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(71) Applicant(s)
Palmaz Scientific, Inc.

(72) Inventor(s)
Palmaz, Julio C.

(74) Agent / Attorney
Houlihan², Level 1 70 Doncaster Road, BALWYN NORTH, VIC, 3104

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(71) **Applicant** *(for all designated States except US)*: **PALMAZ SCIENTIFIC, INC.** [US/US]; 2828 North Harwood Avenue, Suite 1700, Dallas, TX 75201 (US).

(72) **Inventor; and**
(75) **Inventor/Applicant** *(for US only)*: **PALMAZ, Julio, C.** [US/US]; 4031 Hagen Road, Napa, CA 94558 (US).

(74) **Agents**: **ROSENBAUM, David, G.** et al.; Rosenbaum & Silvert, P.C., 1480 Techny Road, Northbrook, IL 60062 (US).

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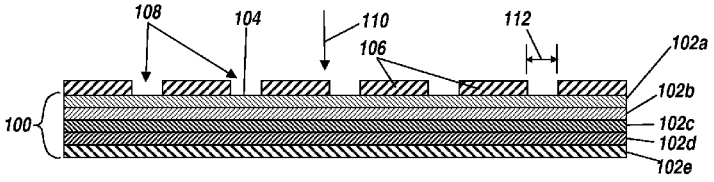

FIG. 11B

(57) **Abstract**: An implantable biocompatible material includes one or more vacuum deposited layers of biocompatible materials deposited upon a biocompatible base material. At least a top most vacuum deposited layer includes a homogeneous molecular pattern of distribution along the surface thereof and comprises a patterned array of geometric physiologically functional features.

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Title:

[001] IMPLANTABLE MATERIALS HAVING ENGINEERED SURFACES AND METHOD OF MAKING SAME

Background of the Invention

[002] The present invention relates generally to implantable medical devices and more particularly to controlling surface properties of implantable biocompatible materials suitable for fabrication of implantable medical devices.

[003] Implantable medical devices are fabricated of materials that are sub-optimal in terms of the biological response they elicit in vivo. Many conventional materials used to fabricate implantable devices, such as titanium, polytetrafluoroethylene, silicone, carbon fiber and polyester, are used because of their strength and physiologically inert characteristics. However, tissue integration onto these materials is typically slow and inadequate. Certain materials, such as silicone and polyester, elicit a significant inflammatory, foreign body response that drives fibrous encapsulation of the synthetic material. The fibrous encapsulation may have significant adverse effects on the implant. Moreover, conventional biomaterials have proved inadequate in eliciting a sufficient healing response necessary for complete device integration into the body. For example, in devices that contact blood, such as stents and vascular grafts, attempts to modify such devices to promote endothelial cell adhesion may have a concomitant effect of making the devices more thrombogenic.

[004] There still remains a need for a medical device that stimulates endothelial proliferation and movement when implanted in order to form an endothelial layer over the medical device. Furthermore, there is a remaining need for a method of fabricating such a medical device.

Summary of the Invention

[005] In one embodiment, an implantable biocompatible material includes one or more vacuum deposited layers of biocompatible materials deposited upon a biocompatible base material. At least a top most vacuum deposited layer includes a homogeneous molecular pattern of distribution along the surface thereof and comprises a patterned array of geometric physiologically functional features characterized by including a topmost removable contaminant layer.

[006] In another embodiment, an implantable biocompatible material includes a plurality of layers of biocompatible materials formed upon one another into a self-supporting multilayer structure. The plurality of layers includes a vacuum deposited surface layer having a

homogeneous molecular pattern of distribution along the surface thereof and comprises a patterned array of geometric physiologically functional features.

[007] In a further embodiment, a method for making an implantable biocompatible material is presented. The method includes the steps of providing an implantable biocompatible material having at least one surface intended to contact tissue of body fluids in vivo and providing a mask having a defined pattern of openings corresponding in size and spacing to a predetermined distribution of binding domains to be imparted to the at least one surface.

[008] The method further includes the steps of treating the at least one surface of the biocompatible material through the mask by at least one of three techniques. The first technique includes vacuum depositing a layer of material onto the at least one surface, wherein the vacuum deposited layer is different from the at least one surface immediately therebeneath in a material property selected from the group of material properties consisting of: grain size, grain phase, grain material composition, surface topography, and transition temperature, and removing the mask to yield a plurality of binding domains defined on the at least one surface of the implantable, biocompatible material. The second technique includes vacuum depositing a layer of sacrificial material onto the at least one surface, removing the mask from the at least one surface, vacuum depositing a second layer of material onto the at least one surface, wherein the second vacuum deposited layer is different from the at least one surface immediately therebeneath in a material property selected from the group of material properties consisting of: grain size, grain phase, grain material composition, surface topography, and transition temperature, and removing the sacrificial material to yield a plurality of binding domains defined on the at least one surface of the implantable, biocompatible material. The third technique includes photo irradiating the at least one surface to photochemically alter the at least one surface, and removing the mask to yield a plurality of binding domains defined on the at least one surface of the implantable, biocompatible material.

Brief Description of the Figures

[009] **FIG. 1** is a perspective view of one embodiment including evenly distributed elevated geometric physiologically functional features on the surface of an implantable material.

[010] **FIG. 2** is cross-sectional view of **FIG. 1** along line 2 – 2.

[011] **FIG. 3** is a perspective view of one embodiment including evenly distributed chemically defined geometric physiologically functional features on the surface of an implantable material.

[012] **FIG. 4** is a cross-sectional view of **FIG. 3** along line 4 – 4.

[013] **FIG. 5** is a photomicrograph showing one embodiment including geometric physiologically functional features as carbon coated silicon.

[014] **FIGS. 6A-6C** are photomicrographs showing cellular migration on the surface with no inventive geometric physiologically functional features versus on the surface with inventive geometric physiologically functional features.

[015] **FIG. 7** is a photomicrograph showing the stained focal adhesion points close to the geometric physiologically functional features.

[016] **FIGS. 8A-8B** are photomicrographs showing the formation of multiple focal adhesion points of a migrating cell and its attachment to the inventive geometric physiologically functional features.

[017] **FIGS. 9A-9D** are cross-sectional diagrammatic views of one embodiment, the combination of a-d representing the steps to make an inventive implantable material with elevated geometric physiologically functional features.

[018] **FIGS. 10A-10D** are cross-sectional diagrammatic views of one embodiment, the combination of a-d representing the steps to make an inventive implantable material with chemically defined geometric physiologically functional features.

[019] **FIG. 11A** illustrates a cross-sectional view of layers of vacuum deposited material; **FIG. 11B** illustrates a cross-sectional view of a mask disposed over a surface of the layers of vacuum deposited material of **FIG. 11A**; **FIG. 11C** illustrates a plan view of the mask of **FIG. 11B**; **FIG. 11D** illustrates a cross-sectional view of material deposited into a space defined by holes of the mask of **FIG. 11B**; and **FIG. 11E** illustrates a cross-sectional view of geometric physiologically functional features patterned across the surface of **FIG. 11B**.

[020] **FIG. 12A** illustrates a cross-sectional view of vacuum deposition of a layer of material onto a surface of layers of vacuum deposited material and into a space defined by a sacrificial layer of material previously deposited onto the surface; and **FIGS. 12B-12D** illustrate a cross-sectional view of recessed geometric physiologically functional features.

[021] **FIG. 13A** illustrates a cross-sectional view of layers of vacuum deposited material deposited over a bulk material; and **FIG. 13B** illustrates recesses machined to various depths through a surface of the layers of material.

[022] **FIG. 14** is a schematic of plasma surface modification within a plasma reactor.

[023] **FIG. 15** is a schematic of the reaction mechanisms of plasma surface modifications.

[024] **FIG. 16** is a graph of the mean electrostatic force measurements comparing 5 different metal surfaces; measurements were performed using a 5 nm silicon nitride tip in the presence of a 0.01 M. NaCl medium at pH 7.4; force measurement values for each metal represent the mean of data from five different samples on which 5 sites were analyzed using 10 measurements at each site; and mean values were compared using Student's unpaired t-analysis.

[025] **FIG. 17** is a graph of the correlation of mean electrostatic measurements on the different metal surfaces presented in **FIG. 16** with the polar component of total metal surface energy; and total surface energy was calculated by the harmonic method from surface contact angle measurements using water, formamide and xylene as the test liquids.

Detailed Description of the Preferred Embodiments

[026] In accordance with one embodiment, the capacity for complete endothelialization of conventional implantable materials, including metals and polymers, may be enhanced by imparting a pattern of chemically and/or physiochemically active geometric physiologically functional features onto a blood contacting surface of the implantable material. The inventive implantable devices may be fabricated of polymers, pre-existing conventional wrought metallic materials, such as stainless steel or nitinol hypotubes, or may be fabricated by thin film vacuum deposition techniques. The inventive implantable devices may be intravascular stent, stent-grafts, grafts, heart valves, venous valves, filters, occlusion devices, catheters, osteal implants, implantable contraceptives, implantable antitumor pellets or rods, shunts and patches, or other implantable medical devices having any construction or made of any material as will be hereinafter described. A medical device is an instrument, apparatus, implant, in vitro reagent, or other similar or related article, which is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, or intended to affect the structure or any function of the body and which does not achieve any of it's primary intended purposes through chemical action within or on the body. Similarly, the improvement of the embodiments for the methods for manufacturing intravascular stents is also believed to be applicable to the manufacturing of any type of intravascular medical device, stent-grafts, grafts, heart valves, venous valves, filters, occlusion devices, catheters, osteal implants, implantable contraceptives, implantable antitumor pellets or rods, shunts and patches, pacemakers, medical wires or medical tubes for any type of medical device, or other implantable medical devices, as

will also be hereinafter described. A pacemaker (or artificial pacemaker, so as not to be confused with the heart's natural pacemaker) is a medical device that uses electrical impulses, delivered by electrodes contacting the heart muscles, to regulate the beating of the heart. The electrodes may be covered by tubing or other material that includes a surface that may require endothelialization and grooves thereon.

[027] The inventive implantable metal devices may be fabricated of polymers, pre-existing conventional wrought metallic materials, such as stainless steel or nitinol hypotubes, or may be fabricated by thin film vacuum deposition techniques. In accordance with one embodiment, it is preferable to fabricate the inventive implantable materials and resulting devices by vacuum deposition of either or both of the base implant material and the chemically and/or physiochemically active geometric physiologically functional features. Vacuum deposition permits greater control over many material characteristics and properties of the resulting material and formed device. For example, vacuum deposition permits control over grain size, grain phase, grain material composition, bulk material composition, surface topography, mechanical properties, such as transition temperatures in the case of a shape memory alloy. Moreover, vacuum deposition processes will permit creation of devices with greater material purity without the introduction of large quantities of contaminants that adversely affect the material and, therefore, the mechanical and/or biological properties of the implanted device. Vacuum deposition techniques also lend themselves to fabrication of more complex devices than those that are manufactured by conventional cold-working techniques. For example, multi-layer structures, complex geometrical configurations, extremely fine control over material tolerances, such as thickness or surface uniformity, are all advantages of vacuum deposition processing. The embodiments disclosed herein to may replace polymer grafts with metal grafts that can potentially become covered with EC and can heal completely. Furthermore, heterogeneities of materials in contact with blood flow are preferably controlled by using vacuum deposited materials.

[028] In vacuum deposition technologies, materials are formed directly in the desired geometry, e.g., planar, tubular, etc. The common principle of vacuum deposition processes is to take a material in a minimally processed form, such as pellets or thick foils, known as the source material and atomize them. Atomization may be carried out using heat, as is the case in physical vapor deposition, or using the effect of collisional processes, as in the case of sputter deposition,

for example. In some forms of deposition a process such as laser ablation, which creates microparticles that typically consist of one or more atoms, may replace atomization; the number of atoms per particle may be in the thousands or more. The atoms or particles of the source material are then deposited on a substrate or mandrel to directly form the desired object. In other deposition methodologies, chemical reactions between ambient gas introduced into the vacuum chamber, i.e., the gas source, and the deposited atoms and/or particles are part of the deposition process. The deposited material includes compound species that are formed due to the reaction of the solid source and the gas source, such as in the case of chemical vapor deposition. In most cases, the deposited material is then either partially or completely removed from the substrate, to form the desired product.

[029] A first advantage of vacuum deposition processing is that vacuum deposition of the metallic and/or pseudometallic films permits tight process control and films may be deposited that have a regular, homogeneous atomic and molecular pattern of distribution along their fluid-contacting surfaces. This avoids the marked variations in surface composition, creating predictable oxidation and organic adsorption patterns and has predictable interactions with water, electrolytes, proteins and cells. In particular, EC migration is supported by a homogeneous distribution of binding domains that serve as natural or implanted cell attachment sites in order to promote unimpeded migration and attachment.

[030] Secondly, in addition to materials and devices that are made of a single metal or metal alloy layer, the inventive grafts may be comprised of a layer of biocompatible material or of a plurality of layers of biocompatible materials formed upon one another into a self-supporting multilayer structure because multilayer structures increase the mechanical strength of sheet materials, or to provide special qualities by including layers that have special properties such as superelasticity, shape memory, radio-opacity, corrosion resistance etc. Vacuum deposition technologies may deposit layered materials and thus films possessing exceptional qualities may be produced. Layered materials, such as superstructures or multilayers, are commonly deposited to take advantage of some chemical, electronic, or optical property of the material as a coating; a common example is an antireflective coating on an optical lens. Multilayers are also used in the field of thin film fabrication to increase the mechanical properties of the thin film, specifically hardness and toughness.

[031] Thirdly, the design possibilities for possible configurations and applications of the inventive graft are greatly realized by employing vacuum deposition technologies. Specifically, vacuum deposition is an additive technique that lends itself toward fabrication of substantially uniformly thin materials with potentially complex three dimensional geometries and structures that cannot be cost-effectively achieved, or in some cases achieved at all, by employing conventional wrought fabrication techniques. Conventional wrought metal fabrication techniques may entail smelting, hot working, cold working, heat treatment, high temperature annealing, precipitation annealing, grinding, ablation, wet etching, dry etching, cutting and welding. All of these processing steps have disadvantages including contamination, material property degradation, ultimate achievable configurations, dimensions and tolerances, biocompatibility and cost. For example conventional wrought processes are not suitable for fabricating tubes having diameters greater than about 20 mm, nor are such processes suitable for fabricating materials having wall thicknesses down to about 1 μm with sub-μm tolerances.

[032] The embodiments disclosed herein takes advantage of the discovered relationship between chemically or physiochemically-active geometric physiologically functional features defined and distributed on a blood contact surface and enhanced endothelial cell binding, proliferation and migration over the blood contact surface of the implantable material. The embodiments disclosed herein involve focal adhesion point formation during cellular movement and the anchorage dependence, that spreading cells proliferate faster than non-spreading cells. The addition of a patterned array of geometric physiologically functional features, which have a hydrophobic, hydrophilic or surface energy difference relative to the surface onto which the geometric physiologically functional features are added, enhances the binding, proliferation and migration of endothelial cells to and between the geometric physiologically functional features and across the surface.

[033] The geometric physiologically functional features disclosed herein may be formed on, in, or through one or more layers of vacuum deposited biocompatible material. In a first embodiment, the one or more layers of vacuum deposited biocompatible material are deposited on a layer of bulk material. In a second embodiment, a plurality of layers of vacuum deposited biocompatible material is deposited on one another to form a self-supporting multilayer structure. Each of the first and second embodiments includes several aspects. In a first aspect, the geometric physiologically functional features may have a non-zero thickness corresponding to a

thickness of one or more layers of the vacuum deposited material. Alternatively, in other aspects, the geometric physiologically functional features may have a zero thickness or a thickness greater than one or more layers of the vacuum deposited material.

[034] Below about 3 μm in thickness, the interactions between endothelial cells and the geometric physiologically functional features are primarily chemical and electrochemical. Geometric physiologically functional features having thicknesses greater than 3 μm and up to about 20 μm may also be employed in the embodiments disclosed herein, it being understood that as the thickness of the geometric physiologically functional feature increases there is a decreasing chemical and/or electrochemical interaction between the geometric physiologically functional feature and the endothelial cells and an increasing physical interaction (topographic guidance effect).

[035] Additionally, UV irradiation may be employed to oxidize titanium or titanium-alloy surfaces, photochemical alteration of the surface titanium oxides alter the hydrophobicity of the exposed titanium oxides and act as affinity binding and migration sites for endothelial cell attachment and proliferation across a titanium or titanium-alloy surface. Where UV irradiation is employed, the thickness of the photochemically altered regions of titanium oxide are, for all practical purposes, 0 μm. Thus, within the context of the present application, the term "geometric physiologically functional features" is intended to include both physical members and photochemically-altered regions having thicknesses having thicknesses down to 0 μm.

[036] In **FIG. 1**, a portion of an implantable material 10 showing the surface material 12 with described elevated geometric physiologically functional features 14 is illustrated. The geometric physiologically functional features are elevated from the surface of the implantable material to a height ranging from about 1 nm to about 20 μm. Preferably, the height of the geometric physiologically functional feature 14 ranges from about 1 nm to about 3 μm. The shape of geometric physiologically functional features can be either circular, square, rectangle, triangle, parallel lines, straight or curvilinear lines or any combination thereof. Each of the geometric physiologically functional features is preferably from about 1 nm to about 75 μm, and preferably from about 1nm to 50 μm in feature width 16, or feature diameter if the geometric physiologically functional feature is circular. A gap distance 18 between each of the geometric physiologically functional features may be less than, about equal to or greater than the feature width 16, i.e., between about 1 nm to about 75 μm edge-to-edge.

[037] **FIG. 2** is a cross-sectional view along line 2-2 in **FIG. 1**. One of the elevated geometric physiologically functional features 14 is shown on the surface 12 of the implantable material.

[038] In **FIG. 3**, a layer of a titanium or titanium-alloy material 20 is heating to oxidize and form titanium dioxide on the surface of the material 20. In one embodiment, the layer of titanium or titanium-alloy material 20 is deposited over one or more layers of vacuum deposited material in a self-supporting multilayer structure. In another embodiment, the layer of titanium or titanium-alloy material 20 is deposited over a bulk material that may have one or more layers of vacuum deposited material deposited thereon.

[039] The geometric physiologically functional features 24 are formed by exposing the layer of material 20 to UV through a pattern mask. UV irradiation alters the titanium oxides in the areas of geometric physiologically functional features 24, thereby chemically altering the geometric physiologically functional features 24 relative to the surrounding the surrounding surface area 22 of material layer of material 20. The shape of geometric physiologically functional features can be circular, square, rectangle, triangle, parallel lines, intersecting lines or any combination. Each of the geometric physiologically functional features is from about 1 nanometer to about 75 μm, and preferably from about 1 nanometer to about 50 μm in feature width 16, or feature diameter if the geometric physiologically functional feature is circular. The gap distance 28 between each component of the geometric physiologically functional features may be less than, about equal to or greater than the feature width 26.

[040] **FIG. 4** is a cross-sectional view of **FIG. 3** along line 4-4. The described geometric physiologically functional features 24 are indicated by the dotted lines, which indicate that the geometric physiologically functional features 24 are at the same level of the surrounding surface 22.

[041] **FIG. 5** shows geometric physiologically functional features that are evenly distributed across the at least one surface of the implantable material that contacts body fluid, preferably blood. As disclosed in **FIG. 1** and **FIG. 2**, the geometric physiologically functional features are elevated from the rest of the surface to a height ranging from about 1 nanometer to about 20 micrometers. Preferably, the height of the geometric physiologically functional feature ranges from about 1 nanometer to about 3 micrometers. The shape of the geometric physiologically functional features is not confined within the shape that is shown. The shape of the chemically

defined domain can also be any of circle, square, rectangle, and triangle, parallel lines, intersecting lines or any combination of the above.

[042] **FIG. 6A** shows the cell 32 spreading on the surface of hydrophilic treated Si. **FIG. 6B** shows the cell 32 spreading on the surface of hydrophilic treated Si with circular dots that are 15 microns in diameter. Cells in **FIG. 6B** appear to have much more focal adhesion points 36 than those in **FIG. 6A**. Because these geometric physiologically functional features provide for cell attachment, acting as affinity domains, the size of each of these affinity domains relative to the size of an endothelial cell determines the availability of affinity domains to the subsequent round of cell movement. According to one embodiment, the preferred size of each of the individual component of the geometric physiologically functional features is about 1 nm to about 75 μm, and preferably from about 1 nm to 50 μm in feature width, or diameter if the geometric physiologically functional feature is circular. Focal adhesion point formation is the critical step in cell movement and cell proliferation; therefore, geometric physiologically functional features such as carbon dots on the hydrophilic Si surface promote cell movement. Spreading of cells promotes cell proliferation, protein synthesis, and other cell metabolic functions. Promoting cell movement and cell proliferation ultimately accelerates covering of the implanted implantable material with endothelial cells on exposed surfaces having the geometric physiologically functional features. Although the geometric physiologically functional features shown in **FIG. 6B** are circular, the shape of the geometric physiologically functional features are not limited to this particular embodiment.

[043] **FIG. 6C** is a magnification of a portion of the image of **FIG. 6B**. Multiple focal adhesion points 36 are again shown. Wide spreading of the cell is primarily due to the formation of multiple focal adhesion points on the circular geometric physiologically functional features. Extensive spreading of the cells is beneficial towards endothelialization because it promotes cell movement and cell proliferation.

[044] **FIG. 7** shows the stained focal adhesion points 36 of human aotic endothelial cells (HAEC) on the surface of an implantable material with geometric physiologically functional features 14 that are in the form of carbon dots. The focal adhesion points are located at or very close to the geometric physiologically functional features 14. These focal adhesion points serve as tension points for the cell to contract from the opposite end of the cell and hence promote cell movement.

[045] **FIG. 8A** shows the wide spreading of cells 32 and focal multiple focal adhesion points 36 on the surface of an implantable material with geometric physiologically functional features that are in the form of NiTi dots of 25 micrometers in diameter. The NiTi dots are invisible due to the weak contrast between the NiTi dots and surrounding Si surface.

[046] **FIG. 8B** shows a magnified slide of a human aortic epithelial cell 32, as shown in **FIG. 8A**. Multiple focal adhesion points 36 are shown to encapsulate the NiTi dots patterned on the hydrophilic Si surface. Referring to **FIG. 9A**, a portion of an implantable material 46 with surface 42 and 44 is shown. Referring to **FIG. 9B**, according to one embodiment, a machined mask 48 having laser-cut holes 40 of defined size ranging from about 1 nm to about 75 μm, and preferably from about 1 nm to 50 μm, patterned throughout coats at least one surface 42 of the implantable material 46 and is tightly adhered to the covered surface 42. Referring to **FIG. 9C**, a thin film of material 14 was deposited into the space as defined by the holes 40, as seen in **FIG. 9B**, in the mask 48 by thin film deposition procedures. Referring to **FIG. 9D**, after deposition, the mask is removed to reveal the geometric physiologically functional features 49 patterned across the at least one surface 42 of the implantable material 46.

[047] As described above, the shape of the holes in the mask could be in any of the shapes described for the geometric physiologically functional features including: circle, square, rectangle, triangle, parallel lines and intersecting lines, or any combination thereof. In the thin film deposition embodiment of the manufacturing the geometric physiologically functional features, the geometric physiologically functional features are elevated from the surface of the implantable material. The thickness of the geometric physiologically functional features is based upon the thickness of the holes in the mask, the thickness ranging from about 1 nm to about 20 micrometers. Preferably, the thickness of the holes in the mask range from about 1 nm to about 3 micrometers.

[048] The variations of geometric physiologically functional features may be added to a surface of an implantable biocompatible material by vacuum depositing a layer or layers of biocompatible material on the surface. In one embodiment, the geometry of the layer or layers of deposited material defines the geometric physiologically functional features. For example, an implantable material 100 has a surface 104, as illustrated in **FIG. 11A**. In one embodiment, the implantable biocompatible material may comprise one or more layers 102 of vacuum deposited material formed into a self-supporting structure, as illustrated by **FIG. 11A** showing a first layer

102a, a second layer 102b, a third layer 102c, a fourth layer 102d, and a fifth layer 102e. In another embodiment, the implantable biocompatible material includes a bulk material, either a bulk material alone or a bulk material covered by the one or more layers 102a-102e of vacuum deposited biocompatible material. Five layers 102a-102e of vacuum deposited material are illustrated; however, any number of layers may be included as desired or appropriate.

[049] The one or more layers 102, may have thicknesses that are the same or different as desired or appropriate. Each layer may have a thickness in a range from about 1 nanometer to about 20 micrometers, from about 1 nanometer to about 10 micrometers, from about 1 nanometer to about 5 micrometers, or from about 1 nanometer to about 3 micrometers. Alternating layers 102 of varying thicknesses may be applied as to accommodate the geometric physiologically functional features.

[050] In this embodiment, the geometric physiologically functional features may be added to the surface 104 by adding one or more layers 102 of vacuum deposited material. For example, referring to **FIGS. 11B-11E**, in one process, a mask 106 having holes 108 of defined size disposed therethrough and patterned throughout coats and is tightly adhered to at least a first portion of the surface 104. The holes 108 may be cut through the mask 106, for example, by using a laser, wet or dry chemical etching, or other like methods for forming holes through a material, or the mask 106 may be fabricated including the holes 108. The thickness of the holes 108 may range about 1 nanometer to about 20 micrometers, from about 1 nanometer to about 10 micrometers, from about 1 nanometer to about 5 micrometers, or from about 1 nanometer to about 3 micrometers.

[051] The shape of the holes 108 as seen in **FIG. 11C** or as looking in the direction of arrow 110 may be any of the shapes described for the geometric physiologically functional features including: circle, square, rectangle, triangle, polygonal, hexagonal, octagonal, elliptical, parallel lines and intersecting lines, or any combination thereof. The holes 108 may have a width 112, or diameter 112 if the holes are circular, in a range between about 1 nanometer and about 75 micrometers, between about 1 nanometer and about 50 micrometers, between about 1 nanometer and about 2000 nanometers, or between about 1 nanometer and about 200 nanometers. Adjacent holes 108 may be spaced apart by a distance D in a range from about 1 nanometer to about 20 micrometers, from about 1 nanometer to about 10 micrometers, from about 1 nanometer to about 5 micrometers, or from about 1 nanometer to about 3 micrometers. The distance D may be less

than, about equal to or greater than the width 112. In another embodiment (not shown), the width 112 of each of the holes 108 and/or the distance D between adjacent holes 108 may vary in size to form a patterned array of the holes 108.

[052] Referring to **FIG. 11D**, a layer 114 of material was deposited into a space as defined by the holes 108 in the mask 106 by vacuum deposition. The layer 114 has a thickness essentially the same as that of the mask 106. In some embodiments, the thickness of the mask may be variable across the mask 106. After removal of the mask 106, geometric physiologically functional features 116 are revealed patterned across the surface 104 of the implantable material 100. Each of the geometric physiologically functional features 116 includes a top surface 118. Each of the geometric physiologically functional features 116 has dimensions as described hereinabove for the holes 108 in the mask 106.

[053] In another embodiment where geometry of the layer or layers of deposited material defines the geometric physiologically functional features, a patterned array of recesses may be formed each having a hydrophobic, hydrophilic or surface energy difference relative to the surface into which the recesses are added, meaning a top most surface of the deposited layers, the difference enhancing the binding, proliferation and migration of endothelial cells to and between the recesses and across the surfaces, recessed and top most. The hydrophobic, hydrophilic or surface energy differences relative to the surface may be formed, by way of example, any of the methods disclosed in commonly assigned U.S. Patent Application No. 12/428,981, filed April, 23, 2009, incorporated by reference herein.

[054] In this embodiment, the recesses may be formed by a relative lack of deposition of a layer or layers onto a surface, or by machining recesses through a layer or layers of material vacuum deposited on a surface. For example, to produce a pattern of recesses similar to the pattern of geometric physiologically functional features 116 illustrated in **FIG. 11E**, in one example, a process begins by executing the steps described hereinabove with regard to **FIGS. 11A-11E**, to produce the pattern of geometric physiologically functional features 116 illustrated in **FIG. 11E**, except in this embodiment, the layer 114 of material is a sacrificial layer of material that is removed in a subsequent step.

[055] Referring to **FIGS. 12A** and **12B**, a layer 120 of material is deposited into spaces between the geometric physiologically functional features 116 by vacuum deposition. The layer 120 has a thickness essentially the same as that of the geometric physiologically functional

features 116. In this embodiment, after vacuum deposition of the layer 120, the geometric physiologically functional features 116 of the sacrificial layer 114 are removed, for example, by chemical etching, photo etching, laser ablation, or other method reveal geometric physiologically functional features 122 patterned across the surface 104 of the implantable material 100. Each of the geometric physiologically functional features 122 is a recess that has a thickness or depth between a surface 124 of the layer 120 and the surface 104.

[056] The shape of the recesses 122 as seen looking in the direction of arrow 126 in **FIG. 12B** may be any of the shapes described for the geometric physiologically functional features including: circle, square, rectangle, triangle, polygonal, hexagonal, octagonal, elliptical, parallel lines and intersecting lines, or any combination thereof. The recesses 122 may have the width 112, or diameter if the recesses 122 are circular, in a range between about 1 nanometer and about 75 micrometers, alternatively between about 1 nanometer and about 50 micrometers, alternatively between about 1 nanometer and about 2000 nanometers, or alternatively between about 1 nanometer and about 200 nanometers. Adjacent recesses 122 may be spaced apart by the distance D in a range from about 1 nanometer to about 20 micrometers, from about 1 nanometer to about 10 micrometers, from about 1 nanometer to about 5 micrometers, or from about 1 nanometer to about 3 micrometers. The distance D may be less than, about equal to or greater than the width 112. In another embodiment (not shown), the width 112 of each of the recesses 122 and/or the distance D between adjacent recesses 122 may vary in size to form a patterned array of the recesses 122.

[057] In another embodiment, the recesses 122 having width and spacing as described hereinabove with regard to **FIGS. 12A** and **12B** may be formed by machining the recesses 122 through a layer or layers 128 of vacuum deposited material. For example, an implantable material 130 having a surface 132, may comprise a bulk material 134, the one or more layers 128 of vacuum deposited material, or the bulk material 134 and the one or more layers 128 of vacuum deposited material, as illustrated in **FIG. 13A**.

[058] Alternatively, as shown in **FIG. 12C**, the geometric physiologically functional features 116 themselves include a plurality of deposited layers, wherein the geometric physiologically functional features 116 include the first layer 102a, the second layer 102b, and the third layer 102c. The geometric physiologically functional features 116 are deposited through a mask as previously indicated, on top of structural material of the stent or other medical device include

deposited layer 102d and 102e. Alternatively, the geometric physiologically functional features 116 include the first layer 102a and the second layer 102b, deposited through the mask whereby the structural material of the stent or other medical device includes the layers 102c-102d. Alternatively, the geometric physiologically functional features 116 include the first layer 102a, the second layer 102b, the third layer 102c, and the fourth layer 102d, whereby the structural material of the stent or other medical device includes the fifth layer 102e. When additional layers 102a-102d are included in the geometric physiologically functional feature 116, the thickness of the layers as deposited can be modified to be a narrower or decreased thickness as to allow for the geometric physiologically functional feature 116 to be adjusted to a particular thickness. The layers of different vacuum deposited materials can be deposited to create the elevated surfaces having inherently different material properties. Alternatively, layers of the same vacuum deposited material can be deposited having differences in grain size, grain phase, and/or surface topography or variations of hydrophobic, hydrophilic or surface energy difference relative to the surface of the stent or structural material. The grain size, grain phase, and/or surface topography or variations of hydrophobic, hydrophilic or surface energy difference relative to the surface of the stent or structural material may be formed or included on the surface as shown in U.S. Patent Application Serial No. 12/428,981, which was filed April, 23, 2009, incorporated by reference herein.

[059] Alternatively, as shown in **FIG. 12D**, the recesses 122 may include a plurality of layers 102 to provide for differences in grain size, grain phase, and/or surface topography or variations of hydrophobic, hydrophilic or surface energy difference relative to the surface of the stent or structural material. The recesses 122 may be formed by the surface 124 being deposited through a mask as to form the layer 120 that gives rise to the plurality of recesses 122 with a wall 123. As such, the recesses 122 include an inner wall 123 including the first layer 102a, the second layer 102b, and the third layer 102c, whereby the surface 104 is on layer 102d, which is exposed on the bottom of the recess 122 and surface 124 is on top of layer 102a. Alternatively, the recesses 122 may include a wall of the first layer 102a and the second layer 102b, whereby the surfaces 124 are deposited through a mask, and the structural material of the stent or other medical device includes the layers 102d-102e. Alternatively, the recesses 122 include a wall of the first layer 102a, the second layer 102b, the third layer 102c, and the fourth layer 102d, and surfaces 124 are deposited through a mask whereby surface 102e that acts as the surface 104 of the structural

material of the medical device. When additional layers 102a-102d are included as the wall in the geometric physiologically functional feature 116, the thickness of the layers as deposited can be modified to be a narrower or decreased thickness as to allow for the geometric physiologically functional feature 116 to be adjusted to a particular thickness. The layers of different vacuum deposited materials can be deposited to create recesses having inherently different material properties. Alternatively, layers of the same vacuum deposited material can be deposited having differences in grain size, grain phase, and/or surface topography or variations of hydrophobic, hydrophilic or surface energy difference relative to the surface of the stent or structural material.

[060] Referring to **FIG. 13B**, recesses 136 may be machined into the surface 132 of the implantable material 130 to have a depth greater than a thickness of a first layer of material 128a or recesses 138 may be machined into the surface 132 of the implantable material 130 to have a depth greater than a thickness of the first and second layers 128a, 128b of material. Two layers are illustrated for convenience of explanation and illustration; however, any number of layers 128 of material may be used as desired or appropriate. In this embodiment, each of the recesses 136 has a thickness or depth between the surface 132 of the layer 128a and a surface 140 that is within a second layer 128b. Similarly, each of the recesses 138 has a thickness or depth between the surface 132 of the layer 128a and a surface 142 that is within the bulk material 134.

[061] An implantable material including geometric physiologically functional features comprising a layer or layers of vacuum deposited material, as illustrated by the geometric physiologically functional features 116 in **FIG. 11E**, recesses disposed through one or more layers of vacuum deposited material, as illustrated by the recesses 122 in **FIG. 12B** or the recesses 136 or 138 in **FIG. 13B**, has an inherently different structure than a block of material having recesses cut into it. The reason for this inherent difference lies in the differences in the materials making up surfaces exposed by the recesses. For example, in the case of a block of material and assuming that the block material is uniform in regard to material properties, an undisturbed surface of the block and a surface within a recess or groove cut into the block have the same material properties.

[062] In contrast, layers of different vacuum deposited materials can be deposited to create recessed and/or elevated surfaces having inherently different material properties. In fact, layers of the same vacuum deposited material can be deposited having differences in grain size, grain phase, and/or surface topography. The alternative grain size, grain phase, and/or surface

topography may be included or formed, by way of example, any of the methods disclosed in commonly assigned U.S. Patent Application No. 12/428,981, filed April, 23, 2009, incorporated by reference herein. For example, surfaces of the recesses 122, 136 can be deposited to have a roughened surface topography and a large grain size and surfaces of the material deposited defining the recesses 122, 136, for example the layer 120 illustrated in **FIG. 12B**, can have a relatively smoother surface topography and/or a smaller grain size. Alternative grain sizes and surfaces may be formed and included as shown in U.S. Patent Application Serial No. 12/428,981, which was filed April, 23, 2009, previously incorporated by reference.

[063] It is contemplated that a factor in increasing endothelialization of a surface of an implanted medical device may be the cleanliness of the surface. In this context, cleanliness refers to the presence or lack of contaminant molecules bonding to otherwise unsaturated chemical bonds at the surface. A perfectly clean surface, for example as may exist in a vacuum, comprises unsaturated bonds at the surface that have not bound to any contaminant molecules. The unsaturated bonds provide the surface with a higher surface energy as compared to a contaminated surface having fewer unsaturated bonds, which have a lower surface energy. Measurements of surface energy may be accomplished by contact angle measurements, as disclosed in U.S. Patent Application Serial No. 12/428,981, which was filed April, 23, 2009.

[064] Unfortunately, unsaturated chemical bonds at the surface will bond to contaminant molecules when exposed thereto. For example, there are many air-borne chemistries such as phthalates, hydrocarbons, and even water that may bond to unsaturated bonds or otherwise attach to reactive spots such as, for example, residual negative charges on the surface of a metal oxide. Such contaminant molecules, for example, normally occurring hydrocarbons, SO_2, NO, etc., occupy otherwise unsaturated bonds thereby reducing the number of unsaturated bonds and lowering the surface energy of the surface. Such reduction in the number of unsaturated bonds decreases the availability of such unsaturated bonds for interaction with blood proteins.

[065] The air atmosphere around the surface include normally occurring impurities which will be attracted to the unsaturated chemical bonds at levels in the air around 1x109 to 1x106 so it will take a few seconds before the surface is contaminated by their Brownian motion, after 1 min, most of the unsaturated bond are saturated with contaminants. One molecular monolayer (i.e. a single layer of molecules) will be adsorbed on the surface. On longer time scales, additional molecules may bond to the surface and build multi-layers of contaminant molecules.

The surface of a few molecular monolayers of contaminants may have thickness of about 0.1-2nm, which may be detected by sensitive surface analysis as indicated above.

[066] Thus, as relates to endothelialization, a cleaner surface having more unsaturated bonds provides increased potential for interaction with blood proteins. It is contemplated that a contaminated surface of a vacuum deposited or bulk material can be activated, or made more likely to interact with blood proteins, by removing the contaminant molecules that occupy the otherwise unsaturated bonds at the surface. There may be several techniques for accomplishing such activation, including by way of example and not limitation, chemical etching, wet chemical etching, oxidation, electrochemical treatment, thermal treatment, UV-ozone cleaning, coating by evaporation or sputtering, etc. For example, another technique for activating a vacuum deposited surface may be by using plasma electron bombardment under vacuum, a technique also known as plasma etching. The contaminant layer may be detected by surface-sensitive spectrosscopies, such as Auger electron spectroscopy (AES), x-ray photoemission spectroscopy (XPS or ESC), infrared reflection absorption spectroscopy (IRAS, FT-IR, etc.) secondary ion mass spectroscopy (SIMS), and those disclosed in U.S. Patent Application Serial No. 12/428,981.

[067] Plasma etching the sample to be treated is positioned within a controlled electrical gas discharge (a plasma), as schematically shown in **FIG. 14**. The plasma may be formed by applying a high voltage (AC or DC) over a gas under considerably lower pressure than one atmosphere (typically 0.1-1mm Hg, or a vacuum). Because of the low pressure and because gas purity is vital for the process, the discharge and the sample must be housed in a hermetically closed system that can be evacuated by vacuum pumps, and whose gas composition can be controlled. The plasma also has sufficient energy and momentum to remove atoms and molecules that are adsorbed on unsaturated bonds, or are constituents of the native surface. As such, the contamination layer bond to unsaturated bonds may be removed, to recreate the unsaturated bonds on the surface and thus increasing the surface energy. Depending on the parameters of the discharge (gas pressure and composition, applied voltage, current density, position of the sample, etc.) the surface treatment can be mild (mainly removal of the contamination layer) or more aggressive. The complete surface oxide layer on a metal may be removed so that the bare metal is exposed. The latter occurs only provided that no oxidizing or other reactive gases are present, i.e., the used gas must be a noble gas such as Ar, Kr, or Xe. By controlling the gas atmosphere, the composition of the newly formed surface is controlled; if

oxygen is added, oxide will be formed; if nitrogen or hydrocarbons are added, surface nitride or surface carbide, respectively, will form, etc. The gas purity must be high, as impurities within the gas will react to the high energy cleaned surfaces.

[068] Because of the omnipresence of contaminant molecules in the environment, a surface once activated may not remain activated until implantation into a patient. Thus, an important consideration of the activation process is how to preserve the activated surface long enough to provide the benefit of activation upon implantation. In this context, the activated surface may be preserved by introducing a contaminant gas or liquid into the plasma etching process in a controlled manner, which may be easily removed before use of the medical device. The contaminant layer may be a known biodegradable material or may be a contaminant layer or coating of inorganic or organic nature or a mixture of both. For example, the contaminant layer may be layer readily removed by a saline or water solution, which are typically used in flushing procedures or washing procedures.

[069] Alternatively, the activated surface may be coated with a protective coating, for example, a biodegradable material that dissolves upon exposure to the *in vivo* environment when implanted. The biodegradable material may alternatively be dissolved via introduction of an externally delivered fluid solvent during implantation. Alternatively, the protective coating may be a fluid in which the activated device is immersed until implantation. For example, it is contemplated that storing the activated surface in water facilitates preservation of the activation as compared to exposure of the activated surface to air. The biodegradable material may be any material, natural or synthetic, that may be broken down by living organisms, including, but not limited to a biodegradable organic substance, biodegradable polymer substances (Poly(lactic acid) PLA, poly(L-lactic acid) (PLLA), poly(lactic-co-glycolic acid) PLGA, poly(glycolicacid) (PGA), Polyethylene glycol, PEG, polytetrafluoroethylene (PTFE), and the like), peptides or proteins, carbohydrates, nucleic acids, fatty acids, carbon-containing compounds, nanoparticles, microparticles, biocomposites, sol-gel coatings, hydrogels water-soluble bioactive agent and poly(alkyl cyanoacrylate) polymer coating; nanoparticle coating formed by electrospraying; a poly(diol citrates)-based coatings; natural biodegradable hydrophobic polysaccharides coatings, hydrophilic polymers, and the like. Alternatively, other materials may be used, such as gold, other metals, heparin, silicon carbide, titanium-nitride-oxide, phoshphorylcholine, and other medical device coatings.

[070] The method disclosed herein comprehends the creation of a patterned array of geometric physiologically functional features elevated relative to a surface of an implantable biocompatible material, recessed relative to the surface, or disposed on the surface. For example, in accordance with an alternative embodiment, the implantable biocompatible material is formed of a bulk material of titanium, nickel-titanium alloy or other titanium-rich alloy metals or a top most layer of titanium, nickel-titanium alloy or other titanium-rich alloy metals deposited over the bulk material. The titanium, nickel-titanium alloy or other titanium-rich alloy metal is oxidized to convert surface titanium to titanium dioxide, then covered with a pattern-mask and exposed to high intensity UV irradiation. It is well-known that titanium dioxide (TiO_2) absorbs UV radiation and has been used in a variety of applications as a UV inhibitor to prevent UV transmission across a TiO_2 barrier layer. It has been discovered that upon exposure to UV irradiation, an originally hydrophobic and oleophilic titanium oxide layer becomes amphiphilic.

[071] The effect of UV irradiation on a titanium oxide surface is believed to occur because of unsymmetrical cleavage of the Ti—O bond to leave Ti^{3+} ions on the surface in some regions. Presently, these amphiphilic surfaces are being used in a range of technological applications, such as self-cleaning paints and anti-misting glasses. It has been recognized that these amphiphilic titanium oxide layers have use in medical applications. Zarbakhsh, A., *Characterization of photon-controlled titanium oxide surfaces, ISIS Experimental Report,* Rutherford Appelton Laboratory, May 16, 2000 (which may be found on the internet at: www.isis.rl.ac.uk/isis2001/reports/11144.pdf).

[072] The amphiphilic state of the UV irradiated titanium oxide may be advantageously employed as an alternative to depositing patterned elevated or recessed geometric physiologically functional features onto the implantable biocompatible material. An implantable biocompatible material fabricated having a bulk substrate or a top most vacuum deposited layer of titanium or a titanium alloy is masked with a pattern mask having a plurality of openings passing there through. As with the above-described embodiment, the plurality of openings preferably have a size and special array selected to define affinity binding domains and cellular migration cites for promoting endothelial cell binding and proliferation across the substrate surface.

[073] The open surface area of each of the plurality of openings in the pattern mask is preferably in the range of between about 1nm to about 75 μm, and with adjacent pairs of

openings being in a spaced apart relationship such that a distance of about 1nm to about 75 μm exists between the openings, the inter-opening being greater than, about equal to, or less than the size of the opening. By interposing the pattern mask between a UV source and the surface of the implantable biocompatible material, a pattern of UV irradiated regions is imparted to the surface implantable biocompatible material, thereby altering the titanium dioxides present at the irradiated regions and forming affinity domains at the surface implantable biocompatible material.

[074] Referring to **FIG. 10A**, a portion of an implantable material 56 made of titanium or a titanium-alloy is shown having at least one surface 52 and 54 that is oxidized by heating or an equivalent known by the person skilled in the art. Referring to **FIG. 10B**, according to one embodiment, a machined mask 48 that had laser-cut holes 40 of defined size from about 1 nm to about 75 μm, from about 1 nm to about 50 μm, from about 1 nm to about 2000 nm, and preferably from about 1 nm to about 200 nm, patterned throughout to coat the at least one surface 52 of the implantable material 56 and is tightly adhered to the covered surface 52.

[075] Referring to **FIG. 10C**, the implantable material 56 covered with the mask 48 is then illuminated by the ultraviolet rays. Because TiO_2 is sensitive to ultraviolet, the chemical composition in holes 58 is different from the area that is covered by the mask. In contrast to the geometric physiologically functional features illustrated in **FIGS. 9C**, **11E**, **12B**, and **13B**, the geometric physiologically functional features 59 in **FIG. 10C** are not elevated and therefore have zero thickness relative to the surrounding surface of the implantable material.

[076] Referring to **FIG. 10D**, after ultraviolet irradiation, the mask is removed to reveal the surface 52 that surrounds the geometric physiologically functional features 59 formed by ultraviolet irradiation. As described above, because the shape of the holes 58 in the mask 48 could be in any of the shapes described for the geometric physiologically functional features including: circle, square, rectangle, triangle, parallel lines and intersecting lines, and combinations thereof, the geometric physiologically functional features 58 accordingly adopts such shapes also.

[077] EXAMPLE 1

[078] Nickel-titanium sheets were heated to oxidize titanium present at the surface of the sheet. Pattern masks fabricated from machined metal were laser drilled a pattern of holes having diameters ranging from 15 μm to 50 μm, with a single diameter of holes on each pattern mask. A

single pattern mask was placed over a single nickel-titanium sheet and the assembly was exposed to high intensity ultra-violet irradiation. After UV irradiation, the irradiated nickel-titanium sheet was placed on a fully endothelialized test surface and maintained at 37° C. under simulated in vivo flow conditions and under static flow conditions. Qualitative observations were periodically made and it was found that endothelial cells bound to the pattern of UV irradiated affinity domains and migrated across the nickel-titanium sheet by proliferating across the pattern of affinity domains, eventually fully seeding endothelium on the nickel-titanium sheet.

[079] EXAMPLE 2

[080] Selected metal pieces (Flat, 1x1 cm square pieces (1/16 in. thick) of electropolished 316L stainless steel, electropolished and heat-treated, electropolished Nitinol, gold and titanium) were subjected to radiofrequency plasma glow discharge using an EMS-100 glow discharge unit (Electron Microscopy Services, Fort Washington, PA). For this procedure, the flat metal piece is placed on a flat metal platform within the glow discharge vacuum chamber. The plasma treatments were conducted at a base vacuum pressure of 10-2 mbar in the presence of a purified argon gas atmosphere. The sample was always at negative potential as the cathode using an applied current of 20 mamps for the treatment time of 3 min. Under these conditions the surface of the sample is bombarded with argon ions resulting in the removal of surface oils and other surface contaminating molecules. Electrostatic force analyses were performed on these samples within 2 hr after removal from glow discharge treatment.

[081] For calculation of metal surface energy values, contact angle measurements were performed using a VCA-2500XE video contact angle system (AST systems, Billerica, MA) on the flat metal pieces after cleaning as described above. The surface energy of all materials studied was determined by the advancing contact angle measurement of three standard liquids; water, formamide and xylene; on each metal surface and calculated by the harmonic mean method. Ten videocaptures per second of the advancing fluid droplet/solid interface were obtained for water and formamide and 65 captures per second for xylene. All experiments were repeated 4 times.

[082] Glow discharge plasma treatment is a method of cleaning and removing surface contaminants from metallic as well as other surfaces, schematically shown in **FIG. 15**. Glow discharge treatment of many metallic surfaces causes their surfaces to change from very hydrophobic surfaces on which water beads to a hydrophilic surface on which water rapidly

spreads. This can be quantitatively measured using contact angle measurement techniques, described above. In the case of stainless steel, a change in water contact angle was measured from 98° prior to treatment to 7° after glow discharge. With this profound alteration in surface characteristics associated with glow discharge treatment, it was important to examine whether these physical alterations in surface behavior might be associated with an alteration in surface electrostatic forces. Gold, stainless steel and electropolished Nitinol all exhibit net attractive forces subsequent to glow discharge treatment, as shown in **FIG. 16**. Nitinol and gold now exhibit highly attractive forces that are significantly higher ($p<.001$) than that observed on stainless steel.

[083] It is likely based upon the profound change in measured surface electrostatic energy associated with glow discharge treatment and a similar dramatic change in water contact angle measurements that the two approaches to surface characteristics might be fundamentally related. To fully explore this possibility, contact angles on gold, stainless steel, electropolished Nitinol, and heat-treated oxidized Nitinol were measured using water, xylene, and formamide. Using the Harmonic Mean method, these measurements were used to calculate the total surface energy associated with each of the metallic surfaces. The final total surface energy value represents the sum of the polar and hydrophobic dispersive forces. To evaluate a possible association with these components of total surface energy to AFM measured electrostatic forces, the possible correlations between electrostatic force and either total surface energy were examined, the polar component of surface energy or the dispersive component. As demonstrated in **FIG. 17**, a significant correlation was observed between the polar component of total surface energy and AFM measured electrostatic force. Within this comparison it is noteworthy that electropolished Nitinol exhibits the lowest polar energy component of all four surfaces and, furthermore, that when its surface becomes heavily oxidized that the polar component increases almost 3 –fold (from 1.3 to 3.4 dynes/cm), again, paralleling changes observed in surface electrostatic force (FIG. 16).

[084] Where the terms "comprise", comprises", "comprising", "include", "includes", "included" or "including" are used in this specification, they are to be interpreted as specifying the presence of the stated features, integers, steps or components referred to, but not to preclude the presence or addition of one or more other feature, integer, step, component or group thereof.

The Claims defining the invention are as follows:

1. An implantable, biocompatible material, comprising one or more vacuum deposited layers of biocompatible materials deposited upon a biocompatible base material, wherein at least a top most vacuum deposited layer includes a homogeneous molecular pattern of distribution along the surface thereof and comprises a patterned array of geometric physiologically functional features characterized by including a topmost removable contaminant layer.

2. The implantable, biocompatible material of Claim 1, wherein the biocompatible base material and each of the one or more vacuum deposited layers of biocompatible materials differ in a material property selected from the group of material properties consisting of: grain size, grain phase, grain material composition, surface topography, and transition temperature.

3. The implantable, biocompatible material of Claim 1 or Claim 2, wherein a gap distance measured between immediately adjacent geometric physiologically functional features measures between about 1 nanometer and about 2000 nanometers, and wherein the gap distance measures about the same as a width of each of the geometric physiologically functional features.

4. The implantable, biocompatible material of Claim 3, wherein each vacuum deposited layer of biocompatible material has a thickness between about 1 nm and about 3 μm.

5. The implantable, biocompatible material of Claim 4, wherein the patterned array of geometric physiologically functional features comprises recesses having a depth including a plurality of vacuum deposited layers.

6. The implantable, biocompatible material of Claim 4, wherein the patterned array of geometric physiologically functional features comprises recesses having a depth at least equal to the thickness of top most vacuum deposited layer.

7. An implantable, biocompatible material, comprising a plurality of layers of biocompatible materials formed upon one another into a self-supporting multilayer structure, wherein the plurality of layers includes a vacuum deposited surface layer having a homogeneous molecular pattern of distribution along the surface thereof and comprises a patterned array of geometric physiologically functional features characterized by including a topmost removable contaminant layer.

8. The implantable, biocompatible material of Claim 7, wherein the vacuum deposited surface layer is different from at least a second layer immediately therebeneath in a material property selected from the group of material properties consisting of: grain size, grain phase, grain material composition, surface topography, and transition temperature.

9. The implantable, biocompatible material of Claim 7 or Claim 8, wherein a gap distance measured between immediately adjacent geometric physiologically functional features measures between about 1 nanometer and about 2000 nanometers, and wherein the gap distance measures about the same as a width of each of the geometric physiologically functional features.

10. The implantable, biocompatible material of Claim 9, wherein the vacuum deposited surface layer has a thickness between about 1 nm and about 3 μm.

11. A method for making an implantable, biocompatible material, comprising the steps of:

a. providing an implantable, biocompatible material having at least one surface intended to contact tissue of body fluids in vivo;

b. providing a mask having a defined pattern of openings corresponding in size and spacing to a predetermined distribution of binding domains to be imparted to the at least one surface;

c. treating the at least one surface of the biocompatible material through the mask by at least one of:

i. vacuum depositing a layer of material onto the at least one surface, wherein the vacuum deposited layer is different from the at least one surface immediately therebeneath in a material property selected from the group of material properties consisting of: grain size, grain phase, grain material composition, surface topography, and transition temperature, and removing the mask to yield a plurality of binding domains defined on the at least one surface of the implantable, biocompatible material;

ii. vacuum depositing a layer of sacrificial material onto the at least one surface, removing the mask from the at least one surface, vacuum depositing a second layer of material onto the at least one surface, wherein the second vacuum deposited layer is different from the at least one surface immediately therebeneath in a material property selected from the group of material properties consisting of: grain size, grain phase, grain

material composition, surface topography, and transition temperature, and removing the sacrificial material to yield a plurality of binding domains defined on the at least one surface of the implantable, biocompatible material;

iii. photo irradiating the at least one surface to photochemically alter the at least one surface, and removing the mask to yield a plurality of binding domains defined on the at least one surface of the implantable, biocompatible material; or

iv. treating the at least one surface with glow discharge plasma;

d. activating the at least one surface of the implantable, biocompatible material by removing contaminant molecules that occupy otherwise unsaturated bonds at the at least one surface; and

e. adding a removable contaminant layer to the activated surface.

12. The method of Claim 11, wherein the implantable, biocompatible material in the providing step comprises a bulk material.

13. The method of Claim 11 or Claim 12, wherein a gap distance measured between immediately adjacent openings in the mask measures between about 1 nanometer and about 2000 nanometers, wherein the gap distance measures about the same as a width of each of the openings, and wherein the mask has a thickness between about 1 nm and about 3 μm.

14. The method of any one of Claims 11 to 13, wherein the activating step further comprises activating the at least one surface of the implantable, biocompatible material by a technique for activation selected from the techniques for activation of the at least one surface consisting of: chemical etching, electrochemical treatment, thermal treatment, and plasma etching.

15. The method of any one of Claims 11 to 14, wherein the adding a removable contaminant layer step further includes coating the activated at least one surface with a biodegradable material or a mixture of inorganic and organic material, or immersing the activated at least one surface in a fluid until implantation.

16. The method of any one of Claims 11 to 14, wherein the adding a removable contaminant layer step further comprises forming the removable contaminant layer during plasma etching.

17. The implantable, biocompatible material of Claim 1 wherein the contaminant layer comprises a biodegradable material, inorganic or organic material, or a mixture of inorganic and organic material.

18. The implantable, biocompatible material of Claim 7 wherein the contaminant layer comprises a biodegradable material, inorganic or organic material, or a mixture of inorganic and organic material.

19. The implantable, biocompatible material of Claim 1 wherein the contaminant layer is a protective coating which further comprises a fluid in which the implantable, biocompatible material is immersed until implantation.

20. The implantable, biocompatible material of Claim 7 wherein the contaminant layer is a protective coating which further comprises a fluid in which the implantable, biocompatible material is immersed until implantation.

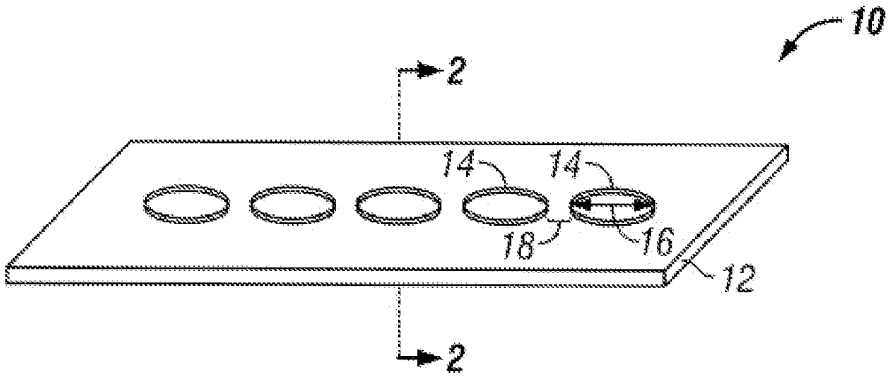


FIG. 1

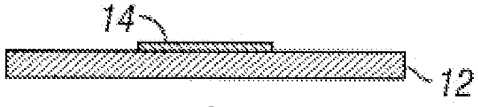


FIG. 2

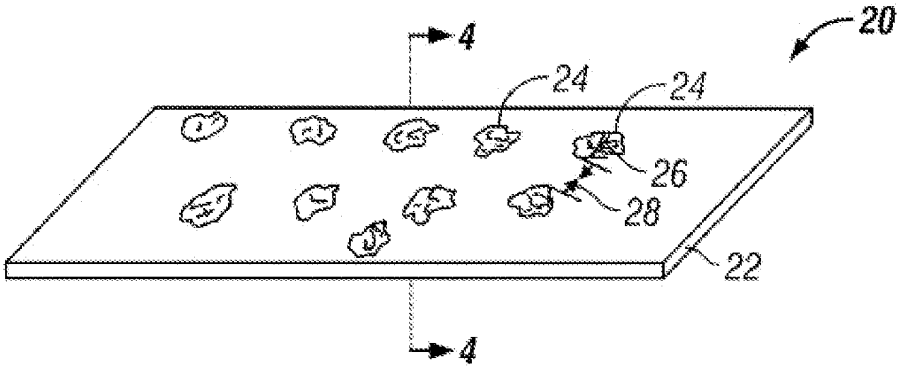


FIG. 3

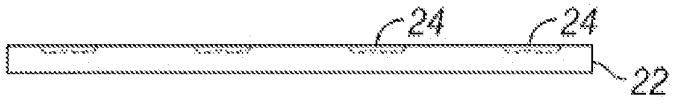


FIG. 4

FIG. 5

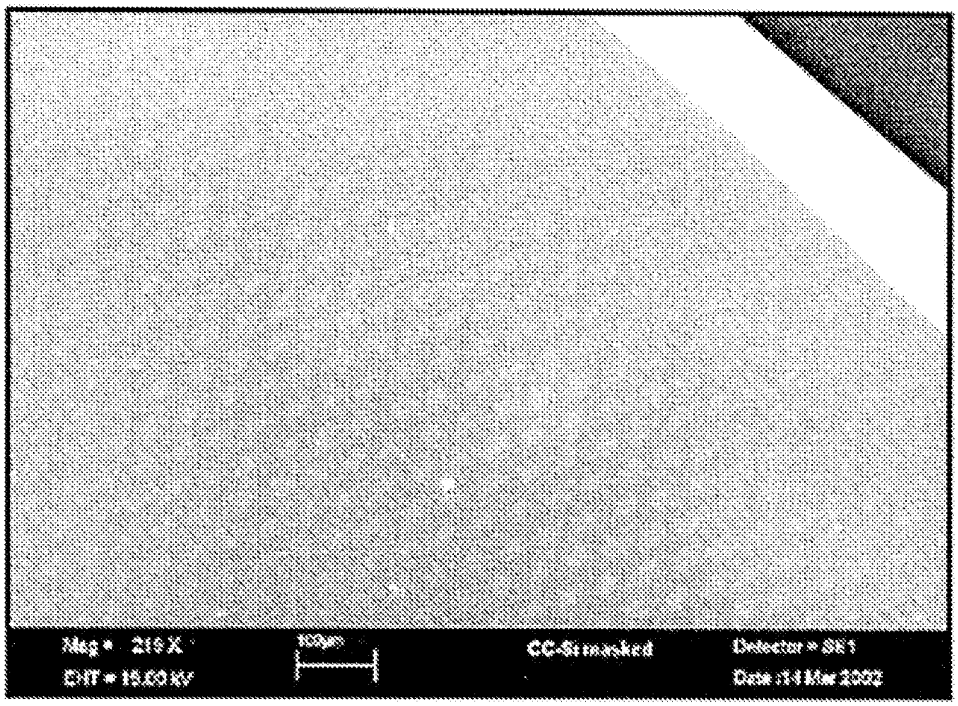
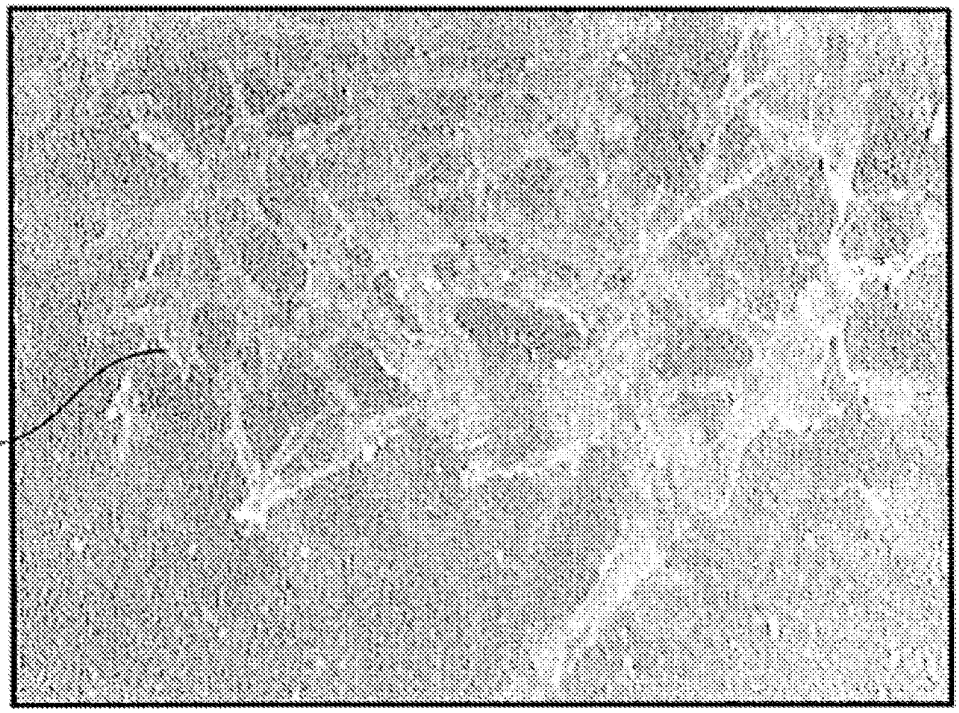

Mag = 219 X
EHT = 15.00 kV
100µm
CC-Si masked
Detector = SE1
Date :14 Mar 2002

FIG. 6A


32

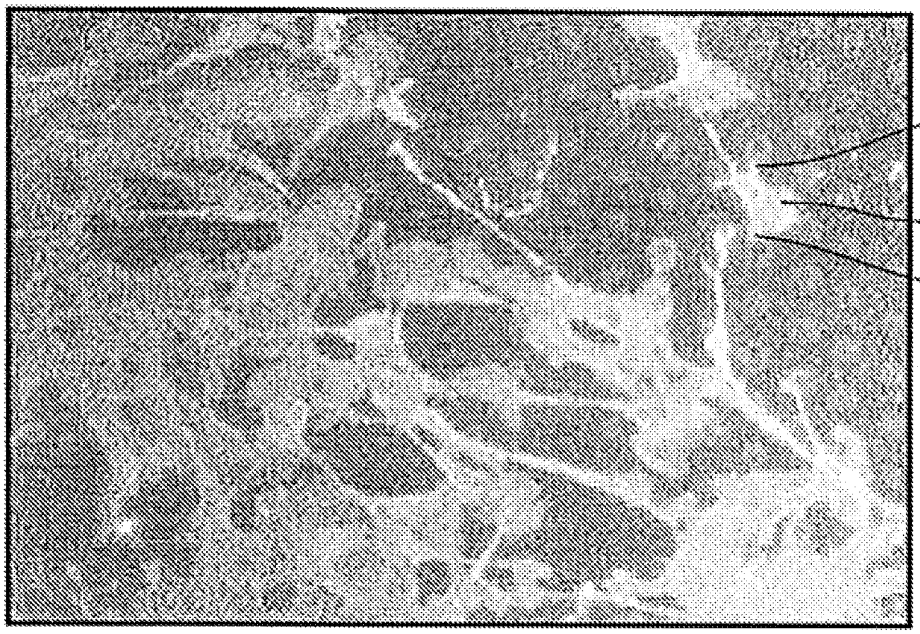


FIG. 6B

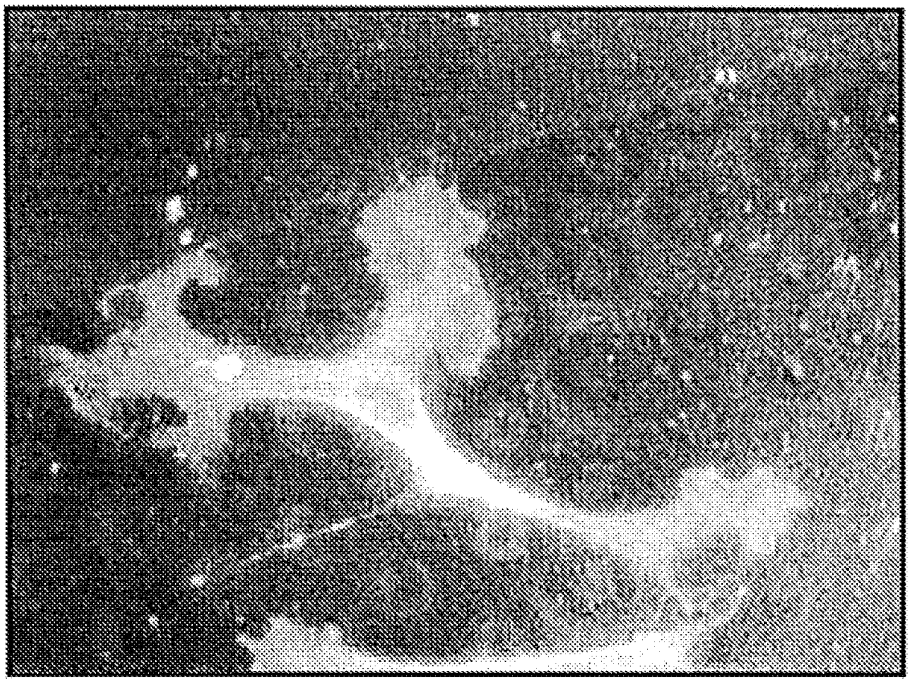


FIG. 6C

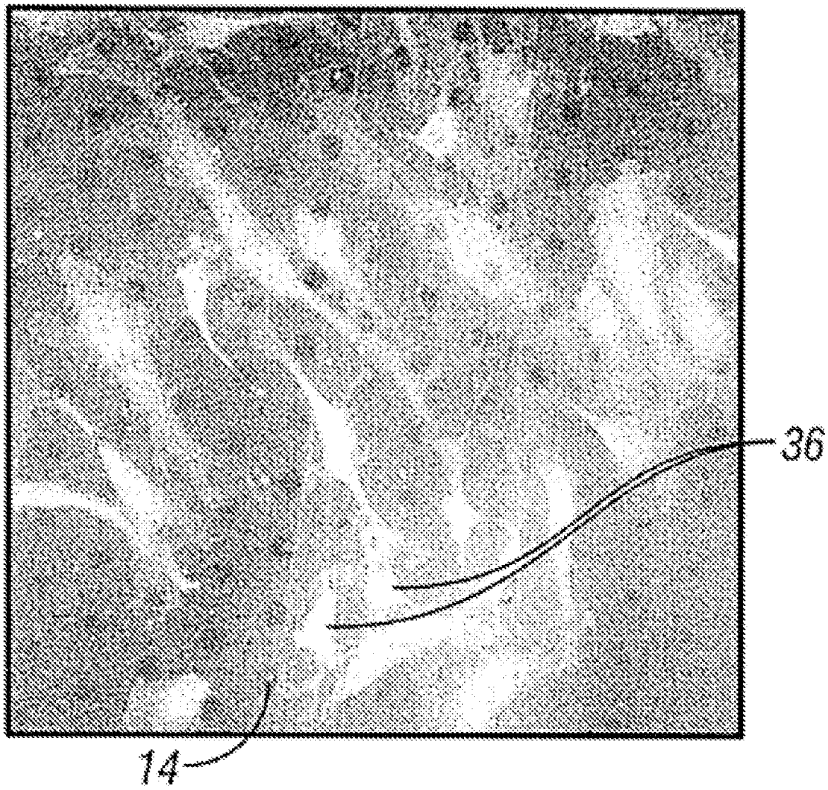


FIG. 7

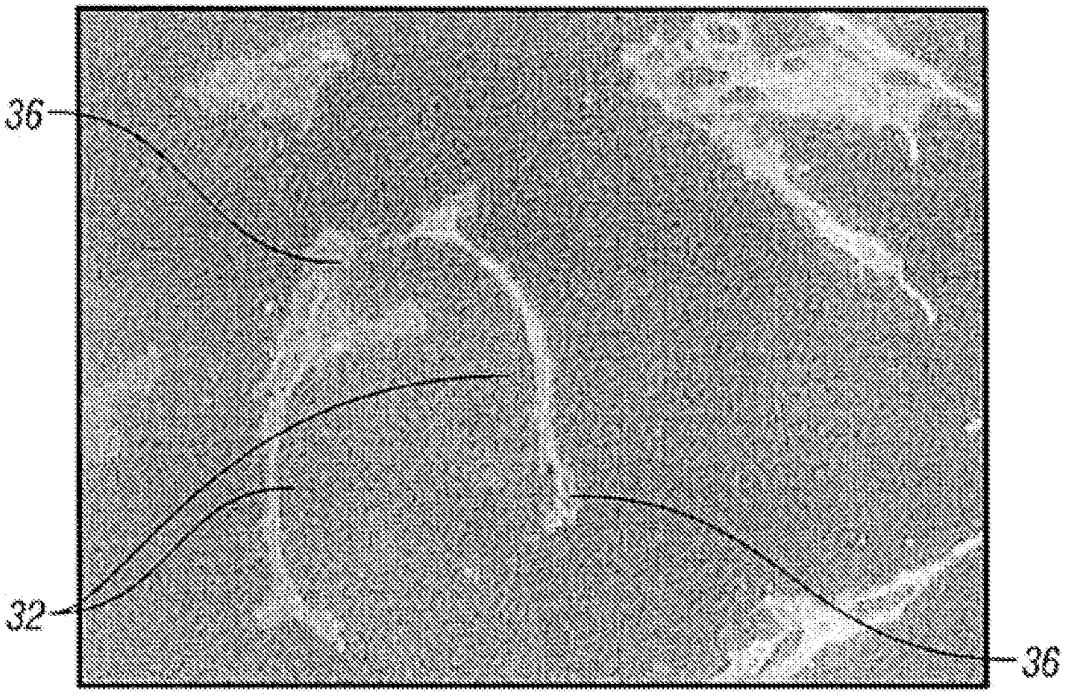
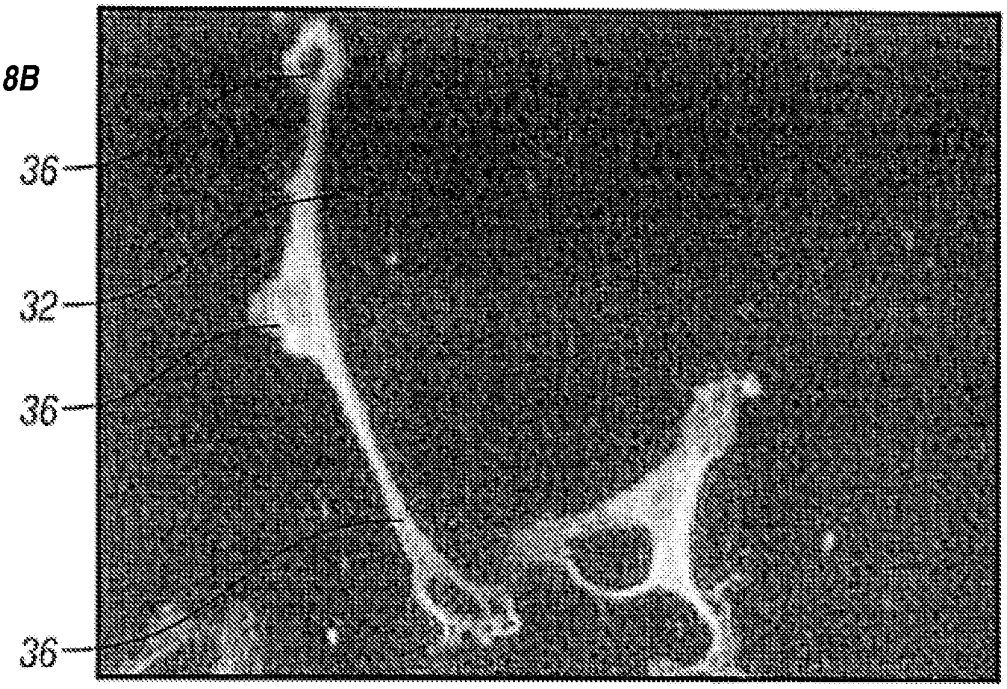


FIG. 8A

FIG. 8B



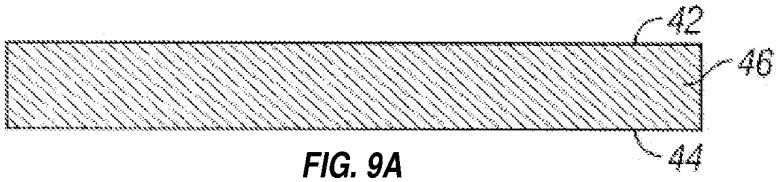


FIG. 9A

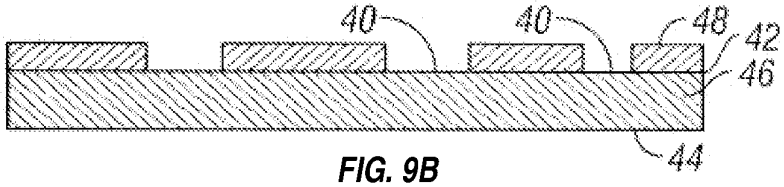


FIG. 9B

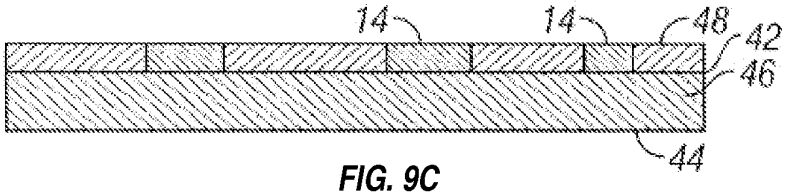


FIG. 9C

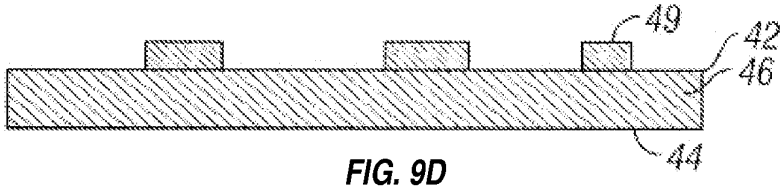


FIG. 9D

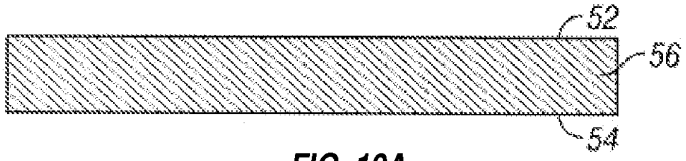


FIG. 10A

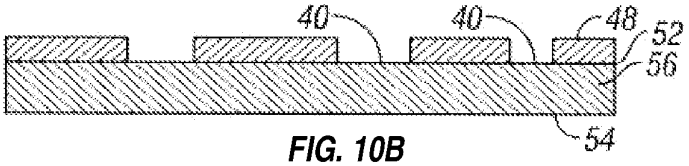


FIG. 10B

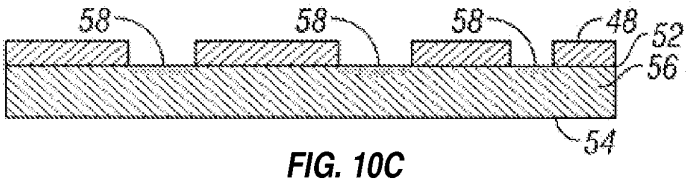


FIG. 10C

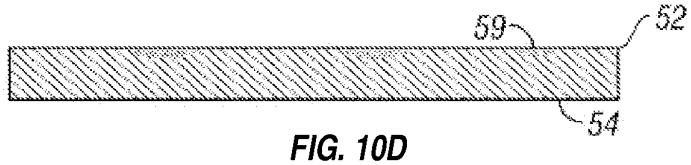


FIG. 10D

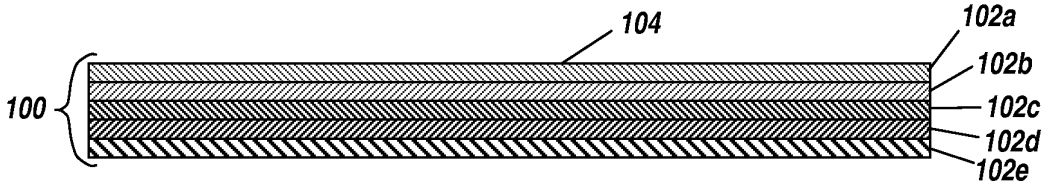


FIG. 11A

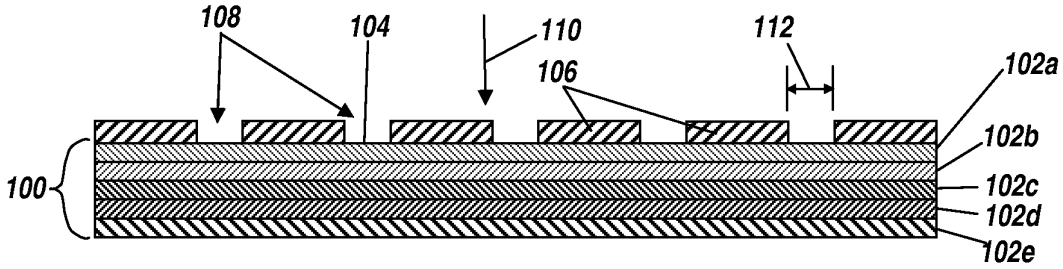


FIG. 11B

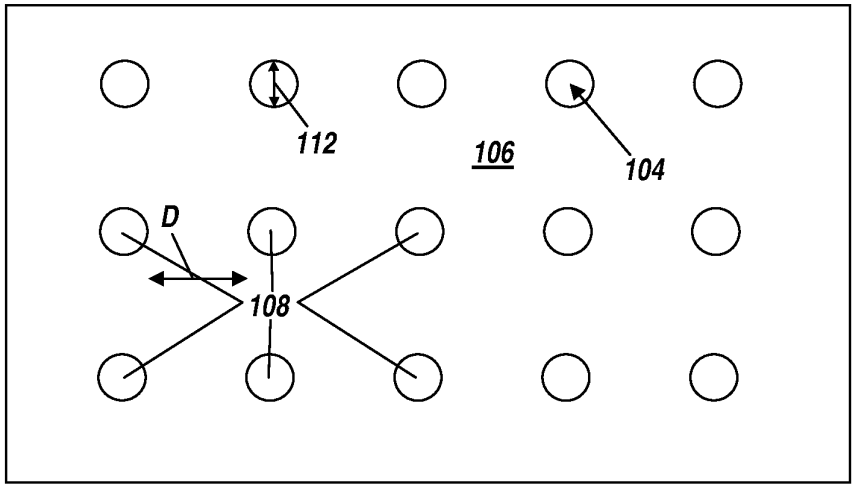


FIG. 11C

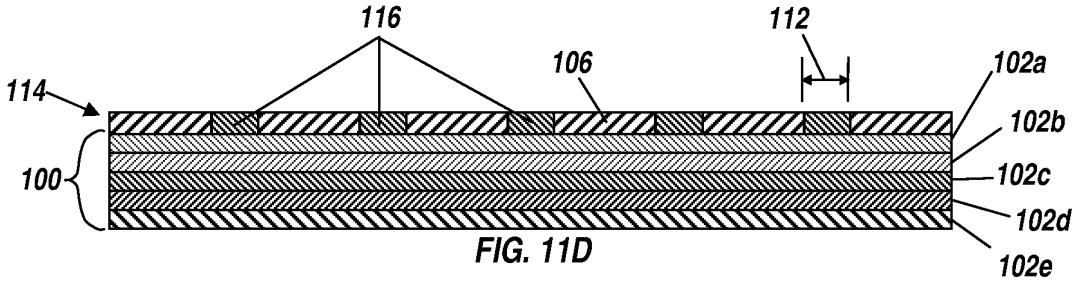


FIG. 11D

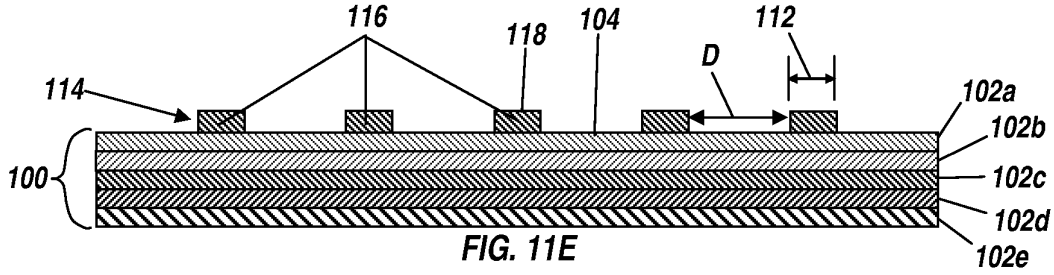


FIG. 11E

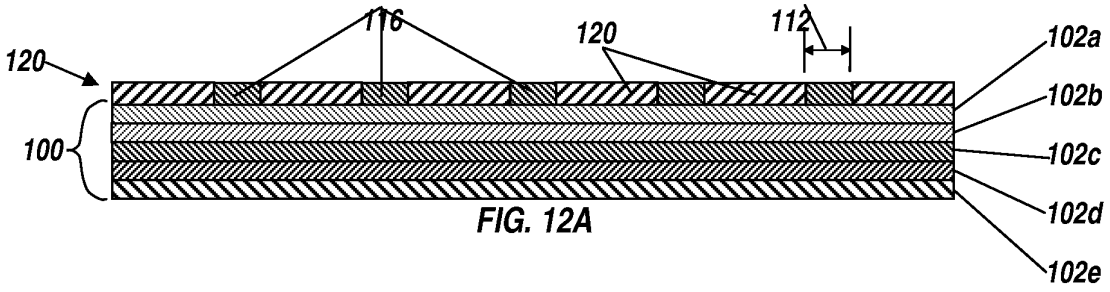


FIG. 12A

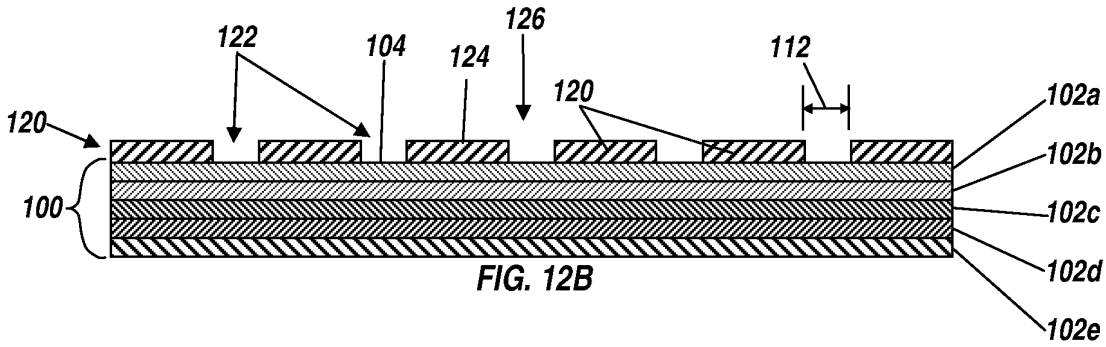


FIG. 12B

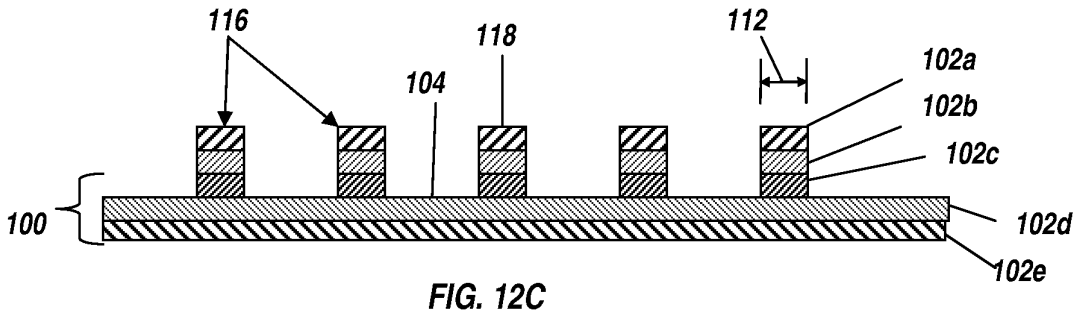


FIG. 12C

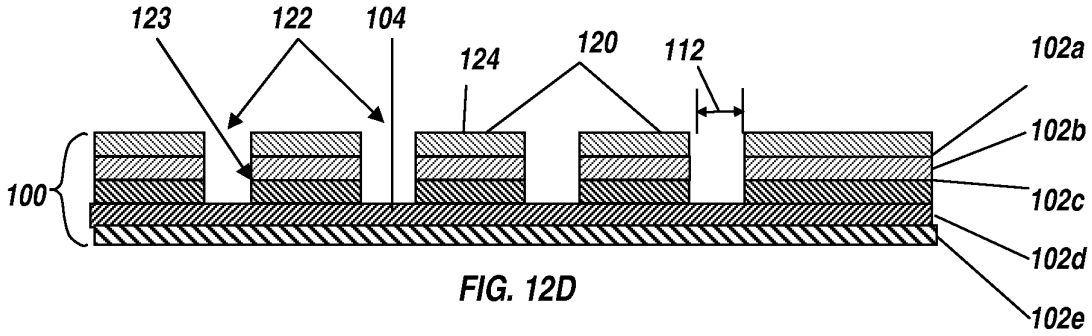


FIG. 12D

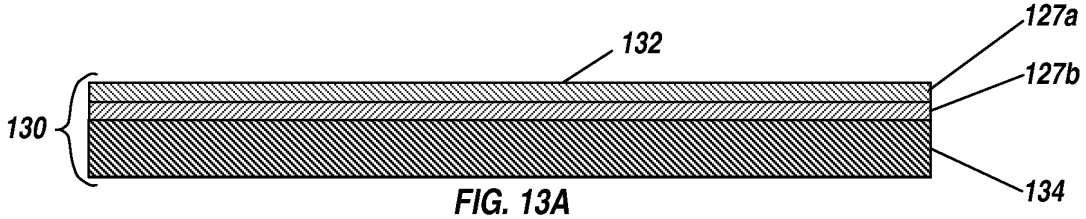


FIG. 13A

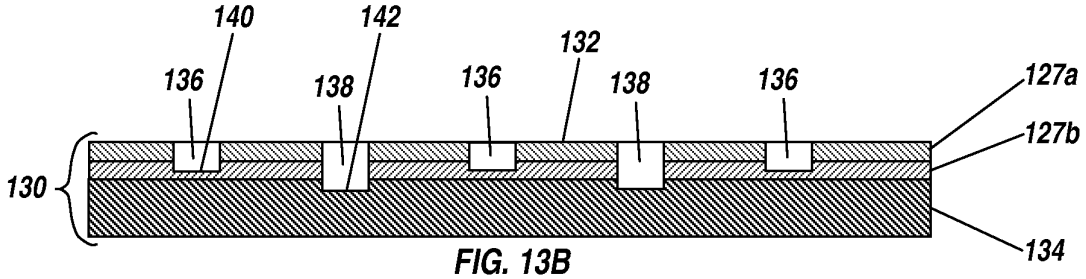


FIG. 13B

FIG. 14

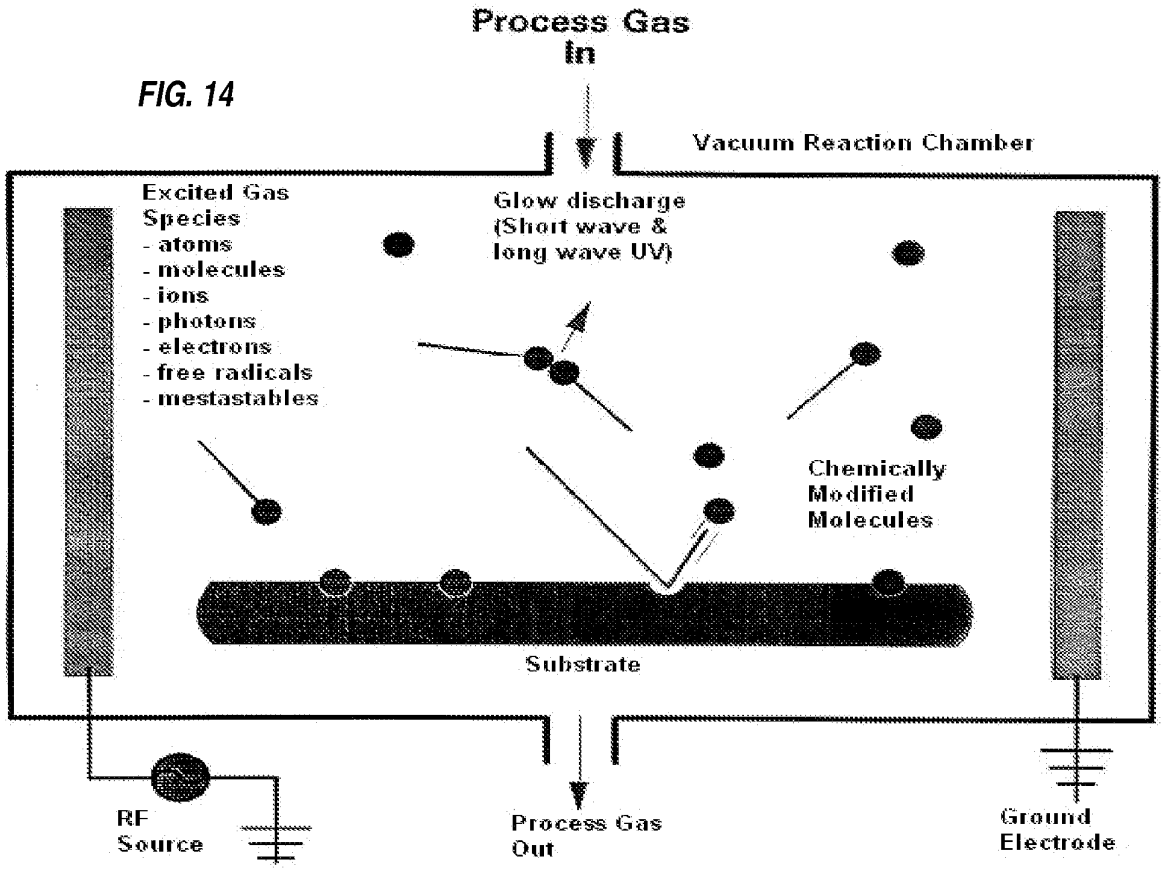

Process Gas In
Vacuum Reaction Chamber
Excited Gas Species
- atoms
- molecules
- ions
- photons
- electrons
- free radicals
- mestastables
Glow discharge (Short wave & long wave UV)
Chemically Modified Molecules
Substrate
RF Source
Process Gas Out
Ground Electrode

FIG. 15

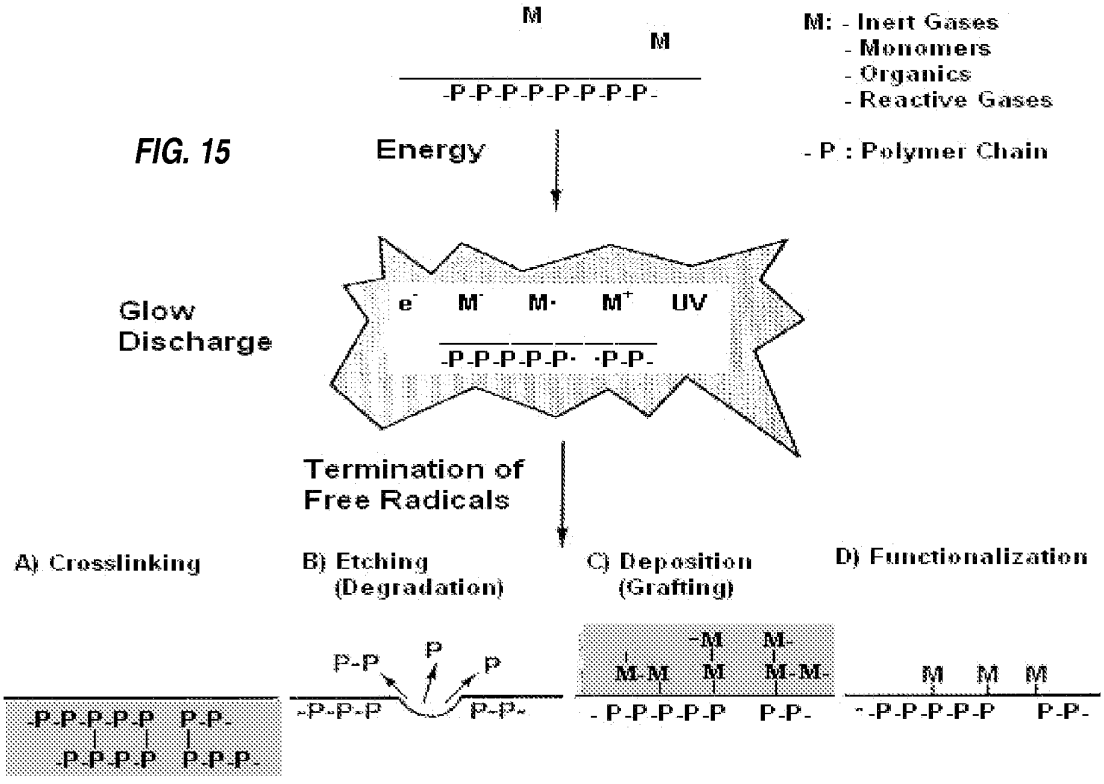
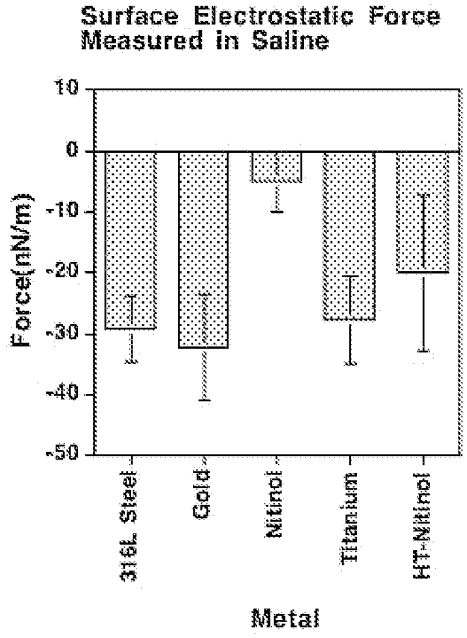

M
M
-P-P-P-P-P-P-P-P-
M: - Inert Gases
- Monomers
- Organics
- Reactive Gases
- P : Polymer Chain
Energy
Glow Discharge
e⁻ M⁻ M· M⁺ UV
-P-P-P-P-P- -P-P-
Termination of Free Radicals
A) Crosslinking
B) Etching (Degradation)
C) Deposition (Grafting)
D) Functionalization

FIG. 16


Surface Electrostatic Force
Measured in Saline
Force(nN/m)
10
0
-10
-20
-30
-40
-50
316L Steel
Gold
Nitinol
Titanium
HT-Nitinol
Metal

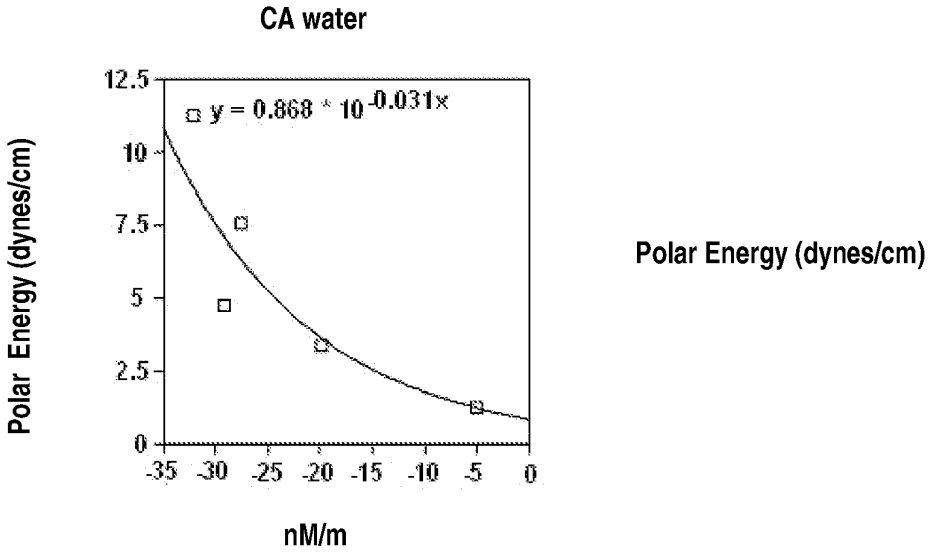

CA water
Polar Energy (dynes/cm)
12.5
10
7.5
5
2.5
0
y = 0.868 * 10^-0.031x
-35 -30 -25 -20 -15 -10 -5 0
nM/m
Polar Energy (dynes/cm)

FIG. 17