185±5	0.94
2	306±5	1.35	192±4	0.98
8	300±7	1.31	190±2	0.97

Table 2 QCM quantification of OTS and ODPA coverage on adhesion layer **27**

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Surface loading of organics bound to PET and PEEK were determined through **30a** by reaction with DANSYL-cys to give **30b**. The fluorescently-labeled polymers were monitored by fluorescence spectroscopy using techniques as described in Dennes, T. J.; Hunt, G. C.; Schwarzbauer, J. E.; Schwartz, J. High-Yield Activation of Scaffold Polymer Surfaces to Attach Cell Adhesion Molecules. *J. Am. Chem. Soc.* **2007**, *129*, 93-97 (p. 94, below Schemes 1 & 2, col. 2 lines 25 – 34; p. 95, below Scheme 3, col. 1 lines 1 – 20; p. 96, below Figure 1, col. 2 lines 1 – 24; p. 97, col. 1 lines 1 – 15 & col. 2 lines 1 - 3) and Danahy, M. P.; Avaltroni, M. J.; Midwood, K. S.; Schwarzbauer, J. E.; Schwartz, J. Self-assembled Monolayers of α,ω -Diphosphonic Acids on Ti Enable Complete or Spatially Controlled Surface Derivatization. *Langmuir* **2004**, *20*, 5333-5337 (p. 5335, below Scheme 3, col. 1 lines 1 - 15), incorporated herein by reference, to measure the stability of **30b** in aqueous conditions and to quantify the amount of material bound to the polymer surface. After the initial removal of synthetic residues, PET and PEEK coated with **30b** showed no desorption of fluorescent material over 7 days. When **30b** was cleaved from the polymer surface by treatment with aqueous solution at pH 12.5, 90 pmol/cm² was measured on both PET and PEEK surfaces, indicating sub-monolayer coverage of the adhesion layer **27**.

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Now referring to FIGURES 11A-11D, *in vitro* experiments were conducted with osteoblast cells to evaluate osteoblast attachment on derivatized PEEK, **30a**, and PEEK-C12BP,

which was prepared by deposition of 1,12-dodecylbisphosphonic acid on **27** via the T-BAG method referenced hereinabove. FIGURE 11A depicts cells on RGD-modified PEEK (**30a**), FIGURE 11B depicts C12BP-modified PEEK, and FIGURE 11C depicts PEEK control surfaces after 3 h, fixed and stained with anti-vinculin antibodies and fluorescein-conjugated secondary antibodies. Scale bars are 50 μm . FIGURE 11D indicates then number of cells per 10x microscope field counted for untreated PEEK, RGD-derivatized, and C12BP-derivatized PEEK. Average values from at least three fields are shown with error bars representing ± 1 standard deviation. Both **30a** and PEEK-C12BP showed increased osteoblast adhesion after 3h versus the PEEK control ($p = 2.3 \times 10^{-4}$ and 6.3×10^{-4} , respectively); **30a** supported significantly greater osteoblast spreading when compared to a PEEK control (Figure 11C).

Adhesion Layer Interfacial Shear Strength Testing

Evaluating interfacial resistance to shear force can help determine a coating's mechanical stability and its utility in implant applications. The current standard in orthopedic implant technology utilizes an hydroxyapatite coating with an interfacial shear strength of ca. 10 MPa. See, Silverman, B. M.; Wieghaus, K. A.; Schwartz, J. Comparative Properties of Siloxane vs. Phosphonate Monolayers on a Key Titanium Alloy. *Langmuir* **2005**, *21*, 225-228 (p. 227, below Table 1, col. 1 lines 1 - 16), and Schwartz, J.; Avaltroni, M.; Danahy, M. Cell attachment and spreading on metal implant materials. *Materials Science & Engineering C* **2002**, *23*, 395-400 (p. 398, col. 2 lines 1 - 9; p. 399, col. 1 lines 1 - 6), incorporated herein by reference. To determine the unoptimized interfacial shear strength of adhesion layer **27** on PEEK, a modified version of a previously reported (Silverman et al, *Langmuir* **2005**, *21*, 225-228) shear strength test was developed. Coupons of PEEK were coated with adhesion layer **27** and epoxy-glued to Ti-6Al-4V coupons. Shear force was exerted parallel to the interface on the glued coupons until a breaking point was achieved. These tests measured interfacial shear strength of 7.8 ± 0.2 MPa before failure for adhesion layer **27**, compared with 3.0 ± 0.2 MPa for control PEEK.

Thus nanoscale metal oxide/alkoxide adhesion layers **27** generated on the surfaces of PEEK and PET are effective for activation of those polymers for further organic chemical transformation. Silanes, carboxylic acids, and phosphonic acids can be easily attached to PET and PEEK through adhesion layer **27**, which allows comprehensive control of their surface wetting properties. This approach was illustrated by tethering cell attractive peptide RGD to the surface of PEEK in high yield (90 pmol/cm^2 or 20 % surface coverage). RGD attachment to PEEK films via adhesion layer **27** proved effective to increase osteoblast adhesion and spreading on that surface; in addition, PEEK surfaces derivatized with C12BP were shown to increase cell

adhesion. Since this activation process involves metal complex coordination to surface groups, it is broadly applicable to other polymers that contain such groups, including polyamides, polyurethanes, polyimides, and poly-thiophenes.

Experimental Section

5 *General.* All reagents were obtained from Aldrich and used as received unless otherwise noted. IR spectra were collected using a Midac Model 2510 spectrometer equipped with a Surface Optics Corp. specular reflectance attachment. Fluorimetry measurements used a Photon Technology International Fluorescence Spectrometer. AFM analysis of films was done using a
10 Digital Instruments Multimode Nanoscope IIIa SPM equipped with silicon tips (Nanodevices Metrology Probes; resonant frequency, 300 kHz; spring constant, 40 N/m) in tapping mode. Quartz crystal microbalance (QCM) measurements were made using an International Crystal Manufacturing standard (clock) oscillator, model 35360, and 10 MHz, AT-cut quartz crystals (ICM) equipped with SiO₂/Si-coated (1000 Å Si/100 Å Cr/1000 Å Au undercoat) electrodes. Curve fitting of core-level XPS peaks was done using CasaXPS software with a Gaussian-
15 Lorentzian product function and non-linear Shirley background subtraction. Standard atomic photoionization cross-section values from the SPECS database were used for quantitative estimations of surface compositions. Dubey, M.; Gouzman, I.; Bernasek, S. L.; Schwartz, J. Characterization of Self-Assembled Organic Films Using Differential Charging in X-Ray Photoelectron Spectroscopy. *Langmuir* **2006**, *23*, 4649-4653 (p. 4650, col. 1 lines 41 - 55)

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Metal oxide/alkoxide adhesion layers. Coupons of PET, PEEK, and Kapton® polyimide film (Goodfellow) and a QCM crystal were placed in a deposition chamber that was equipped with two stopcocks for exposure either to vacuum or to vapor of zirconium tetra(tert-butoxide) (**1**) or titanium tetra(tert-butoxide) (**2**). The chamber was evacuated to 10⁻³ torr for 30 minutes, and
25 polymer films were exposed to vapor of **1** or **2** (with external evacuation) for 30 seconds followed by 5 min exposure without external evacuation. At this time, the stopcock of the metal alkoxide was closed, heating tape was applied, and the samples were heated to 75 °C for 5 min, then allowed to cool to room temperature. The chamber was then evacuated for 30 min at 10⁻³ torr to ensure removal of excess **1** or **2** and to give surface activated polymers. The QCM crystal
30 was rinsed with THF and methanol; its measured change in frequency indicated the amount of alkoxide complex that had been deposited. The above procedure yields an adhesion layer of ca. 1 nm, or two monolayers. If exposure and heating times are increased, thicker layers can be achieved (Table 1).

Formation of surface metal-carboxylate complexes. Polymer surfaces activated with the metal oxide/alkoxide adhesion layer were placed in a dry solution of either 3-maleimidopropionic acid (0.1 mM) in acetonitrile for 1 hr to generate maleimido-derivatized surfaces, or 0.1 mM solutions of DANSYL-cys or fluorescein for 1 hr to generate fluorophore-derivatized surfaces.

5

Silanization of polymer surfaces. After deposition of the metal oxide/alkoxide adhesion layer, polymers were soaked in deionized water for 1 hr to hydrolyze all remaining *tert*-butoxide ligands. The hydrolyzed surfaces were dried *in vacuo* and were then soaked for 1 hr in a dry 0.1 mM solution of 3-aminopropyltriethoxysilane or octadecyltrichlorosilane in acetonitrile. The silane films were soaked in a 75/25 (v/v) solution of acetonitrile/water for 15 min for crosslinking, and were then sonicated first in acetonitrile for 15 min, then in ethanol for 15 min.

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Formation of phosphonate monolayers on polymer surfaces. Polymer surfaces derivatized with adhesion layer 27 were hydrolyzed in water overnight, sonicated in ethanol for 5 min, and functionalized via the T-BAG method as previously described. Briefly, polymer samples were suspended in a 0.1 mM solution of a phosphonic acid (11-hydroxyundecyl phosphonic acid or octadecylphosphonic acid in THF, or 1,12-dodecylbisphosphonic acid in 95/5 (v/v) THF/methanol). The solvent was allowed to evaporate over 3-5 hrs, and samples were then baked at 120 °C (below the T_g) for 24 hrs. Samples were sonicated in ethanol for 15 min, yielding phosphonate monolayers. The use of THF as a solvent with PEEK is to be avoided; methanol is used instead.

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Determination of hydrolytic stability and surface loading. DANSYLATED polymer films were immersed in pH 7.5 aqueous solution for 3 days and were monitored via fluorescence spectroscopy for loss of DANSYL from the polymer surfaces. Surface loading was determined via cleavage of the remaining DANSYL molecules in aqueous solution (pH 12.5) for 3 hrs.

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Quartz Crystal Microgravimetry Crystal Roughness Factor (R_f) Determination. Surface roughness was measured using a modified Brunauer-Emmett-Teller (BET) experiment. See, Carolus, M. D.; Bernasek, S. L.; Schwartz, J. Measuring the Surface Roughness of Sputtered Coatings by Microgravity. *Langmuir* **2005**, *21*, 4236-4239 (p. 4237, col. 1 lines 29 - 57), incorporated herein by reference. An ICM oscillator drove silicon QCM crystals whose resonant frequencies were monitored using a Hewlett Packard 5200 series frequency counter. Each QCM crystal was rinsed with methanol, blown dry in a stream of N_2 , and mounted in a

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vacuum chamber equipped with ports for electrical wiring. The pressure inside the chamber was reduced to less than 1 torr and the frequency of the QCM crystal was allowed to stabilize. The chamber was next isolated from active vacuum, and opened to a vial containing tetramethylsilane (TMS), which was held in a water bath at room temperature. The vacuum chamber was filled with TMS ($P_{\text{vap}} = 630$ torr), reevacuated, and again filled with TMS while frequency readings were recorded in 10 torr increments. An adsorption isotherm was obtained by plotting the frequency of the crystal from 0-630 torr of TMS. The roughness factor was calculated as follows: A plot was made of $\chi/\Delta f(1-\chi)$ versus χ , where χ is the partial pressure of TMS, for $0.05 < \chi < 0.35$. A linear fit of this plot gave a slope and intercept, which was used to obtain a dimensionless constant, C (4), and allowed calculation of the frequency change at monolayer coverage (f_m , (5)). The Sauerbrey equation (3) allowed calculation of the mass of probe molecules adsorbed at monolayer coverage, which could be extrapolated to an area for monolayer coverage of TMS, assuming the molecular “footprint” of TMS to be 40 \AA^2 . The roughness factor was calculated as the quotient of the monolayer derived area and the nominal area of the QCM crystal.

$$C = 1 + \text{slope/intercept} \quad (4)$$

$$f_m = 1/[C(\text{intercept})] \quad (5)$$

In Vitro cell response. Osteoblast response to PEEK surfaces was evaluated *in vitro*. Osteoblasts maintained in DMEM with glutamine, Penn Strep, G418, and 10% calf serum (Hyclone) were removed from TCPS plates using 0.1 mg/mL trypsin LE express (Invitrogen) and were prepared as previously described. See, Danahy, M. P.; Avaltroni, M. J.; Midwood, K. S.; Schwarzbauer, J. E.; Schwartz, J. Self-assembled Monolayers of α,ω -Diphosphonic Acids on Ti Enable Complete or Spatially Controlled Surface Derivatization. *Langmuir* **2004**, *20*, 5333-5337 (p. 5335, below Scheme 3, col. 1 lines 16 - 33). Cells (1.0×10^5 cells/mL in serum-free media) were added to 24-well tissue culture plates containing PEEK samples and incubated at $34 \text{ }^\circ\text{C}$. After 90 min, medium was replaced with fresh, serum-free DMEM. At 3 h cells were fixed, permeabilized, and stained with anti-vinculin antibody (Sigma) followed by fluorescein goat anti-mouse secondary antibody. Images were obtained as described previously. See, Midwood, K. S.; Schwarzbauer, J. Tenascin-C Modulates Matrix Contraction via Focal Adhesion Kinase- and Rho-mediated Signaling Pathways. *Mol. Biol. Cell* **2002**, *13*, 3601 (p. 3602, col. 2 lines 5 - 57). Cell adhesion was quantified by counting the number of attached cells in at least 3 microscope fields.

Shear Strength Testing. PEEK coupons (Goodfellow) were cut to be 1.125" x 0.5". These PEEK coupons were sanded with 220- and 400- grit SiC paper to a smooth finish, sonicated in EtOH for 15 min, and surface functionalized with adhesion layer **27**. The adhesion layer-coated surfaces were hydrolyzed in water for 5 min, sonicated in EtOH for 15 min, and joined to clean
5 Ti-6Al-4V coupons using a 1.5 cm² piece of Cytec Fiberite FM 1000 epoxy, which was placed between the coupons in a vise. The samples were heat-cured by ramping the oven temperature from 25 °C to 170 °C at 2 degrees per min, and holding the temperature at 170 °C for 90 min. The joined coupons were placed in a stainless steel holder, which was placed in an Instron Model 1331 load testing machine, and the samples were pulled apart at 100 µm/sec while a
10 computer interface recorded the point of maximum shear stress, when failure occurred.

Experiment 2

Patterned Zirconium Oxide/Alkoxide Adhesion Layers on PET and PEEK

The deposition of metal oxide/alkoxide adhesions layers on polymers is also amenable to spatial
15 control via photolithography. The initial chemical vapor deposition of a metal alkoxide precursor allows precise control over spatial substrate exposure. Now referring to FIGURE 12, to demonstrate this, samples of PET and PEEK were patterned with photoresist as described in detail below in the below Experimental Section, and treated with vapor of zirconium tetra(tert-
butoxide) (**1**). The samples were heated to generate patterned areas of the zirconium
20 oxide/alkoxide adhesion layer **27** and reacted with 3-maleimidopropionic acid (to give a surface active for RGDC coupling) or fluorescein (to generate samples for fluorescence microscope imaging). Samples were sonicated in acetone to remove the remaining photoresist, giving **33**
and **34**. Now referring to FIGURES 12A and 12B, when **33** was imaged with a fluorescence microscope, patterned features as small as 2x2 µm were observed; this is likely sufficient
25 resolution to allow control of cell shape.

A reaction scheme was devised that would allow two species to be patterned at the surfaces of PET and PEEK. Clean samples of PET and PEEK were exposed to vapor of **1** and heated to give comprehensive coverage of adhesion layer **27**, which was hydrolyzed in water for 5 min. The polymers were next patterned photolithographically and were again exposed to
30 vapor of **1** and heated to give patterned areas of adhesion layer **27**, which were reacted immediately with 3-maleimidopropionic acid (to generate RGDC binding sites) or fluorescein (for fluorescence microscope imaging). Next, samples were sonicated in acetone to remove remaining photoresist, derivatized with HUPA via the T-BAG method, and reacted with PEG-SS (to deactivate the background for cell adhesion) or 5(6)-carboxy-X-rhodamine N-

succinimidyl ester (for fluorescence microscope imaging). Now referring to FIGURE 13, fluorescently-labeled samples indicated that the reaction scheme was successful, with fluorescein clearly bound in active areas and rhodamine bound in background areas.

5 Evaluation of Cell Response to Patterned Substrates

The response of NIH3T3 cells to **32**-derivatized Nylon 6/6 and **34**-derivatized PET was observed *in vitro*. Now referring to FIGURES 14A-14C, cells adhered preferentially to the RGD-patterned areas of **32** within 3 h, and on staining for vinculin, focal adhesions were visualized. Cells seeded on RGD islands on Nylon 6/6 (FIGURES 14A and 14B) and PET
10 (FIGURE 14C) are depicted. Cells were stained for vinculin-containing focal adhesions (FIGURES 14A and 14B) and labeled with Cell Tracker Green (Molecular Probes, Inc). Circles indicate pattern boundaries in FIGURE 14C. Cells clustered inside square RGD “islands” and spread to fill them. On **34**, cells were labeled with Cell Tracker Green (Molecular Probes, Inc.) and allowed to attach and spread for 3 h. Cells preferentially attached and spread inside circular
15 RGD islands.

Thus, spatially-controlled derivatization of Nylon 6/6, PET, and PEEK was made possible by the coupling of traditional photolithography with the chemical vapor deposition of zirconium alkoxides. Fluorescence microscopy showed the conformance of the chemistry to the predetermined patterns, and *in vitro* cell response on the patterned polymers was achieved,
20 allowing spatial control of cell adhesion and spreading on the polymer substrates. Doubly-patterned substrates are believed to improve the ability of patterned polymeric surfaces to holistically control cell attachment and morphology.

Experimental Section

General. All chemicals were obtained from Aldrich and used as received unless
25 otherwise noted. Acetonitrile and THF were dried over CaH₂ and KOH, respectively, and were distilled prior to use. Fluorescence microscope images were obtained using a Nikon Optiphot-2 microscope (Garden City, NY), and images were captured using a Photometrics Coolsnap camera (Tucson, AZ) and analyzed using IP lab software.

Photolithography. Films of nylon 6/6, PET, Kapton® polyimide film, and PEEK
30 (Goodfellow) were sonicated in ethanol for 15 minutes and blown dry in a stream of N₂ prior to use. For spatial control of surface functionalization, polymer films were spin-coated with 2 drops AZ® 5214-E photoresist at 4000 rpm for 30 s. The samples were annealed at 95 °C for 45 s, and were exposed to UV (365 nm) at 950 mW/cm² for 5 min. Samples were developed in a

50/50 (v/v) solution of AZ® 312 MIF developer and water for 1 minute, rinsed in deionized water, blown dry in a stream of N₂, and evacuated at 10⁻³ torr for 1 hr.

Spatially-controlled formation of Zr-amidate. Photopatterned nylon 6/6 was placed in a deposition chamber that was equipped with two stopcocks for exposure either to vacuum or to vapor of **1**. The chamber was evacuated to 10⁻³ torr for 30 minutes, and polymer films were exposed to vapor of **1** (with external evacuation) for 30 seconds followed by 5 min exposure without external evacuation. This cycle was repeated twice, and the chamber was then evacuated for 30 min at 10⁻³ torr to ensure removal of excess **1**, and gave surface amidate complexes.

Spatially-controlled formation of metal oxide/alkoxide adhesion layers. Photopatterned PET, PEEK, and Kapton® (a registered trademark of DuPont) polyimide film (obtained from Goodfellow) were placed in a deposition chamber that was equipped with two stopcocks for exposure either to vacuum or to vapor of **1**. The chamber was evacuated to 10⁻³ torr for 30 minutes, and polymer films were exposed to vapor of **1** (with external evacuation) for 30 seconds followed by 5 min exposure without external evacuation. At this time, the stopcock for the metal alkoxide was closed, a heating tape was applied, and the samples were heated to 75 °C for 5 min, and allowed to cool to room temperature. The chamber was then evacuated for 30 min at 10⁻³ torr to ensure removal of excess **1**, and to give surface activated polymers. The above procedure yields an adhesion layer of ca. 1 nm. If exposure and heating times are increased, thicker layers can be achieved.

Fluorophore Derivatization. Patterned samples were immersed in a dry, 0.1 mM solution of fluorescein in acetonitrile for 1 hr, removed, and rinsed/sonicated in acetone to remove remaining photoresist. Sonication for 15 min in ethanol followed by drying in a stream of N₂ gave fluorescein patterned polymers that were imaged with a fluorescence microscope.

RGD derivatization. Patterned samples were immersed in a dry 0.1 mM solution of 3-maleimidopropionic acid for 1 hr and sonicated in acetone to remove remaining photoresist. After a 15 min sonication in ethanol, samples were placed in a 0.1 mM aqueous solution of RGDC (American Peptide) for 24 hrs, which was adjusted to pH 6.5 using aqueous NaOH. Samples were soaked in deionized water for 30 min, blown dry in a stream of N₂, and stored for tissue culture studies.

Doubly-patterned RGD and PEG derivatization on nylon 6/6. Zr-complex patterned samples were immersed in a dry 0.1 mM solution of 3-maleimidopropionic acid for 1 hr and sonicated in acetone to remove remaining photoresist. After a 15 min sonication in ethanol, samples were blown dry with N₂ and placed in a deposition chamber that was equipped with two stopcocks for exposure either to vacuum or to vapor of **1**. The chamber was evacuated to 10⁻³ torr for 30 minutes, and polymer films were exposed to vapor of **1** (with external evacuation) for 30 seconds followed by 5 min exposure without external evacuation. This cycle was repeated twice, and the chamber was then evacuated for 30 min at 10⁻³ torr to ensure removal of excess **1**, and gave surface amidate complexes that backfilled the previously blank areas. Samples were placed in a dry 0.1 mM solution of 11-hydroxyundecylphosphonic acid in THF for 1 hr, sonicated in ethanol for 15 min, and blown dry in a stream of N₂. Samples were next placed in a dry 0.1 mM solution of polyethylene glycol succinimidyl succinate (5000 MW, Laysan Inc.) in acetonitrile for 36 hrs. After a 15 min ethanol sonication, samples were placed in a 0.1 mM aqueous solution of RGDC (American Peptide) for 24 hrs, which was adjusted to pH 6.5 using aqueous NaOH. Samples were soaked in deionized water for 30 min, blown dry in a stream of N₂, and stored for tissue culture studies.

Doubly-patterned RGD and PEG derivatization on PET and PEEK. Clean polymer samples were placed in a deposition chamber that was equipped with two stopcocks for exposure either to vacuum or to vapor of **1**. The chamber was evacuated to 10⁻³ torr for 30 minutes, and polymer films were exposed to vapor of **1** or **2** (with external evacuation) for 30 seconds followed by 5 min exposure without external evacuation. At this time, the stopcock for the metal alkoxide was closed, a heating tape was applied, and the samples were heated to 75 °C for 5 min, and then allowed to cool to room temperature. The chamber was then evacuated for 30 min at 10⁻³ torr to ensure removal of excess **1**, and to give surface activated polymers. The polymers were sonicated for 1 min in dry THF, and subsequently hydrolyzed in water for 5 min. Samples were photolithographically patterned as previously described and were again placed in a deposition chamber that was equipped with two stopcocks for exposure either to vacuum or to vapor of **1** or **2**. The chamber was evacuated to 10⁻³ torr for 30 minutes, and polymer films were exposed to vapor of **1** or **2** (with external evacuation) for 30 seconds followed by 5 min exposure without external evacuation. This cycle was repeated twice, and the chamber was then evacuated for 30 min at 10⁻³ torr to ensure removal of excess **1** to give surface metal complexes that were reacted immediately with 3-maleimidopropionic acid (0.1 mM solution in dry

acetonitrile) for 1 hr. The remaining photoresist was washed away in acetone and a layer of 11-hydroxyundecylphosphonic acid was backfilled into the unreacted areas via the T-BAG method of Hansen et al. previously referenced hereinabove (*J. Am. Chem. Soc.* **2003**, *125*, 16074-16080). The samples were reacted with a 0.1 mM solution of polyethylene glycol succinimidyl succinate (PEG-SS, 5000 MW, Laysan) in dry acetonitrile for 36 hrs. The samples were sonicated in ethanol and reacted for 24 hrs in a 0.1 mM solution of RGDC (American Peptide), which had been adjusted to pH 6.5 with NaOH (aq). Doubly-patterned samples were soaked in deionized water for 30 min, blown dry in a stream of N₂, and stored in a desiccator for later use.

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Doubly-patterned fluorophore derivatization. Polymer samples were treated in the same way as described for doubly-patterned RGD and PEG, but fluorescein was used in lieu of 3-maleimidopropionic acid, and 5(6)-carboxy-X-rhodamine N-succinimidyl ester (Fluka) was used in lieu of PEG succinimidyl succinate. Samples were visualized with a fluorescence microscope to show correspondence with the expected pattern.

15

In vitro cell performance. Cell response to polymer surfaces was evaluated *in vitro*. NIH3T3 cells maintained in Dulbecco's Modified Eagle's Medium (DMEM) with 10% calf serum (Hyclone) were prepared for cell adhesion experiments as previously described (Danahy et al., *Langmuir* **2004**, *20*, 5333-5337). Cells (1 x 10⁵/mL in DMEM with 10% calf serum) were added to 24-well tissue culture dishes containing untreated or derivatized polymer surfaces. After 90 minutes, medium with non-adherent cells was removed and replaced with fresh DMEM. At 3 hr cells were fixed, permeabilized, and stained with anti-vinculin antibody (Sigma) followed by fluorescein goat anti mouse secondary antibody (for focal adhesions), and DAPI (for DNA). Images were obtained as described previously (Midwood et al., *Mol. Biol. Cell* **2002**, *13*, 3601-3613). Brightness and contrast of color levels were adjusted with IPLab software.

20

25

Control of Stem Cell Differentiation. It has been shown that the shape of mesenchymal stem cells (MSC's) influences their differentiation. Chen, et al., Micropatterned surfaces for control of cell shape, position, and function, *Biotechnol. Prog.* **1998**, *14*, 356-363 (p. 357, col. 2 lines 36 – 67 and p.360, below Figure 3, col. 1 lines 6 - 19); McBeath et al., Cell Shape, Cytoskeletal Tension, and RhoA Regulate Stem Cell Lineage Commitment. *Develop. Cell* **2004**, *6*, 483-495 (p. 485-486; p. 487, col. 2 lines 1 – 8; p. 488-489; p. 490, col. 2 lines 1 – 43),

30

incorporated herein by reference. MSC's that were forced to spread maximally inside $100\ \mu\text{m}^2$ fibronectin squares (adsorbed on tissue-culture polystyrene) differentiated preferentially into osteoblasts, while MSC's constrained on circles of $10\ \mu\text{m}$ diameter became adipocytes (Figure 7-1). Since simple adsorption is not a favorable surface functionalization scheme for a device (see, Falconnet et al., Surface engineering approaches to micropattern surfaces for cell-based assays *Biomaterials* **2006**, 27, 3044-3063, (p. 3045, col. 1 lines 17 - 28)), the new polymer surface-patterning schemes presented hereinabove present an alternative for improved control of cell shape on a polymeric tissue scaffold, enabling preferential development of different tissues at different sites in a scaffold.

10

Experiment 3

Polymer Metallization

As described hereinabove, the zirconium oxide/alkoxide adhesion layer **27** nucleates the growth of copper metal on and adhesion to PET and Kapton® polyimide film surfaces; this approach provides a basis for patterned metallization of polymer-based device substrates.

Adhesion layer **27** can serve as a matrix to enable polymer surface metallization. In a typical procedure Kapton® polyimide film was coated with a 5 nm thick layer of adhesion layer **27** and was then soaked in a 200 mM aqueous solution of CuSO_4 . Samples were rinsed in deionized water, and EDX analysis confirmed the presence of Cu and S (Figure 7-2). After subsequent (slow) reduction by dimethylamine borane (1M, aqueous, 6 hrs, $50\ ^\circ\text{C}$), metallic copper was formed. Metallization was also done using adhesion layer **27** patterned on Kapton® polyimide film. The metallized surface was subjected to sonication in water and physical rubbing with a Q-tip, which was followed by EDX (FIGURES 15A and 15B). In this way it was shown that patterns of both Zr and Cu on the Kapton® polyimide film surface faithfully replicated the mask design (FIGURES 16A and 16B).

Now referring to FIGURES 17A and 17B, a corresponding pattern was also observed by AFM. The thickness of the generated copper "seed" was measured via AFM to be ca. 20 times thicker than the starting film of adhesion layer **27** (Figure 17A); indicating that adhesion layer **27** nucleates the growth of CuSO_4 (observed by EDX, FIGURES 15A and 15B) at the polyimide surface. Interestingly, CuSO_4 -treated Kapton® polyimide film was reduced rapidly using aqueous sodium borohydride, which also gave copper metal; here, AFM analysis shows the Cu pattern to be buried into the polymer surface in pits the tops of which in many cases were about 500 nm below the polymer surface (FIGURE 17B). It is believed that the relatively faster

borohydride reduction is sufficiently exothermic so that the polymer melts in the vicinity of the reduction reaction.

Because adhesion layer 27 is thin (ca. 5 nm), it is resistant to cracking by physically flexing the polymer, adhesion layer 27 is a suitable matrix for polymer metallization with copper. Copper "seed" layers can serve as nucleation sites for bulk copper growth by electroless deposition processes (Gu et al., Organic Solution Deposition of Copper Seed Layers onto Barrier Metals. *Mat. Res. Soc. Symp. Proc.* **2000**, 612, D9.19.1-D9.19.6 (p. D9.19.2, lines 33 – 40; p. D9.19.5, lines 14 - 22)). In conjunction with photolithographic patterning, this further metallization of the polymer provides a means to prepare copper-based electrical circuitry on a variety of flexible substrates under simple laboratory conditions.

Experimental Section

General. All chemicals were obtained from Aldrich and used as received unless otherwise noted. Acetonitrile and THF were dried over CaH_2 and KOH, respectively, and were distilled prior to use. Fluorescence microscope images were obtained using a Nikon Optiphot-2 microscope (Garden City, NY), and images were captured using a Photometrics Coolsnap camera (Tucson, AZ) and analyzed using IP lab software. AFM analysis of films used a Digital Instruments Multimode Nanoscope IIIa SPM equipped with silicon tips (Nanodevices Metrology Probes; resonant frequency, 300 kHz; spring constant, 40 N/m) in tapping mode.

Metallization of Kapton® polyimide film and PET. Patterned or un-patterned copper metallization of the polymer surfaces was achieved by soaking an activated polymer surface in a 200 mM aqueous solution of CuSO_4 overnight, followed by reduction in 1M aqueous dimethylamine borane or sodium borohydride for 6 hrs. Copper metallization was confirmed by Energy Dispersive X-ray Analysis, which was done using a FEI XL30 FEG-SEM equipped with a PGT-IMIX PTS EDX system.

Although certain presently preferred embodiments of the invention have been specifically described herein, it will be apparent to those skilled in the art to which the invention pertains that variations and modifications of the various embodiments shown and described herein may be made without departing from the spirit and scope of the invention. Accordingly, it is intended that the invention be limited only to the extent required by the appended claims and the applicable rules of law.

All references cited herein are incorporated fully by reference.

CLAIMS

What is claimed is:

1. A process for activating a polymer surface comprising the steps of a) contacting a metal alkoxide with the surface; and b) subjecting the metal alkoxide to conditions adequate to form an oxide adhesion layer on the surface, the conditions selected from one or more of the group consisting of pyrolysis, microwaving, complete hydrolysis and partial hydrolysis.
5
2. The process according to claim 1, wherein step a) comprises vapor deposition or immersion deposition.
10
3. The method of claim 1, wherein step b) comprises heating the metal alkoxide to between about 50°C and the melting point of the polymer.
4. The method of claim 1, wherein the metal alkoxide is zirconium tetra(tert-butoxide).
15
5. The method of claim 1, wherein the metal is a Group 3-6 or Group 13-14 transition metal.
6. The method of claim 1, wherein the alkoxide is selected from the group consisting of ethoxide, propoxide, iso-propoxide, butoxide, iso-butoxide, tert-butoxide and fluorinated alkoxide.
20
7. The method of claim 1, further comprising reacting the oxide adhesion layer with an additional material selected from an organic, metallic, organometallic or inorganic compound to bind the additional material to the polymer surface via the oxide adhesion layer.
25
8. The method according to claim 7 wherein the additional material comprises an organic compound sufficiently acidic to react with a metal oxide or alkoxide.
9. The method according to claim 8 wherein the additional material comprises an organic compound selected from the group consisting of a carboxylic, phosphonic, phosphoric, phosphinic, sulfinic, sulfonic and hydroxamic compound.
30
10. The method according to claim 7 wherein the additional material comprises a metallic compound.

11. The method according to claim 10 wherein the metallic compound comprises Cu, Ag, Au, Al, Ni, Rh, Pd, Pt.
12. The method according to claim 10 wherein the metallic compound is copper sulfate.
- 5 13. The method according to claim 10 wherein the metallic compound is silver nitrate.
14. The method according to claim 7 wherein the additional material comprises an organometallic compound that can react with an oxide, alkoxide, hydroxide or hydroxyl or π -
10 bond.
15. The method according to claim 7 wherein the additional material comprises an inorganic compound.
- 15 16. The method according to claim 7 wherein the additional material is selected from the group consisting of silanes, siloxanes, carboxylates, phosphonates, alkenes, alkynes, alkyl halides, epoxides, carboxylic esters, amides, phosphonate esters and imides.
17. The method according to claim 7 wherein the additional material is introduced to the oxide
20 adhesion layer by evaporative or sputter deposition.
18. The method according to claim 7 wherein the additional material is introduced to the oxide adhesion layer by immersion or extractive deposition.
- 25 19. The method according to claim 7, comprising optionally subjecting the oxide adhesion layer to complete or partial hydrolysis prior to deposition of the additional material.
20. The method according to claim 7, further comprising subjecting a deposited additional material to heat or microwave treatment.
- 30 21. The method according to claim 20 wherein the additional material is a metal.
22. The method according to claim 20 wherein the additional material is an inorganic compound with a high dielectric constant.

23. The method according to claim 20 wherein the additional material comprises a flexible circuit device.
24. The method according to claim 7 wherein the additional material comprises one or more
5 polymers.
25. The method according to claim 1 comprising functionalizing the adhesion layer to elicit a biological response.
- 10 26. The method according to claim 25 wherein the biological response is cell attraction and the adhesion layer comprises a material selected from an organic acid, nucleic acid, protein, and peptide.
27. The method according to claim 1, wherein the adhesion layer is continuous.
- 15 28. The method of claim 1, wherein the polymer surface contains a surface coordinating group that is capable of coordinating with the metal atom of the metal alkoxide.
29. The method of claim 1, wherein the polymer is selected from the group consisting of
20 polyamides, polyurethanes, polyureas, polyesters, polyketones, polyimides, polysulfides, polysulfoxides, polysulfones, polythiophenes, polypyridines, polypyrroles, polyethers, silicones, polyamides, polysaccharides, fluoropolymers, amides, imides, polypeptides, polyethylene, polystyrene and polypropylene.
- 25 30. The method of claim 1, wherein the polymer is selected from the group consisting of polyethylene terephthalate (PET), polyetheretherketones (PEEK), and nylon.
31. A composition comprising a polymer substrate having a surface, and an oxide adhesion layer bonded to the surface, wherein the oxide adhesion layer comprises a metal alkoxide
30 subjected to treatment by one or more of the group consisting of pyrolysis, microwaving, complete hydrolysis and partial hydrolysis.
32. The composition of claim 31, wherein the metal alkoxide is zirconium tetra(tert-butoxide).

33. The composition of claim 31, wherein the metal is a Group 3-6 or Group 13-14 metal.
34. The composition of claim 31, wherein the alkoxide is selected from the group consisting of ethoxide, propoxide, iso-propoxide, butoxide, iso-butoxide, tert-butoxide and fluorinated
5 alkoxide.
35. The composition of claim 31, comprising an additional material selected from an organic, metallic, organometallic or inorganic compound disposed on the oxide adhesion layer.
- 10 36. The composition according to claim 35 wherein the additional material comprises an organic compound sufficiently acidic to react with a metal oxide or alkoxide.
37. The composition according to claim 35 wherein the additional material comprises an organic compound selected from the group consisting of a carboxylic, phosphonic, phosphoric,
15 phosphinic, sulfinic, sulfonic and hydroxamic compound.
38. The composition according to claim 35 wherein the additional material comprises a metallic compound or metal.
- 20 39. The composition according to claim 31 wherein the metallic compound comprises Cu, Ag, Au, Al, Ni, Rh, Pd or Pt or a salt thereof.
40. The composition according to claim 31 wherein the metallic compound is copper sulfate.
- 25 41. The composition according to claim 31 wherein the metallic compound is silver nitrate.
42. The composition according to claim 31 wherein the additional material comprises an organometallic compound that can react with an oxide, alkoxide, hydroxide, hydroxyl or π -bond.
- 30 43. The composition according to claim 35 wherein the additional material comprises an inorganic compound.

44. The composition according to claim 35 wherein the additional material is selected from the group consisting of silanes, siloxanes, carboxylates, phosphonates, alkenes, alkynes, alkyl halides, epoxides, carboxylic esters, amides, phosphonate ester and imides.
- 5 45. The composition according to claim 35 wherein the additional material is introduced to the oxide adhesion layer by evaporative or sputter deposition.
46. The composition according to claim 35 wherein the additional material is introduced to the oxide adhesion layer by immersion or extractive deposition.
- 10 47. The composition according to claim 35, wherein the oxide adhesion layer is optionally subjected to complete or partial hydrolysis prior to deposition of the additional material.
48. The composition according to claim 35, comprising subjecting a deposited additional
15 material to heat or microwave treatment.
49. The composition according to claim 48 wherein the additional material is a metal.
50. The composition according to claim 48 wherein the additional material is an inorganic
20 compound with a high dielectric constant.
51. The composition according to claim 48 wherein the additional material comprises a flexible circuit device.
- 25 52. The composition according to claim 35 wherein the additional material comprises one or more polymers.
53. The composition according to claim 31 wherein the adhesion layer is functionalized to elicit a biological response.
- 30 54. The composition according to claim 53 wherein the biological response is cell attraction and the adhesion layer comprises a material selected from an organic acid, nucleic acid, protein, and peptide.

55. A cardiovascular or vascular implant device comprising the composition according to claim 31.

56. The device according to claim 55 selected from the group stents, replacement heart valves, replacement heart valve components, leaflets, sewing cuffs, orifices, annuloplasty rings, pacemakers, pacemaker polymer mesh bags, pacemaker leads, pacing wires, intracardiac patches/pledgets, vascular patches, vascular grafts, intravascular catheters, and defibrillators.

57. A tissue scaffold device comprising the composition according to claim 31.

10

58. The device according to claim 57 selected from the group non-woven meshes, woven meshes, and foams.

59. The composition according to claim 31 wherein the adhesion layer is functionalized to increase osteoconductivity.

15

60. The composition according to claim 59 wherein the adhesion layer comprises a material selected from a Group 3-6 or Group 13-14 metal oxide or a a Group 3-6 or Group 13-14 metal mixed oxide alkoxide.

20

61. An orthopedic implant device comprising the composition according to claim 31.

62. The device according to claim 61 selected from an orthopedic trauma implant, joint implant, spinal implant, plate, screw, rods, plug, cage, pin, nail, wire, cable, anchor, scaffold, artificial joint selected from a hand joint, wrist joint, elbow joint, shoulder joint, spine joint, hip joint, knee joint and ankle joint; bone replacement, bone fixation cerclage and dental and maxillofacial implants.

25

63. A spine implant device comprising the composition according to claim 31.

30

64. The device according to claim 63 selected from the group intervertebral cages, pedicle screws, rods, connectors, cross-links, cables, spacers, facet replacement devices, facet augmentation devices, interspinous process decompression devices, interspinous spacers,

vertebral augmentation devices, wires, plates, spine arthroplasty devices, facet fixation devices, bone anchors, soft tissue anchors, hooks, spacing cages, and cement restricting cages.

5 65. The composition according to claim 31 wherein the adhesion layer is functionalized for bioresistance.

66. The composition according to claim 65 wherein the adhesion layer comprises at least one PEGylated region.

10 67. A device comprising a composition according claim 65 selected from the group of diagnostic implant, biosensor, glucose monitoring devices, external fixation device, external fixation implant, external facial fracture fixation devices and implants, orthopedic trauma implants and devices selected from plates, wires, screws, rods, nails, pins, cables, spacing cages, cement restricting cages; cardiovascular devices and implants selected from stents, replacement
15 heart valves, replacement heart valve components, leaflets, sewing cuffs, orifices, annuloplasty rings, pacemakers, pacemaker polymer mesh bags, pacemaker leads, pacing wires, intracardiac patches/pledgets, vascular patches, vascular grafts, and intravascular catheters; contact lens, intraocular implants, keratoprotheses; neurosurgical devices and implants selected from shunts, coils; general surgical devices and implants selected from drainage catheters, shunts, tapes,
20 meshes, ropes, cables, wires, sutures, skin staples, burn sheets, and vascular patches; and temporary/non-permanent implants.

25 68. The composition according to claim 31 wherein the adhesion layer is disposed on the substrate in a pattern or micropattern.

69. The composition according to claim 35 wherein the additional material is disposed on the adhesion layer in a pattern or micropattern.

30 70. The composition according to claim 31 wherein the adhesion layer and/or the additional material contain at least two different regions of functionalization.

71. The composition according to claim 31, wherein the adhesion layer is continuous.

72. The composition of claim 31, wherein the polymer surface contains a surface coordinating group that is capable of coordinating with the metal atom of the metal alkoxide.

73. The composition of claim 31, wherein the polymer is selected from the group consisting of
5 polyamides, polyurethanes, polyureas, polyesters, polyketones, polyimides, polysulfides, polysulfoxides, polysulfones, polythiophenes, polypyridines, polypyrroles, polyethers, silicones, polysiloxanes, polysaccharides, fluoropolymers, amides, imides, polypeptides, polyethylene, polystyrene, polypropylene, glass reinforced epoxies, liquid crystal polymers, thermoplastics, bismaleimide-triazine (BT) resins, benzocyclobutene polymers, Ajinomoto Buildup Films
10 (ABF), low coefficient of thermal expansion (CTE) films of glass and epoxies, and composites including these polymers.

74. The composition of claim 31, wherein the polymer is selected from the group consisting of
15 polyethylene terephthalate (PET), polyetheretherketones (PEEK), and nylon.

75. The composition of claim 31, wherein the alkoxide is selected from the group consisting of ethoxide, propoxide, iso-propoxide, butoxide, iso-butoxide and tert-butoxide.

76. The composition according to claim 35, wherein the additional material comprises copper.
20

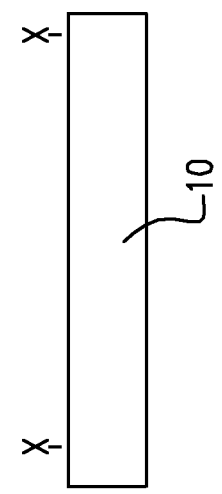
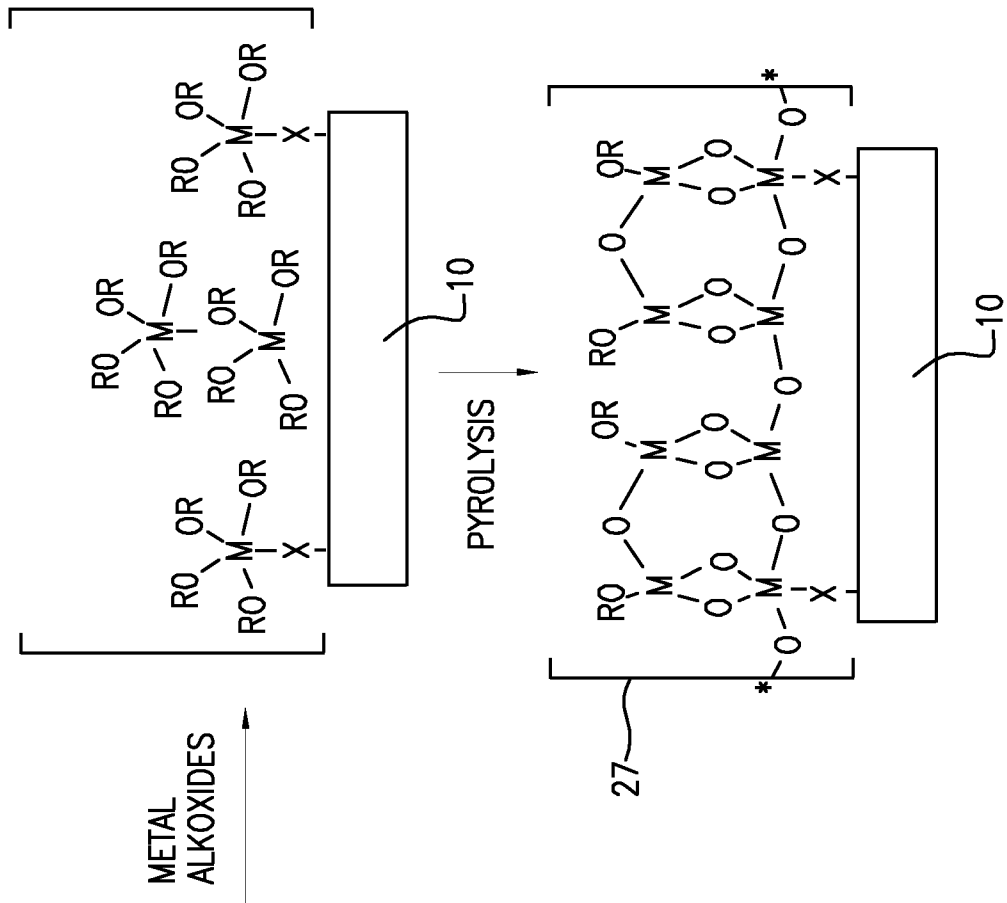
77. The composition according to claim 35, wherein the additional material comprises copper formed from an electroless copper solution.

78. The composition according to claim 31, wherein the polymer is one or more dielectric films,
25 and the additional material comprises a one or more metallic layers.

79. The composition according to claim 31, where the polymer is selected from glass reinforced epoxies, liquid crystal polymers, thermoplastics, bismaleimide-triazine resins, benzocyclobutene polymers, Ajinomoto Buildup Films, low coefficient of thermal expansion films of glass and
30 epoxies, and composites including these polymers.

80. The composition according to claim 31, where the polymer is a patterned dielectric film, and comprising one or more metallic layers forming an electrical circuit.

- 81 A dental implant device comprising the composition according to claim 31.
82. A maxillofacial implant device comprising the composition according to claim 31.
- 5 83 A general surgical device comprising the composition according to claim 31 selected from drainage catheters, shunts, tapes, meshes, ropes, cables, wires, sutures, skin staples, burn sheets, and vascular patches.
- 10 84. A sports medicine device comprising the composition according to claim 31 selected from staples, bone anchors, soft tissue anchors.



X=COORDINATION GROUP
M=METAL
O=OXYGEN
R=ALKYL GROUP

FIG. 1

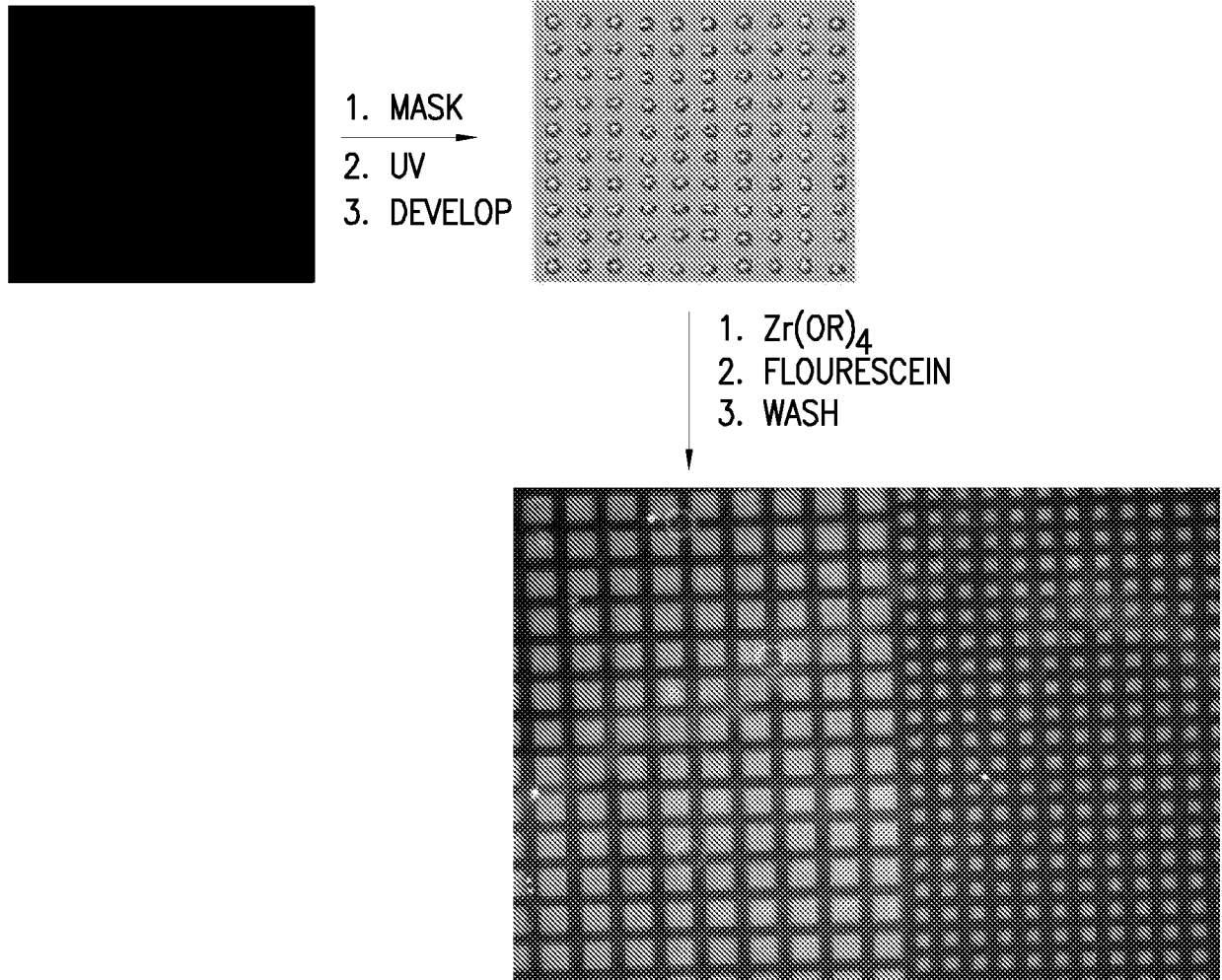


FIG. 4

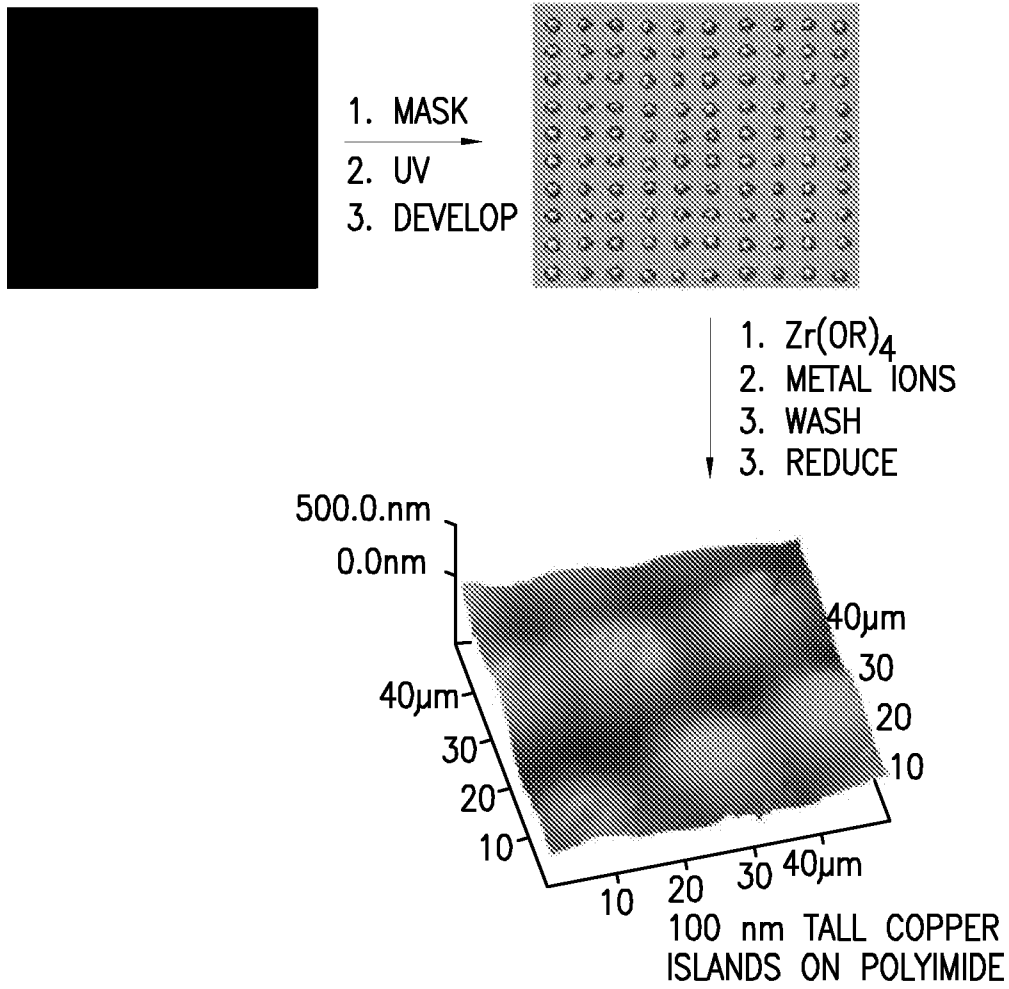


FIG. 5

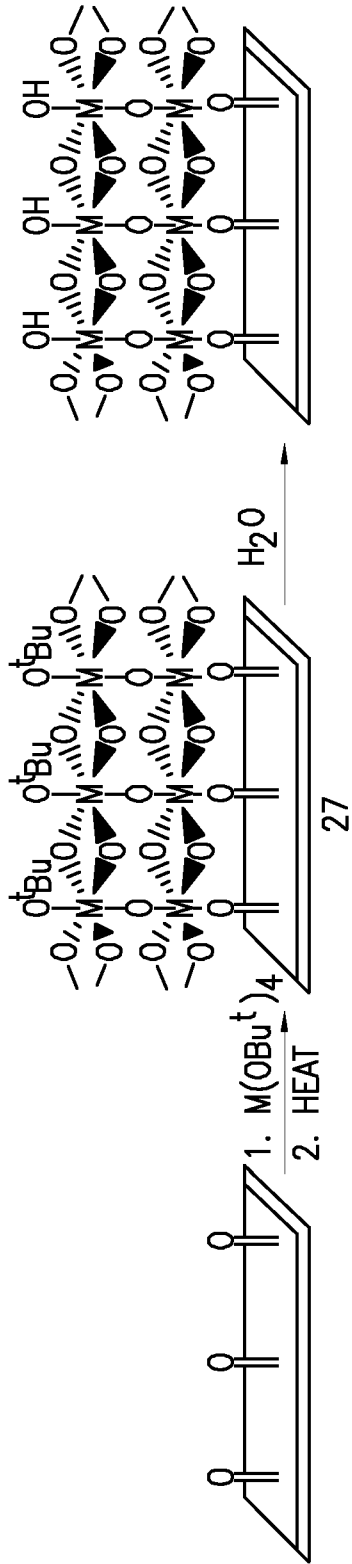


FIG. 6

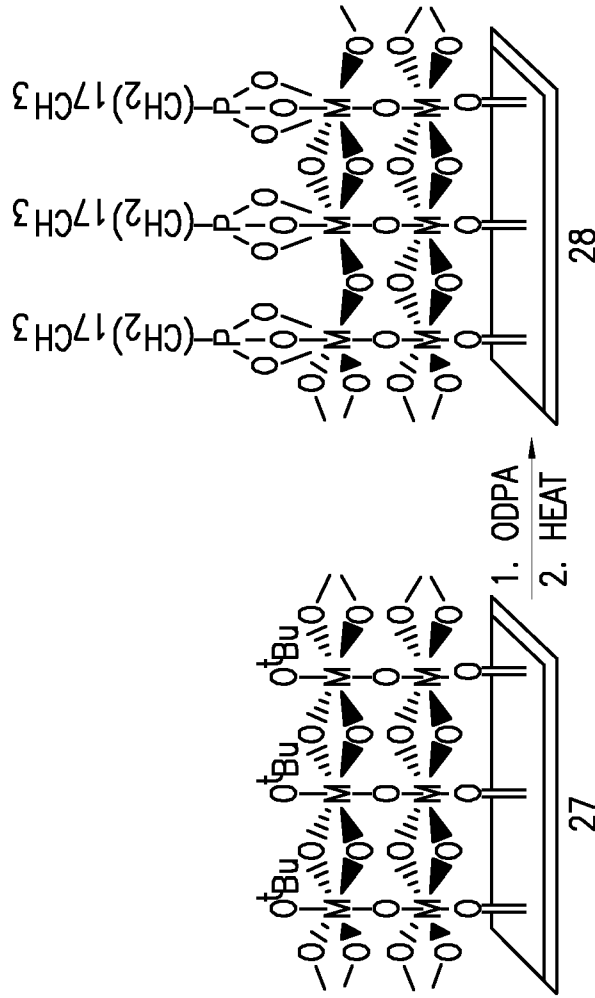


FIG. 7

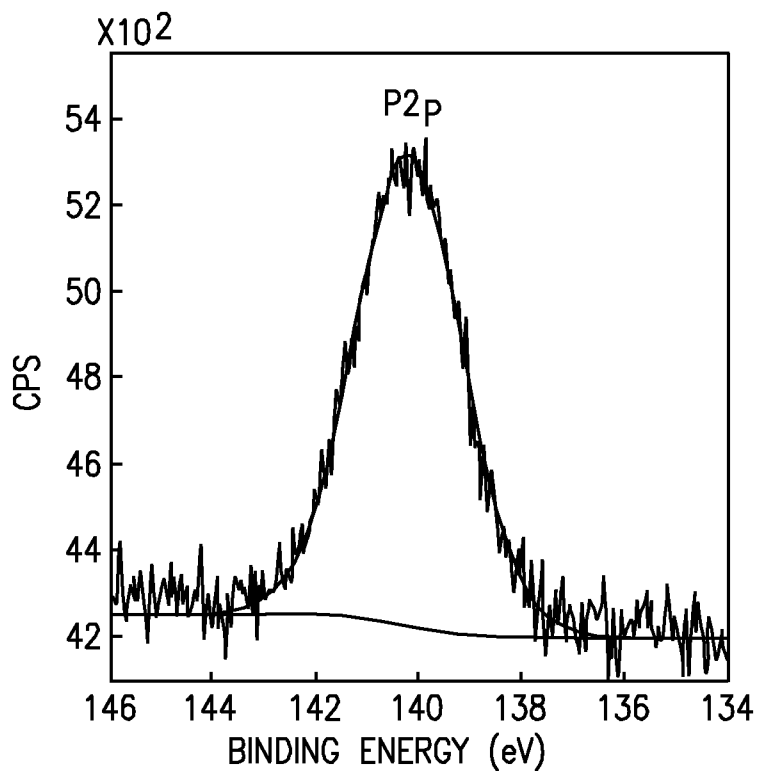


FIG. 8A

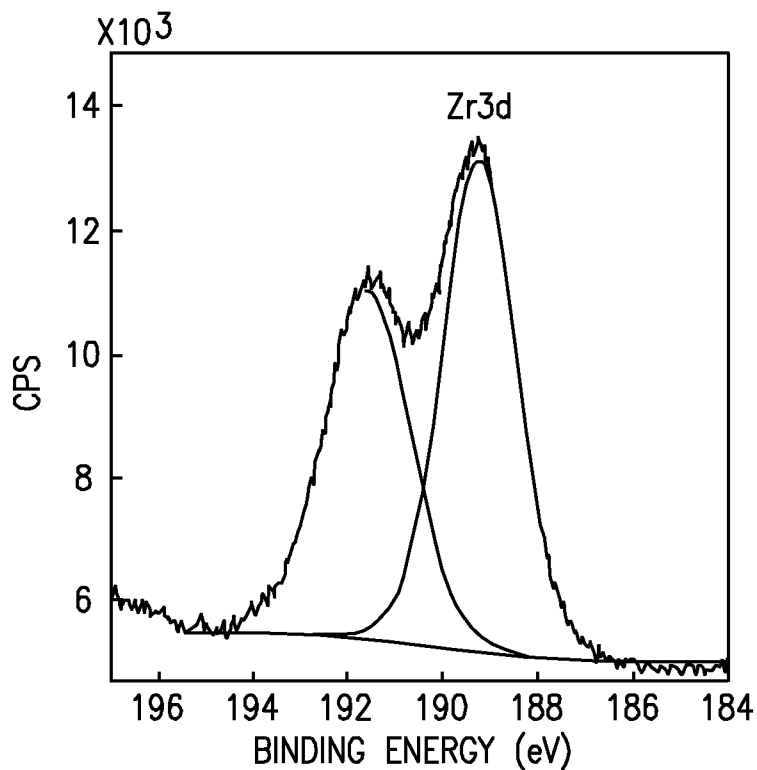


FIG. 8B

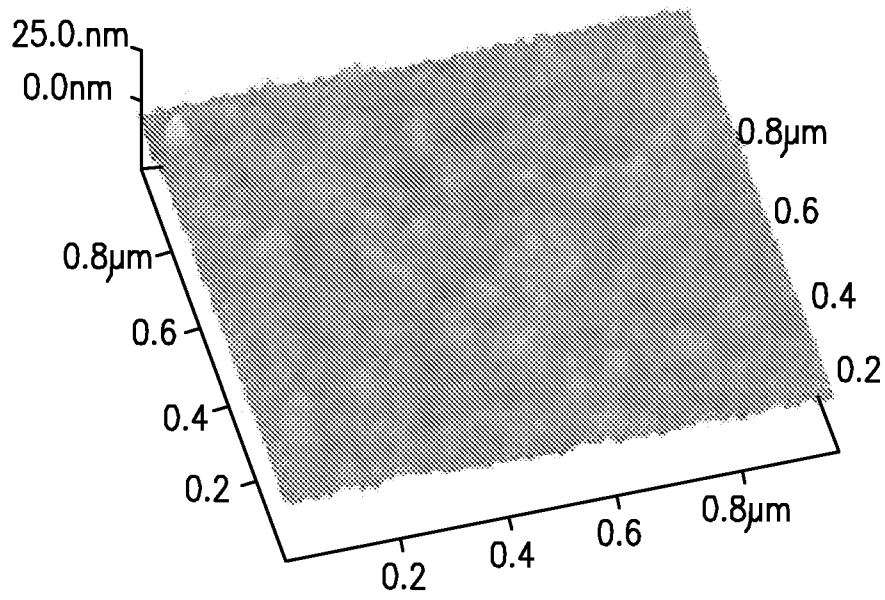


FIG. 9A

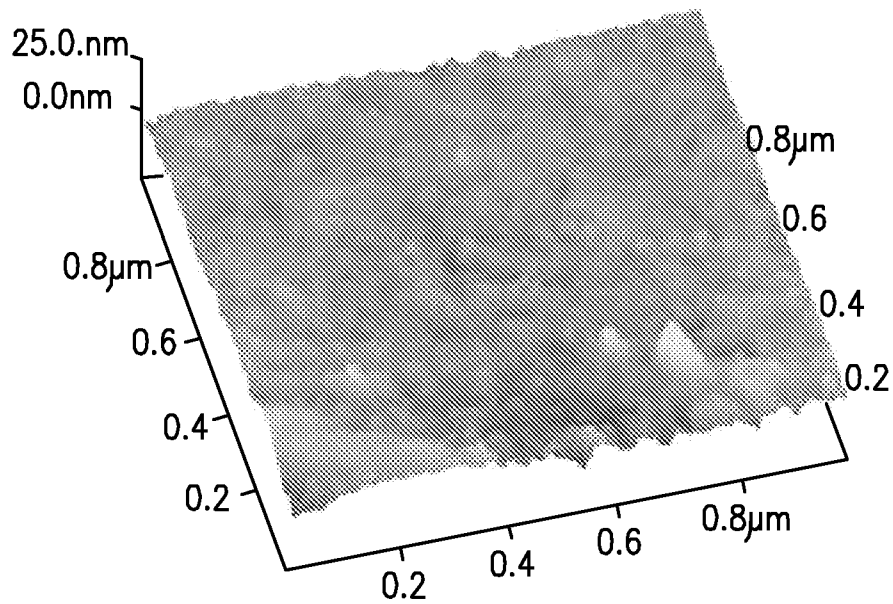


FIG. 9B

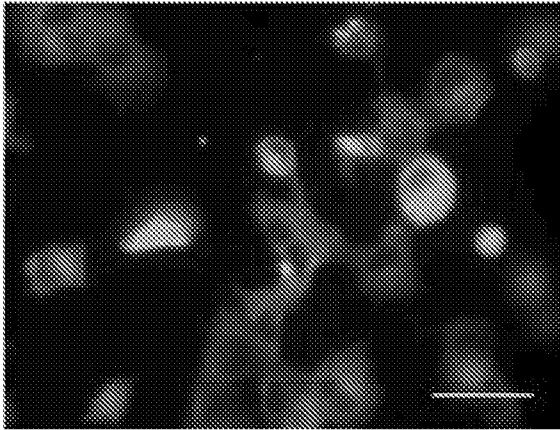


FIG. 11A

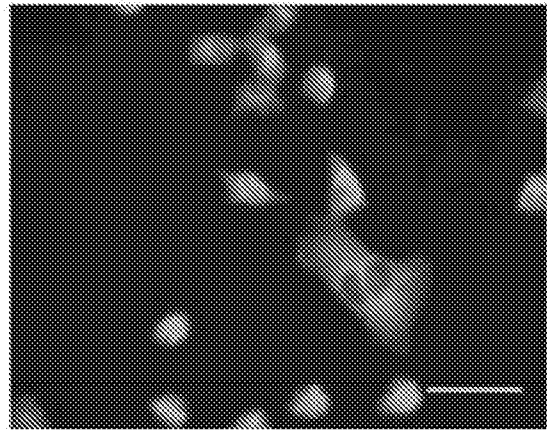


FIG. 11B

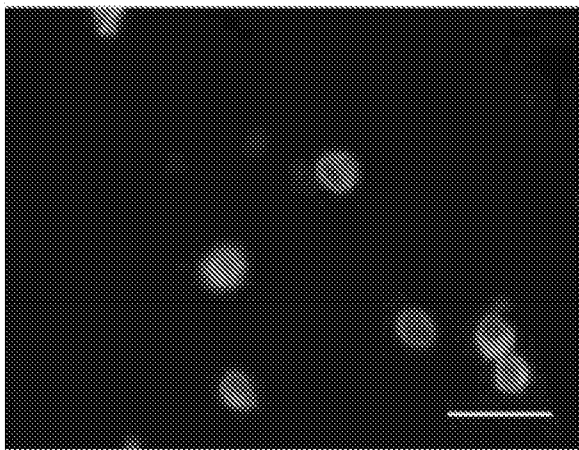


FIG. 11C

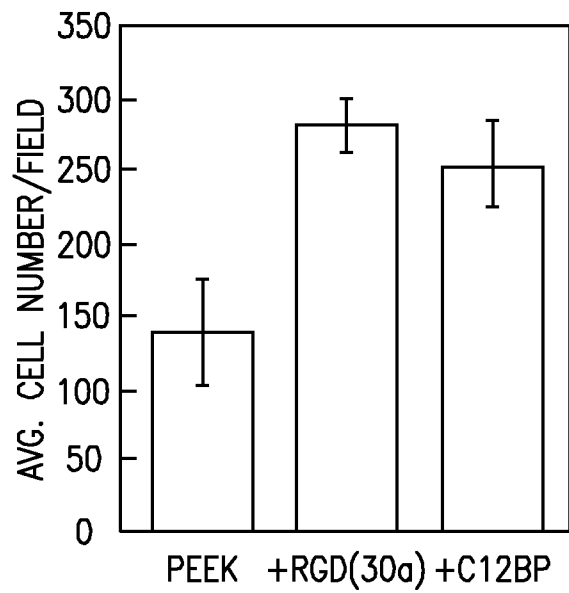


FIG. 11D

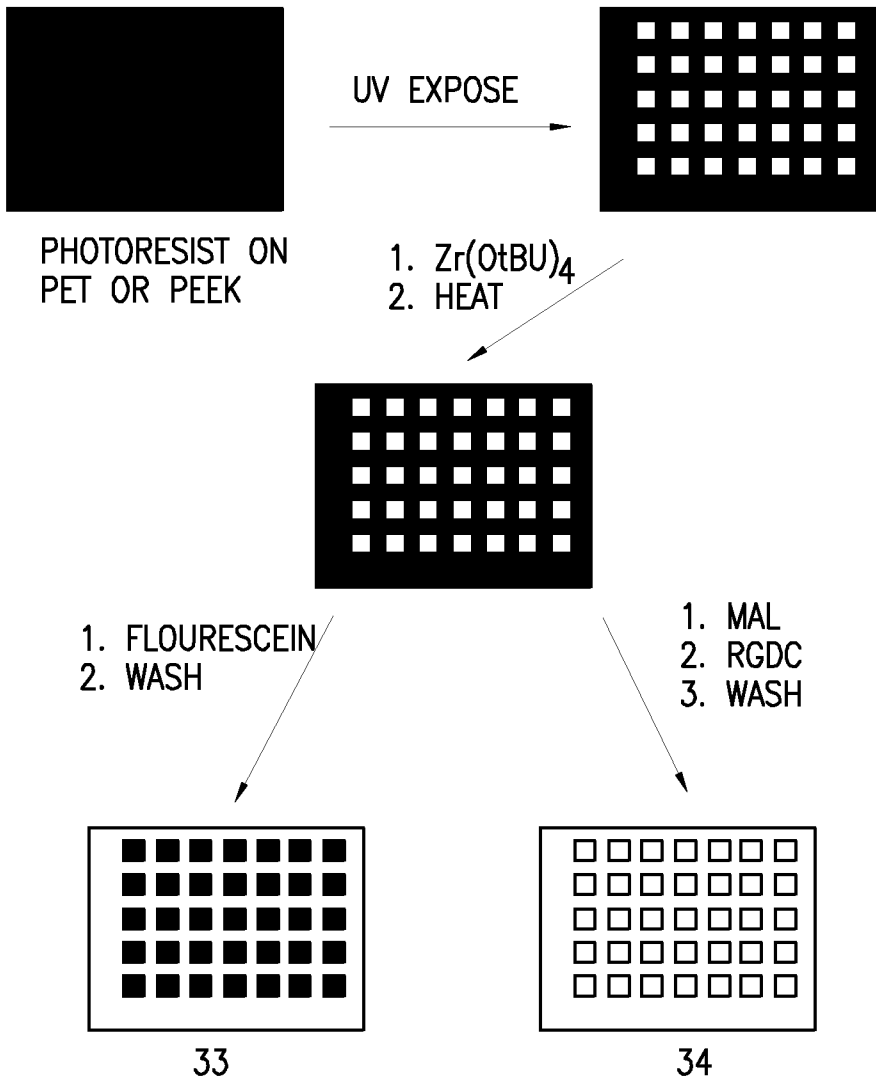


FIG. 12

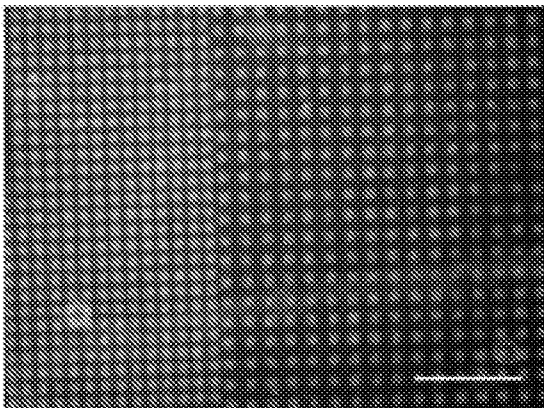


FIG. 12A

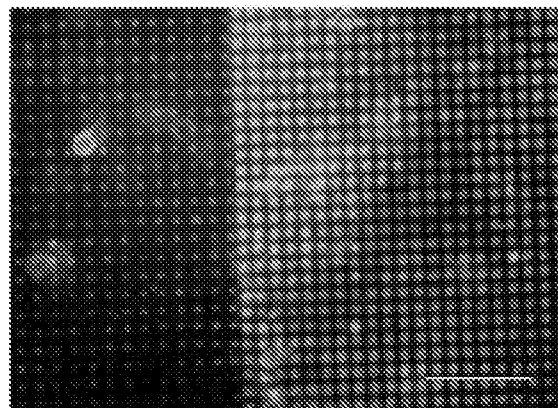


FIG. 12B

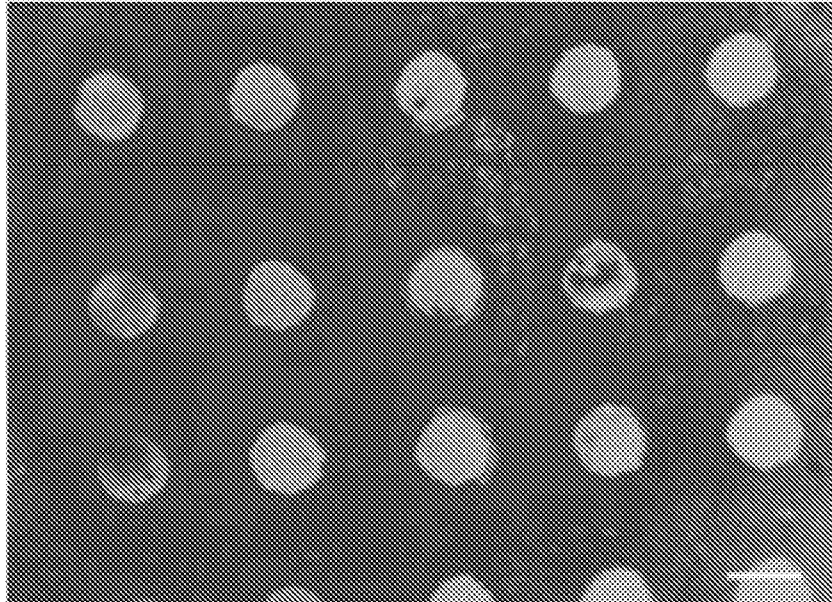


FIG. 13

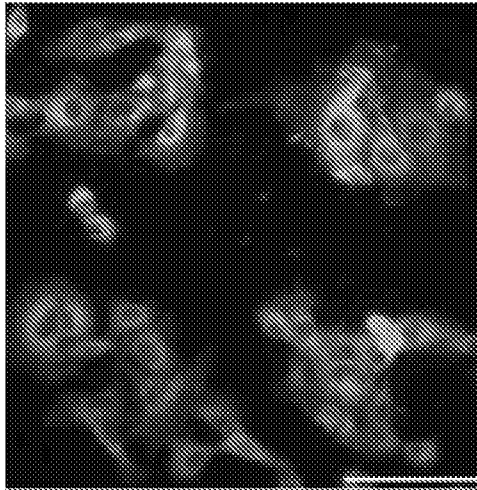


FIG. 14A

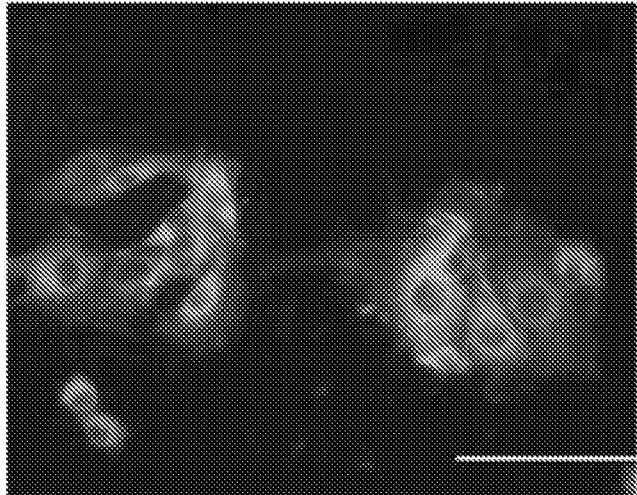


FIG. 14B

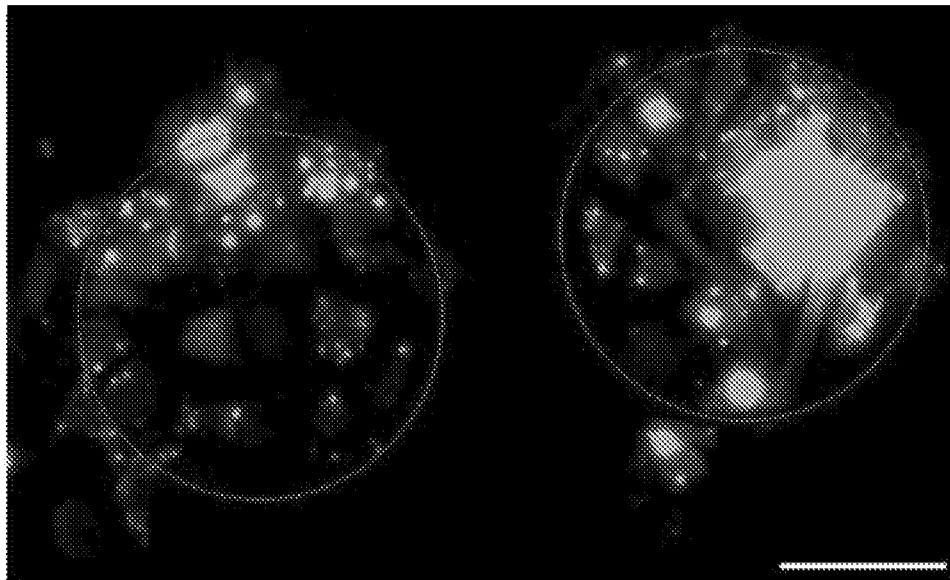


FIG. 14C

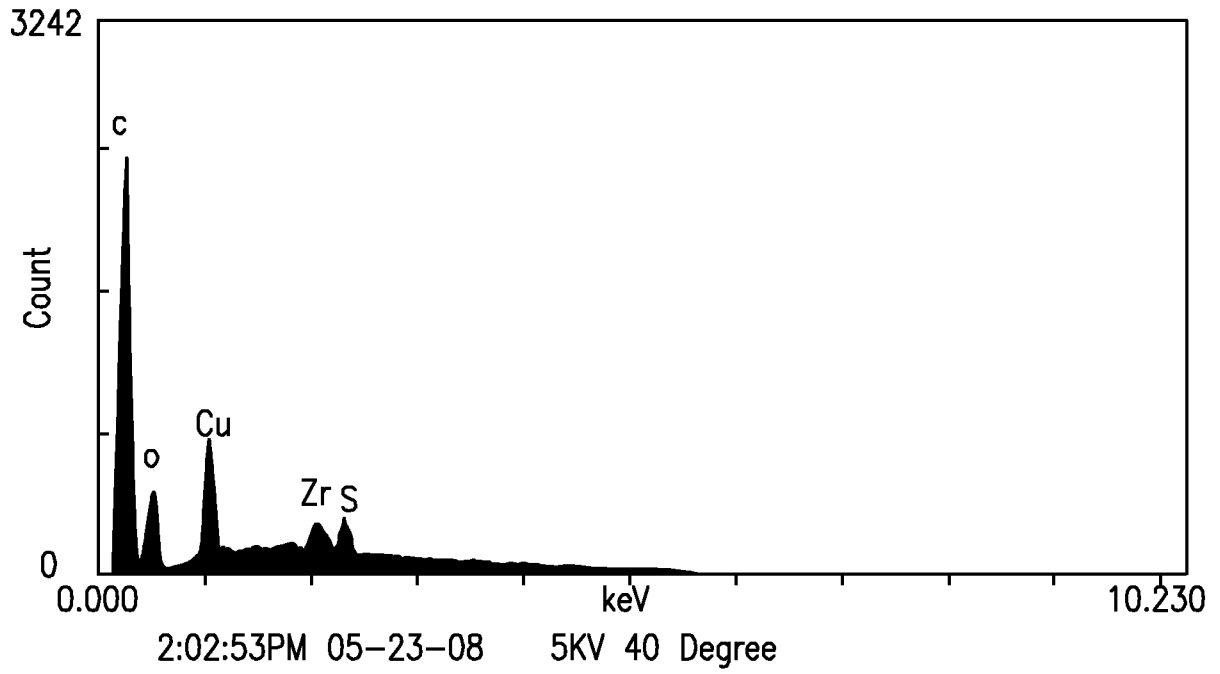


FIG. 15A

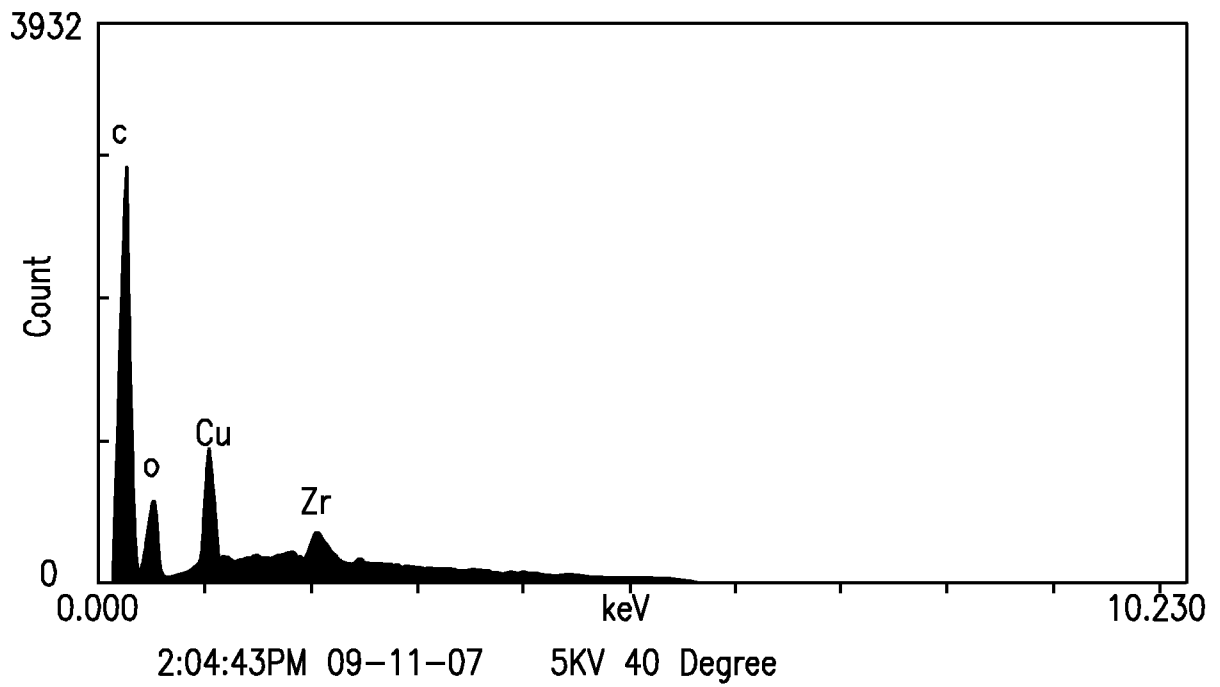
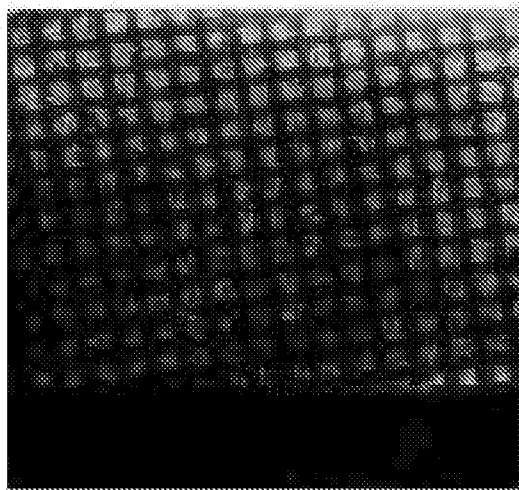
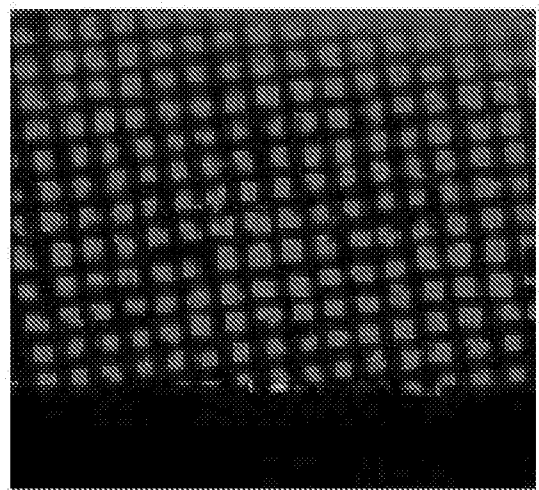


FIG. 15B



100 μ m

FIG. 16A



100 μ m

FIG. 16B

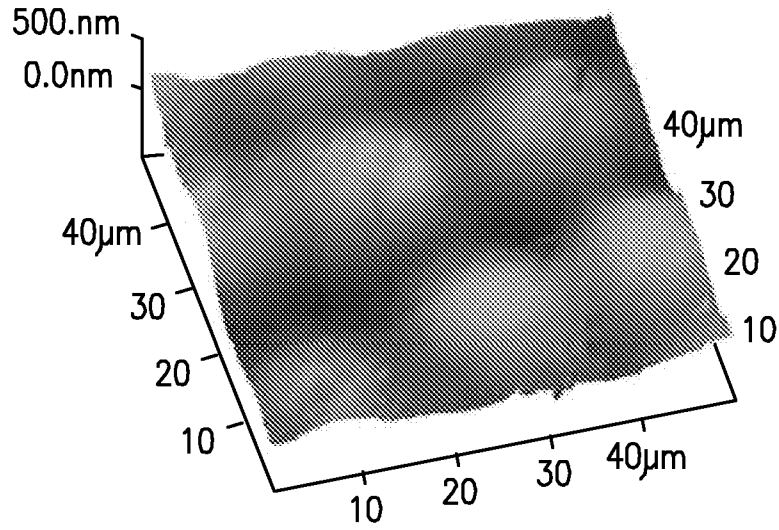


FIG. 17A

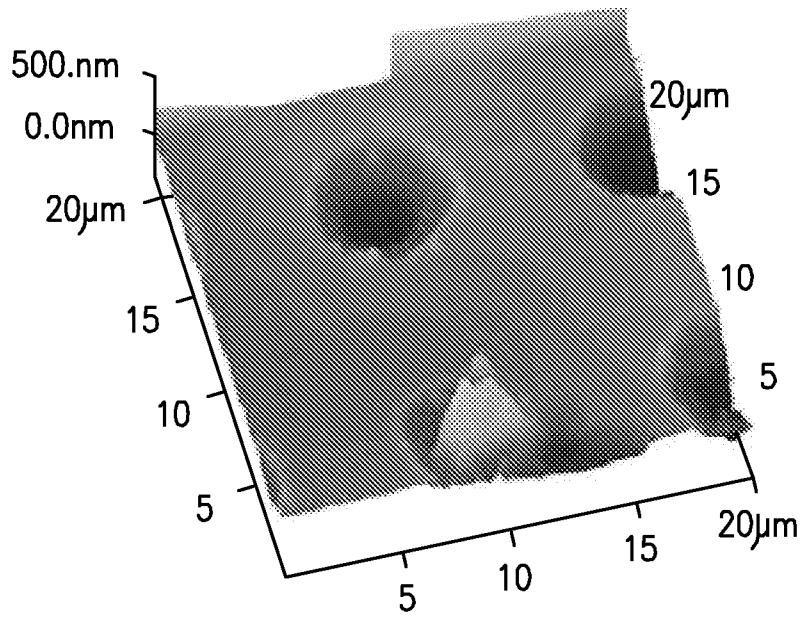


FIG. 17B

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 852-002 PCT	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 08/80273	International filing date (<i>day/month/year</i>) 17 October 2008 (17.10.2008)	(Earliest) Priority Date (<i>day/month/year</i>) 17 October 2007 (17.10.2007)
Applicant PRINCETON UNIVERSITY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

the international application in the language in which it was filed.

a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. This international search report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. Certain claims were found unsearchable (see Box No. II).

3. Unity of invention is lacking (see Box No. III).

4. With regard to the title,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

FUNCTIONALIZED SUBSTRATES WITH THIN METAL OXIDE ADHESION LAYER

5. With regard to the abstract,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. 1

as suggested by the applicant.

as selected by this Authority, because the applicant failed to suggest a figure.

as selected by this Authority, because this figure better characterizes the invention.

b. none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/80273

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - B05D 3/10, B32B 27/00 (2008.04)
USPC - 428/447, 427/385.5
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)
USPC - 428/447, 427/385.5
IPC(8) - B05D 3/10, B32B 27/00 (2008.04)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 428/447, 427/385.5
IPC(8) - B05D 3/10, B32B 27/00 (2008.04) (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT,PGPB,EPAB,JPAB), Google Scholar, DialogPro
Search Terms Used: Polymer substrate, functionalized surface, polyethylene terephthalate (PET), polyetheretherketone (PEEK), polyimide, metal alkoxide, zirconium tetra(tert-butoxide), tantalum pentaethoxide, polyethylene glycol, pegylate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/0194691 A1 (GEORGE et al.) 07 October 2004 (07.10.2004), paras [0001]-[0073]	1-3, 5, 7, 10, 11, 14, 15, 19, 27-31, 33, 35, 38, 39, 42, 43, 47, 68, 71-74, 76, 78, 79
Y	US 6,313,219 B1 (TAYLOR-SMITH) 06 November 2001 (06.11.2001), col 4, ln 27-52; col 5, ln 45	4, 6, 8, 9, 12, 13, 16-18, 20-26, 32, 34, 36, 37, 40, 41, 44-46, 48-67, 69, 70, 75, 77, 80-84
Y	US 2005/0175831 A1 (KIM et al.) 11 August 2005 (11.08.2005), paras [0013]-[0071]	4, 6, 32, 34, 75
Y	US 2006/0194008 A1 (SCHWARTZ et al.) 31 August 2006 (31.08.2006), paras [0021]-[0022], [0063], [0097], [0186]-[0187], [0280], [0294]	8, 9, 16-18, 20-24, 36, 37, 44-46, 48-52
Y	US 2006/0138404 A1 (OKADA et al.) 29 June 2006 (29.06.2006), paras [0020]-[0060]	25, 26, 53-67, 70, 81-84
Y	US 2006/0138404 A1 (OKADA et al.) 29 June 2006 (29.06.2006), paras [0020]-[0060]	12, 13, 22, 23, 40, 41, 50, 51, 69, 77, 80
Y	US 7,166,502 B1 (KWON) 23 January 2007 (23.01.2007), col 4, ln 40; col 5, lns 9-20	12, 13, 40, 41, 77

Further documents are listed in the continuation of Box C.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search 12 December 2008 (12.12.2008)	Date of mailing of the international search report 23 DEC 2008
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