(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 January 2010 (14.01.2010)

PCT

(10) International Publication Number
WO 2010/004261 A2

(51) International Patent Classification:
A61L 27/50 (2006.01) *A61L 27/54* (2006.01)

(21) International Application Number:
PCT/GB2009/001653

(22) International Filing Date:
2 July 2009 (02.07.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0812660.9 10 July 2008 (10.07.2008) GB

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: TEXTURED MEDICAL IMPLANTS

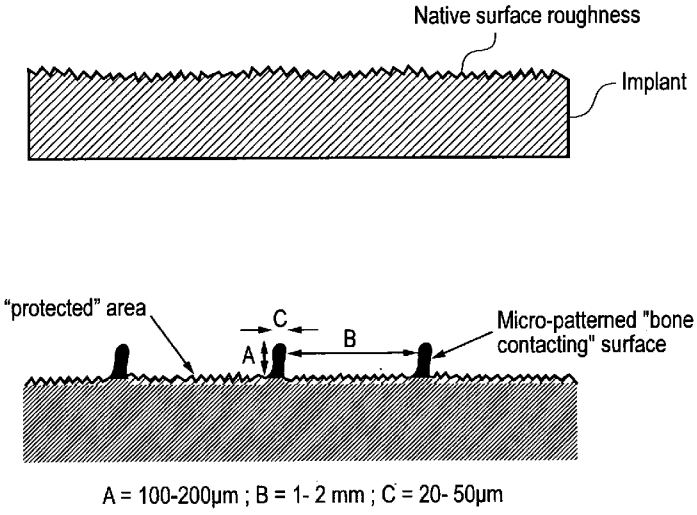

FIG. 3

(57) Abstract: There invention relates to a medical implant having a therapeutic agent immobilised thereon, the implant having a surface asperity such that the therapeutic agent is localised on the implant in a manner whereby the therapeutic agent does not come into contact with the host tissue during implantation.

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TEXTURED MEDICAL IMPLANTS

FIELD OF THE INVENTION

The present invention relates to methods for texturing implantable medical devices as well as the implants produced according to the methods.

BACKGROUND OF THE INVENTION

Implant-associated infections are an ever present and devastating complication of insertion of a foreign object, such as a stent, catheter, intravenous delivery tube, heart valve, dental implant, electro-mechanical device, prosthetic devices and orthopaedic devices, into a body. Sources of these infections include the introduction of foreign bodies during wounding, the introduction of microorganisms during surgery and hematogenous infection, i.e due to an infection that is already present elsewhere in the body.

The majority of periprosthetic infections are caused by *Staphylococcus aureus* and *S.epidermidis*, both gram-positive bacteria; less frequent infections are caused by the gram-negative organisms. Both *S.aureus* and *S. epidermidis* are commonly present in the operating room environment. They adhere to the surface of the implant, propagate rapidly and during this proliferation generate a bio-film. Production of the polysaccharide – enclosed clumps of bacteria, characteristic of a biofilm, completes the process of resisting antibiotic access to the bacterial surface.

About 5-20% of fracture fixation devices (pins, nails, screws, etc.) and about 1-3% of orthopaedic joint implants become infected. Cure of infected orthopaedic implants, such as joint prostheses, usually requires both removal of the prosthesis and administration of a long course of antibiotics. Currently, antibiotics are either administered locally around implants in bone cement, beads, or as a non-covalent coating, however, the activity of such antibiotics is short-lived with these delivery methods. In most cases, this is followed by re-implantation of a new joint prosthesis weeks or months later, after making sure that the infection has been eradicated. This

underscores the tremendous medical (major morbidity in most patients and inability to achieve cure in at least 10-20% of infected cases) and economic impact of infectious complications of orthopaedic implants. For instance, the estimated cost of removing an infected hip joint prosthesis, administering 4-6 week course of IV antibiotics and re-insertion of a new joint prosthesis varies between $100,000 and $150,000.

As illustrated in, for instance US 7,255,872 to Jennison, orthopaedic implants with an antibiotic immobilised thereon have been developed with the objective of preventing the development of a biofilm on the implant surface. However, the mechanism of immobilisation is often based on the covalent tethering of the antibiotic directly to the metal implant surface or to a polymer coating. Due to the mismatch in hardness between the bone and a polymer coating there is a significant risk of mechanical abrasion during insertion, whereby the harder bony surface "plows" grooves into the softer coating material resulting in the removal of antibiotic as illustrated in Figure 1 The scratch hardness of organic coatings is greatly influenced by factors such as the nature of the metal substrate, the thickness of the coating and the temperature and humidity of the surroundings. If antibiotic is removed from the surface during mechanical insertion then the released amount will be of such a low dose that it will have little impact on preventing infection. Moreover, the residual antibiotic detached from the surface will increase the risk of antibiotic resistance whereby the bacterial cell becomes tolerant to the antibiotic that it previously had the ability to destroy.

In order for the therapeutic molecule to remain efficacious, the antibiotic needs to remain tethered to the surface of the medical device after surgical implantation ideally for the life time of the patient to ensure that there are no opportunities for bacterial colonization.

Consequently, the present invention addresses the problem of therapeutic agents being physically removed from an implant surface during insertion of the implant into host tissue.

SUMMARY OF THE INVENTION

According to a first aspect of the invention there is provided a medical implant having a therapeutic agent immobilised thereon, at least a portion of the implant on which the therapeutic agent is immobilised having a tissue-contacting surface with an asperity such that the therapeutic agent does not extend beyond the tissue-contacting surface of the implant

According to a second aspect of the invention there is provided a method of producing a medical implant having a therapeutic agent immobilised thereon, at least a portion of the implant on which the therapeutic agent is immobilised having a tissue-contacting surface with an asperity such that the therapeutic agent does not extend beyond the tissue-contacting surface of the implant, said method comprising the steps of;

i) forming at least one intrusion and/or a plurality of protrusions on the implant surface;

ii) immobilising a therapeutic agent within the intrusion and/or within the space between the protrusions

According to a third aspect of the invention there is provided an implant or a method as herein described with reference to the accompanying Figures and Examples.

The term "medical implant" herein refers to medical devices which are indwelling or implanted in an animal, including humans and non-human animals. These implants can be either permanent or temporary. Examples of such medical implants include orthopaedic implants such as joint prostheses, screws, nails, nuts, bolts, plates, rods, pins, wires, inserters, osteoports, spinal cages, external fixaters such as halo systems and other orthopaedic devices for stabilization or fixation of fractures or disarticulations. Other devices may include non-orthopaedic devices such as tracheostomy devices, intraurethral and other genitourinary implants, stylets, dilators, stents, wire guides and access ports of subcutaneously implanted vascular catheters.

In specific embodiments of the invention the implant is an orthopaedic implant. The implant may be utilised for trauma applications and can include; screws, nails, nuts, bolts, plates, rods, pins, wires, inserters, osteoports, spinal cages, external fixaters such as halo systems and other orthopaedic devices for stabilization or fixation of fractures or disarticulations. The implant may be utilised for reconstructive applications and can include; joint prostheses for use in knee, hip and shoulder replacements.

The therapeutic agent is selected from the group consisting of, antibacterial agents; antimicrobial agents; anticoagulants; antithrombotics; complement inhibitors; antiplatelet agents; antitumor agents; anti-inflammatories; enzymes; cytokines, catalysts; hormones; growth factors or inhibitors of growth factors; drugs; vitamins; antibodies; antigens; nucleic acids; dyes (which act as biological ligands); DNA and RNA; and proteins and peptides, cells (such as stem cells) as well as combinations of any such therapeutic agents with each other and/or with adjuvants, and the like.

In particular the therapeutic agent is a bone healing agent. In particular the therapeutic agent is an osteogenic agent, such as a bone morphogenetic proteins (BMP).

The therapeutic agent can be natural molecule.

The therapeutic agent can be synthetic molecule.

The therapeutic agent can be synthetic analogue of a natural molecule.

In specific embodiments of the invention the therapeutic agent is an antibiotic.

In further specific embodiments of the invention the implant is an orthopaedic implant and the therapeutic agent is an antibiotic.

In further specific embodiments of the invention the implant is an orthopaedic implant and the therapeutic agent is vancomycin or variants thereof.

In further specific embodiments of the invention, a plurality of different antibiotics with different specificities can be immobilised on the implant.
In certain embodiments of the invention the surface asperity is achieved by removing material from or displacing material at the implant surface to form a plurality of intrusions such as recesses, pores, slots, holes, depressions, pits, grooves or troughs into which the therapeutic agent is physically and/or chemically immobilised. The therapeutic agent is localised within the intrusion such that no part of the agent extends above the intrusion so as to be in direct contact with the host tissue. The therapeutic molecule is therefore physically protected from mechanical forces during implant insertion.

The techniques conventionally employed to remove or displace material from a surface include e-beam and laser processing; acid and plasma etching and blasting techniques; with or without a patterned mask.

In sand, glass bead or alumina grit blasting techniques, compressed air is generally used to drive a blasting medium onto the implant surface at a high velocity to deform and, in some instances, remove portions of the implant surface. The surface texture obtained depends upon the size, shape and hardness of the implant material and on the velocity at which the blasting medium is driven onto the implant surface. The most common surfaces produced by sand or glass bead blasting are matte or satin-finish, while alumina grit blasting produces a random roughened surface.

Illustrative of a sand or glass bead blasting technique is the method disclosed in U. S. Pat. No. 5,057,208 to H. R. Sherry, et al wherein the implant surface is shot blasted with metal shot followed by glass bead blasting and then electropolishing.

In acid etching techniques a pattern or mask is placed upon that surface of the implant desired not to be textured, the exposed parts are then typically

treated with an acid that corrodes the exposed surface of the implant whereupon the acid treated surface is washed or neutralized with an appropriate solvent and the pattern or mask is removed.

Illustrative of an acid etching technique is the method disclosed in U. S. Pat. No. 4,778.469 to R. Y. Lin, et al wherein an acid soluble (e. g., aluminum or zinc) space occupier is used. The space occupier contains the pattern to be transferred to the implant surface and is placed on the desired portion of the implant surface that is to be texturized. The space occupier is pressed into the implant surface and is then removed by treating it with acid.

In alternative embodiments of the invention the surface asperity is achieved by adding material to or displacing material at the implant surface to form a plurality of protrusions. The therapeutic agent is physically and/or chemically immobilised within the spaces provided between the protrusions such that no part of the agent extends beyond the pitch of the protrusion. The therapeutic molecule is therefore physically protected from mechanical forces during implant insertion.

The techniques typically employed to add material to or displace material at the surface include: maskless (3D) UV lithography; electron beam (EB) sculpturing; plasma based ion implantation; heat chemical and oxidation; hydroxyapatite and bioglass coatings; welding powder particles to the outer surface and sputtering.

EB sculpturing is a particularly advantageous technique as it creates high aspect ratio slots (50 μm to 2 mm in height) and holes or intrusions and can be applied to most metals (e.g. titanium, stainless steel, aluminium, copper), glasses, ceramics and polymers.

The surface roughness (height, spacing and 3D shape) are tightly controlled by the processing parameters. These include laser power and peak power (for continuous wave and pulsed lasers respectively), laser spot diameter, hatching pitch (scan spacing), scan speed and scanning strategy.

In other embodiments of the invention the surface asperity is achieved by a combination of i) forming protrusions on the surface of the implant and ii) forming intrusions within the surface of the implant.

The dimensions of the textured surface are critical as certain types of roughness can lead to the dead space with no tissue ingrowth, which is a perfect shelter for the bacterial colonies, occasionally leading to serious infection. Equally, the surface topography needs to allow attachment of mammalian cells, such as osteoblasts to ensure that the implant does not become loose over time.

The profiles of the asperities in cross-section can include trapezoidal, square-wave, shark-fin, and sinusoidal producing an array of patterns (in plan view) that include isotropic, circular, cross-hatched, radial, vertical and horizontal as illustrated in Figure 2.

Optimal physical protection is provided to the therapeutic agent when the pitch of the surface asperity is at least about 100 microns. In particular embodiments the pitch of the surface asperity is between about 100 to 200 microns. This is similar to the typical interference fit experienced by orthopaedic implants in bone. If the height or pitch is less than 100 microns, it is unlikely to provide sufficient protection for the immobilised therapeutic agent from the abrasion forces generated by the neighboring host tissue.

The peak width is typically between about 20 and 50 microns.

The peak to peak spacing of the textured surface needs to be wide enough to ensure a high degree of coverage of the immobilized therapeutic agent. The peak to peak spacing is typically between about 1 and 2 mm.

Figure 3 is a schematic of the optimal dimensions of micro-patterning on an implant surface.

To avoid any inflammatory responses that result from tissue damage caused by micromotion against an abrasive surface, the projected areas of the surface will be free of sharp edges.

In further embodiments of the invention an additional nano-texturing step can carried out after the above described micro-texturing step. Nano-texturing of the intrusions (in embodiments in which material has been removed from or displaced at the implant surface) or the nano-texturing of the spaces between the protrusions (in embodiments in which material has been added to or displace at the implant surface), further increases the "pockets" in which the therapeutic agent can be immobilised and hence protected.

In situations where bone ingrowth is not desirable, e.g. trauma fixation devices, the roughness generated by micro-texturing of the implant surface can be reduced temporarily by packing the intrusions or the spaces between the protrusions with resorbable materials in the form of nano-particles, polymeric beads, and thermatropic gels. This will temporarily reduce the "apparent" roughness during the bone healing period reducing the potential for bone ingrowth.

In addition to micro/nano-texturing of the implant surface, other methods for protecting the therapeutic agent include (a) increasing the thickness of the organic coating, (b) use of "temporary" sacrificial coatings (c) use of a "lubricant" shear-layer, (d) deposition of abrasion resistant coating materials containing the active agent and which are discussed in turn below:-

Increasing the thickness of the organic coating is another potential solution for increasing the scratch-resistance. Furthermore, the addition of inorganic silica filler materials within this coating layer of a defined type and particle size is another option for improving the scratch resistance of the coating without a negative impact on the physical and performance properties or application parameters of the original coating material. These filler particles can be added to curable organic coatings containing the active agent.

Sacrificial coatings (between 100 and 200 microns thick) can also be used as a temporary protective barrier to the tethered layer of biomolecules during surgical implantation. The sacrificial layer can be a resorbable

poly(ester) such as poly(glycolic acid) (PGA), poly(lactic acid) (PLA), PLA-PGA copolymers, poly(caprolcatone) (PCL) or a polysaccharide such as dextran. The sacrificial coating is hydrolytically degraded after surgical implantation exposing the underlying organic layer containing the tethered biomolecules.

The lubricant shear-layer protects the coating by reducing the abrasion forces between the implant surface and surrounding tissue on insertion. Materials in this category may also contain complementary active materials such as free vancomycin hydrochloride, adjunct antibiotic or other beneficial additive. They may be readily cleared from the site after insertion or have a prolonged therapeutic effect. The shear-layer lubricants may be powders e.g. micronised polysaccharide such as chitosan, hydrophobic liquids such as biocompatible mineral, vegetable or silicone oils, hydrophilic liquids such as glycerol or low molecular weight polyethylene glycol or aqueous based polymer solutions such as solutions of carboxymethyl cellulose or hyaluronic acid.

Abrasion resistant coating materials prepared by the sol-gel method can also be spin coated onto the implant surface to protect the active agent. These coatings are inorganic/organic hybrid network materials (e.g. bisphenol-A polycarbonate and diallyl diglycol carbonate resin) synthesized from 3-isocyanatopropyltriethoxysilane functionalized organics and metal alkoxide.

DETAILED DESCRIPTION OF THE INVENTION

The following Examples are offered by way of illustration and are not intended to limit the invention in any manner.

Figure 1: (a) Photographs acquired from representative regions of the as-received vancomycin-tethered cobalt chromium test coupons tagged with a fluorescent marker (b) Photographs acquired from representative regions of coupons after insertion into ovine femur.

Figure 2: 2D patterns formed by the surface texture of the implant surface in plan view.

Figure 3: Schematic illustrating the micro-texturing of an orthopaedic implant surface to produce an array of "bone-contacting" sinusoidal peaks and "protected" trough regions on the surface.

Figure 4: Magnified view of the protected region of the implant surface highlighting the nano-textured surface superimposed onto the "protected" region of the surface to increase the number of potential binding sites for the vancomycin.

Figure 5: Schematic illustrating the covalent tethering of vancomycin to the micro/nano-textured surface.

Figure 6: Reaction scheme for synthesis of vancomycin bonded to "protected region" of implant surface.

Figure 7: Removal of vancomycin from the "bone contacting" regions of the surface.

Figure 8: Plot of amount of secondary antibody detected per disc for various surface treatments.

Figure 9: Plot of the amount of secondary antibody remaining (from mean result, n=2) for discs with various surface treatments, following insertion into ovine femur.

EXAMPLE 1

Preparation of an orthopaedic implant surface to which vancomycin is tethered involves the following steps;

Step 1: Preparation of micron-scale topography

The native implant surface is micro-textured to produce a surface with "bone contacting" projections that are between 100 and 200 microns in height (Figure 3).

Step 2: Nano-texturing of "protected region" of implant surface

The micro-textured surface is subsequently exposed to either an acid (H_2SO_4/H_2O_2) or alkali treatment (NaOH) or is subjected to either anodisation or high-resolution electron beam lithography in order to increase the surface area of the "protected" region of the implant increasing the yield of immobilised vancomycin (Figure 4).

Step 3: Tethering of vancomycin to micro/nano-textured surface

Vancomycin is tethered to the micro/nano-textured surface (Figure 5). A silylated surface (anchor) is created and subsequently vancomycin is attached via oligoethylene glycol linker. The entire reaction scheme for synthesis of vancomycin bonded to textured Ti6Al4V is shown in Figure 6.

Step 4: Removal of "non-protected" coating by simulated mechanical insertion in bone

The coated implant is then inserted into sawbone in order to remove any vancomycin that is likely to be cleaved off the bone contacting regions of the surface during surgical implantation (Figure 7). Non-tethered vancomycin generated by this simulated mechanical insertion process is then subsequently washed off the surface.

This step is carried out to minimise the risk of generating labile chemical entities with unknown toxicological properties and residual antibiotic detached from the bone-contacting region of the surface. If this step is not carried out there is a risk of antibiotic resistance whereby the bacterial cell

becomes tolerant to the antibiotic that it previously had the ability to destroy.

Example 2: Effectiveness of various surface treatments in preserving a tethered vancomycin coating during insertion of discs into ovine femur

Method

(i) Sample details:

Ti64 discs (d=12mm, 3mm thickness) were used to generate various surface textures:

1) Grit-blasted "GB" discs were obtained from S&N Orthopaedics. Grit blasting was performed following a standard protocol. This provides a microscopic texture.

2) Acid etched "AE" discs were supplied by S&N Orthopaedics. Acid etching was performed at 75°C for 15mins using a mixture of HCl and H_2SO_4 (1:1). This provides an intermediate texture.

3) Nano-texturing "nano". All discs were textured face down in a Pyrex beaker. Discs previously sonicated in an aqueous solution of Micro-90 (2%v/v) and washed with DI water, were heated in 4M NaOH at 60°C for 2 hours to provide nano-texture. Samples were subsequently sonicated in DI water for 5 minutes and washed thoroughly in DI water. The textured samples were allowed to dry overnight in a vacuum oven at 40°C. The nano-texturing procedure was found to leave the macro scale surface features (e.g grit blast) largely intact. This provides a nanoscale texture.

(ii) Insertion into ovine femur

Discs (3mm in thickness) were forced into slotted bone (2.8mm slot width) using a hammer. The discs were retrieved through the IM canal.

Approximately 67% of the total disc surface area was subjected to abrasion.

(iii) Sample cleanup

Following disc removal, ovine tissue was removed using the following procedure:

PBS with 10 minutes sonication
3 x deionised water washes with 10 minutes sonication
DMF wash with 10 minutes sonication
DI wash
DMF wash with 10 minutes sonication
3 x deionised water washes.

No visible ovine tissue and no perceivable ovine tissue odour remained following this treatment. The discs were stored in a refrigerator prior to analysis.

(iv) Sample analysis

The amount of vancomycin remaining on disc surfaces was estimated using an antibody attachment method. Quantification of tethered vancomycin molecules was undertaken by labelling the test discs with a primary rabbit anti-vancomycin IgG followed by a goat anti-rabbit Alexafluor 488 tagged IgG. Post labelling, the antibodies were removed by placing the sample in 1ml of a tris/tricine/SDS/DTT (100mM/100mM/0.1%/50mM) buffer solution pH8.3 at 50°C for two hours. Quantification was then undertaken using fluorescence (Ex485nm, Em518nm) by comparison against standards of the Alexafluor 488 secondary antibody.

RESULTS

Figure 8 illustrates the amount of secondary antibody detected as (μg) per disc for various surface treatments, for non-inserted and inserted discs.
Figure 9 is a plot of % secondary antibody remaining [from means result (n=2)] for discs with various surface treatments, following insertion into ovine femur.

KEY:

"Control": no surface treatment
"AE": acid etching
"GB": grit blasting
"GB & AE": acid etching and grit blasting
"Nano disc": full sample pre-treatment before surface chemistry to attach vancomycin
"AE + Nano": acid etching and nano surface treatment
"GB + Nano": grit blasting and nano surface treatment
"GB + Nano+ AE": grit blasting, nano surface treatment and acid etching
"Nano no treatment": no pre-treatment with piranha acid before surface chemistry to attach vancomycin
"Nano no HCL/MeOH" no pre-treatment with HCL/methanol before surface chemistry to attach vancomycin

General surface texturing did not dramatically change the initial surface coverage of vancomycin.

In all cases, a significant reduction in secondary antibody concentration was observed between inserted and non-inserted samples, suggesting significant coating abrasion upon insertion into ovine femur. Following abrasion, all samples exhibited a similar vancomycin surface concentration. The amount of abrasion was found to be lowest for a combination of acid etching and nano-texturing.

REFERENCES

Om P. Edupuganti, Valentin Antoci, Samuel B. King, Binoy Jose, Christopher S. Adams, Javad Parvizi, Irving M. Shapiro, Allen R. Zeiger, Noreen J. Hickok and Eric Wickstrom, Covalent bonding of vancomycin to Ti6Al4V alloy pins provides long-term inhibition of Staphylococcus aureus colonization. Bioorganic & Medicinal Chemistry Letters 17 (2007) pp 2692–2696.

Claims

1. A medical implant having a therapeutic agent immobilised thereon, at least a portion of the implant on which the therapeutic agent is immobilised having a tissue-contacting surface with an asperity such that the therapeutic agent does not extend beyond the tissue-contacting surface of the implant.

2. A medical implant according to claim 1, wherein the surface asperity is generated by removing material from or displacing material at the tissue-contacting surface to form at least one instrusion and wherein the therapeutic agent is immobilised within the intrusion.

3. A medical implant according to claim 2, wherein the at least one intrusion is selected from the group consisting of a recess, a pore, a slot, a hole, a depression, a pit, a groove or a trough.

4. A medical implant according to claim 1, wherein the surface asperity is generated by adding material to or displacing material at the tissue-contacting surface to provide a plurality of protrusions on the implant surface, and wherein the therapeutic agent is located between the protrusions.

5. A medical implant according to claim 5, wherein the surface asperity is generated by a combination of removing and displacing material at the tissue-contacting surface to provide an intrusion and adding material to and displacing material at the tissue-contacting surface to form a plurality of protrusions and wherein the therapeutic agent is located within the thereby formed intrusion and/or the spaces between the protrusions.

6. A medical implant according to any preceding claim, wherein the therapeutic agent is selected from the group consisting of, antibacterial agents; antimicrobial agents; anticoagulants; antithrombotics; complement inhibitors; antiplatelet agents;

antitumor agents; anti-inflammatory agents; enzymes; cytokines, catalysts; hormones; growth factors or inhibitors of growth factors; drugs; vitamins; antibodies; antigens; nucleic acids; dyes; DNA; RNA; proteins; peptides or combinations thereof.

7. A medical implant according to any preceding claim, wherein the implant is an orthopaedic device.

8. A medical implant according to any preceding claim, wherein the therapeutic agent is an antibiotic.

9. A medical implant according to claim 8, wherein the antibiotic is vancomycin or variants thereof.

10. A method of producing a medical implant having a therapeutic agent immobilised thereon, wherein at least a portion of the implant on which the therapeutic agent is immobilised having a tissue-contacting surface with an asperity such that the therapeutic agent does not extend beyond the tissue-contacting surface of the implant, said method comprising the steps of;

i) forming at least one intrusion and/or a plurality of protrusions on the implant surface;

ii) immobilising a therapeutic agent within the intrusion and/or within the space between the protrusions.

11. A method according to claim 10, wherein the least one intrusion and/or a plurality of protrusions on the implant surface are formed by micro-texturing of the implant surface.

12. A method according to claim 10, wherein the method further includes the step of nano-texturing the micro-textured surface.

13. A method according to any of claims 10 to 12, wherein the medical implant is an orthopaedic implant.

14. A method according to any of claims 10 to 13, wherein the therapeutic agent is selected from the group consisting of, antibacterial agents; antimicrobial agents; anticoagulants; antithrombotics; complement inhibitors; antiplatelet agents; antitumor agents; anti-inflammatory agents; enzymes; cytokines, catalysts; hormones; growth factors or inhibitors of growth factors; drugs; vitamins; antibodies; antigens; nucleic acids; dyes; DNA; RNA; proteins; peptides or combinations thereof.

15. A method according to claim 14, wherein the implant is an orthopaedic implant and the therapeutic agents is an antibiotic.

16. A method according to claim 15, wherein the antibiotic is vancomycin or variants thereof.

17. A medical implant or method as substantially herein described with reference to the accompanying Figures and Examples.

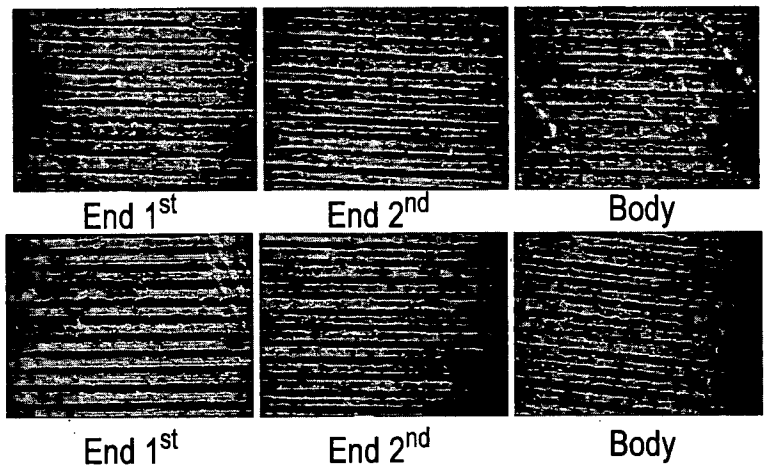
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FIG. 1a

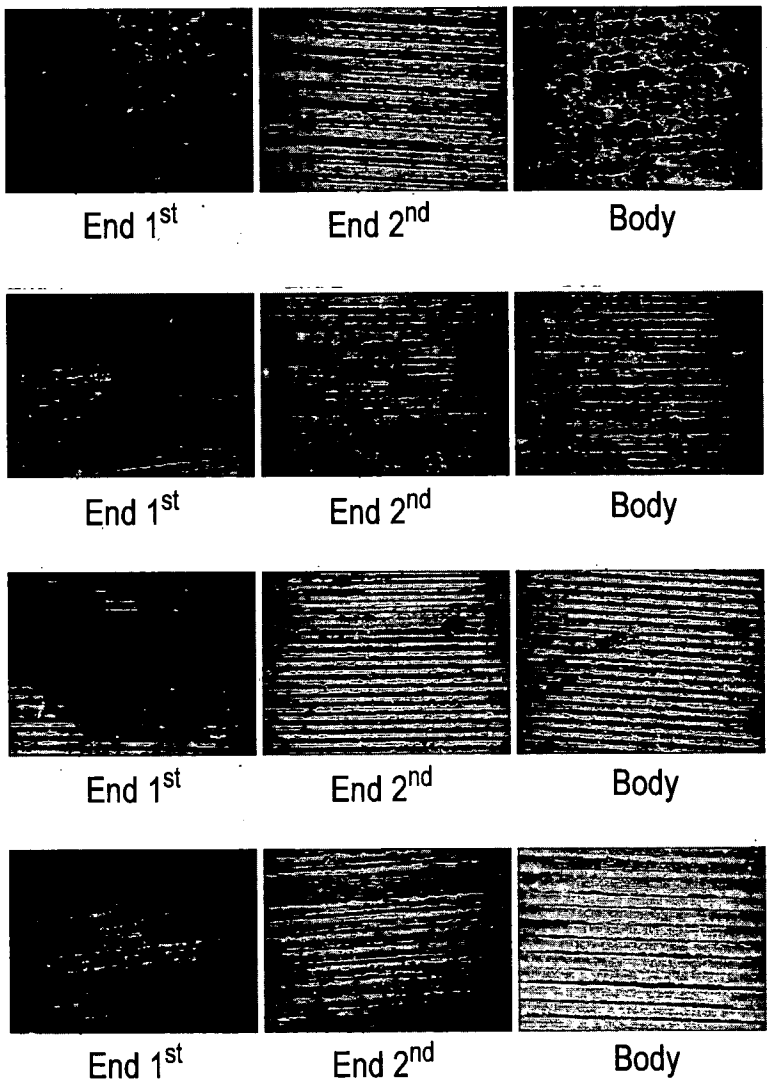
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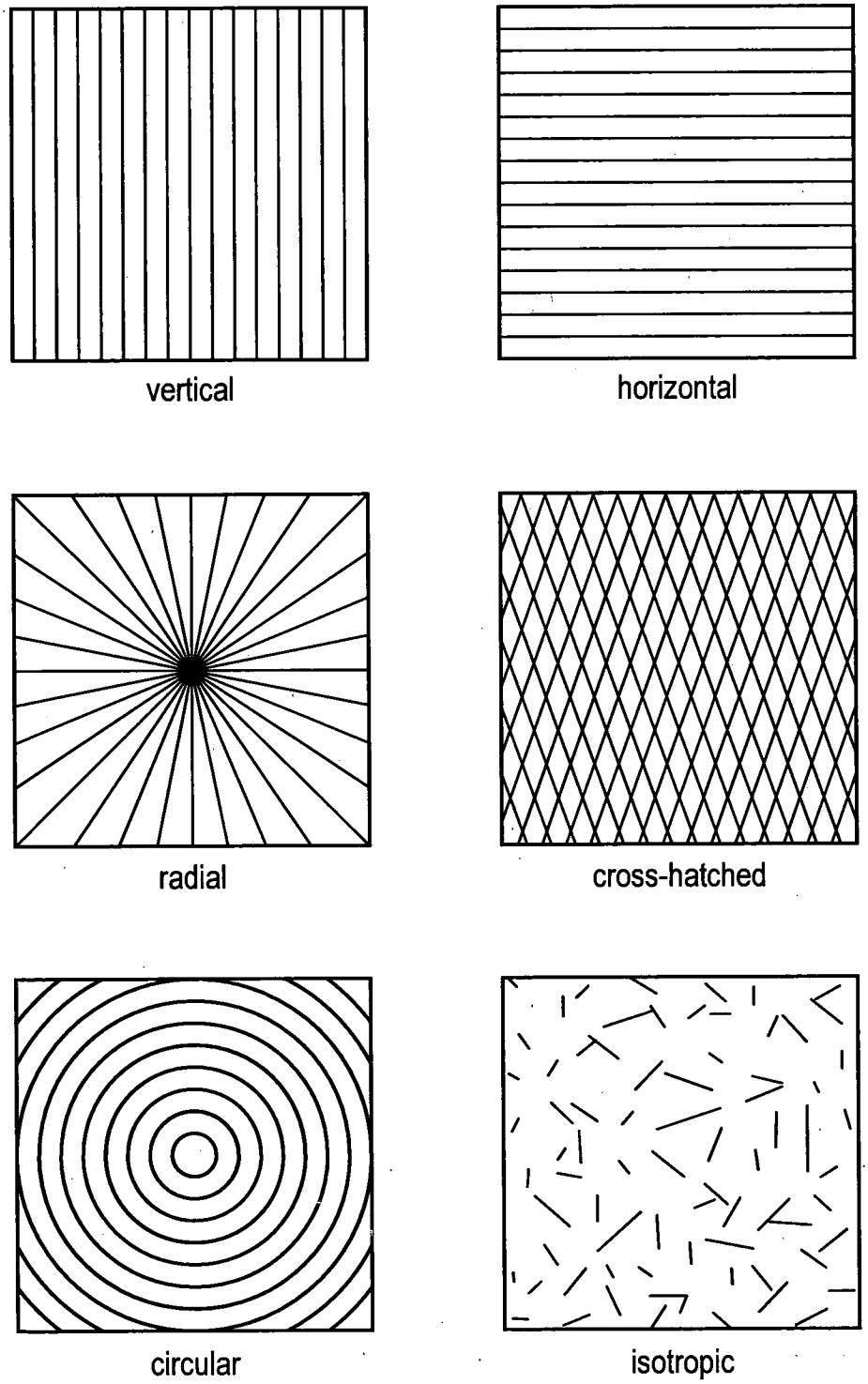
FIG. 1b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isotropic

FIG. 2

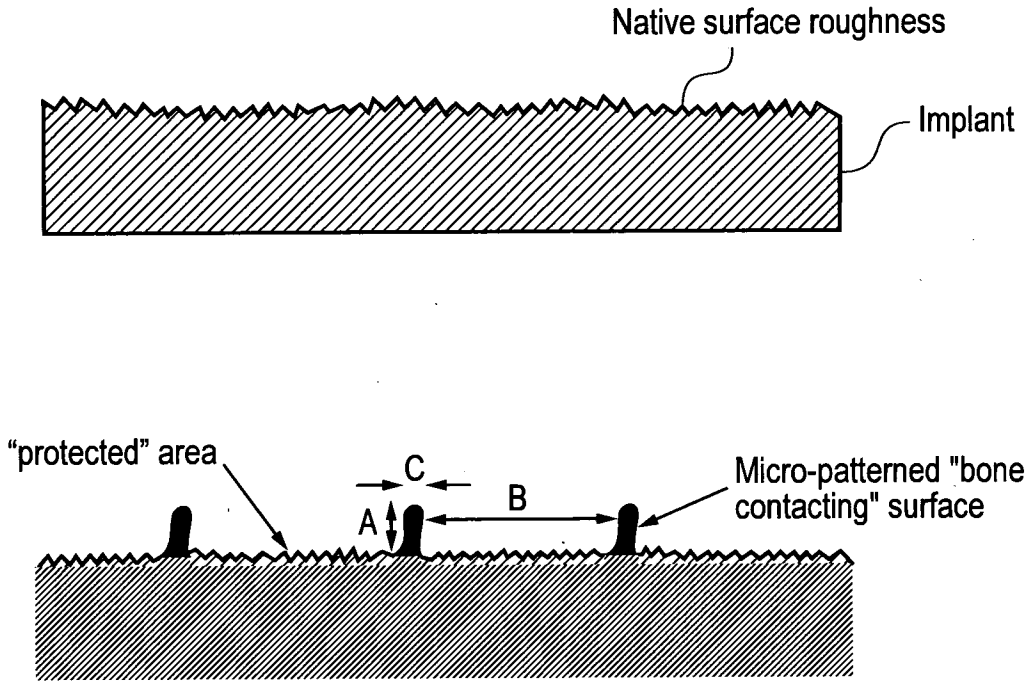
Native surface roughness
Implant
"protected" area
C
B
A
Micro-patterned "bone contacting" surface
A = 100-200µm ; B = 1- 2 mm ; C = 20- 50µm

FIG. 3

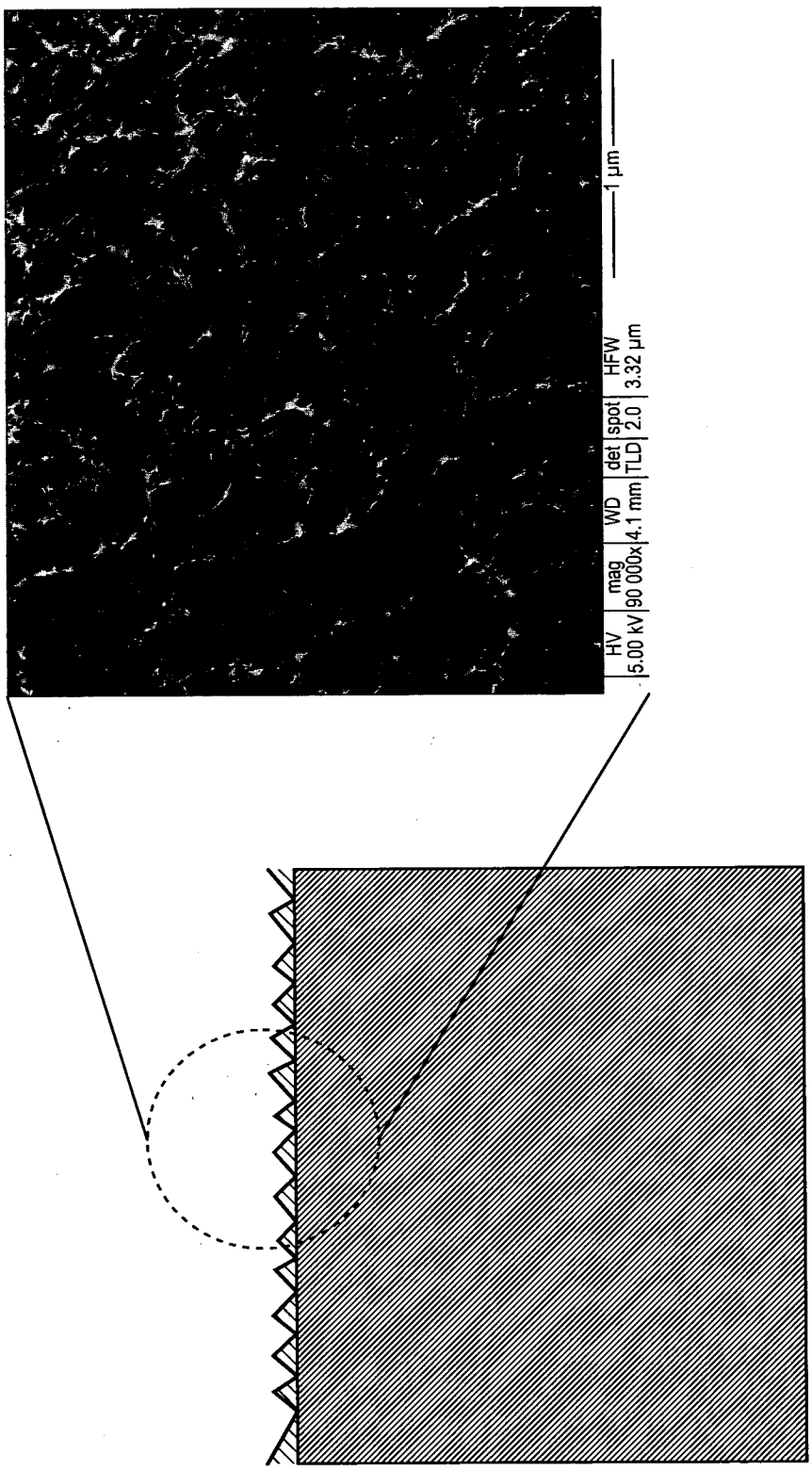

FIG. 4

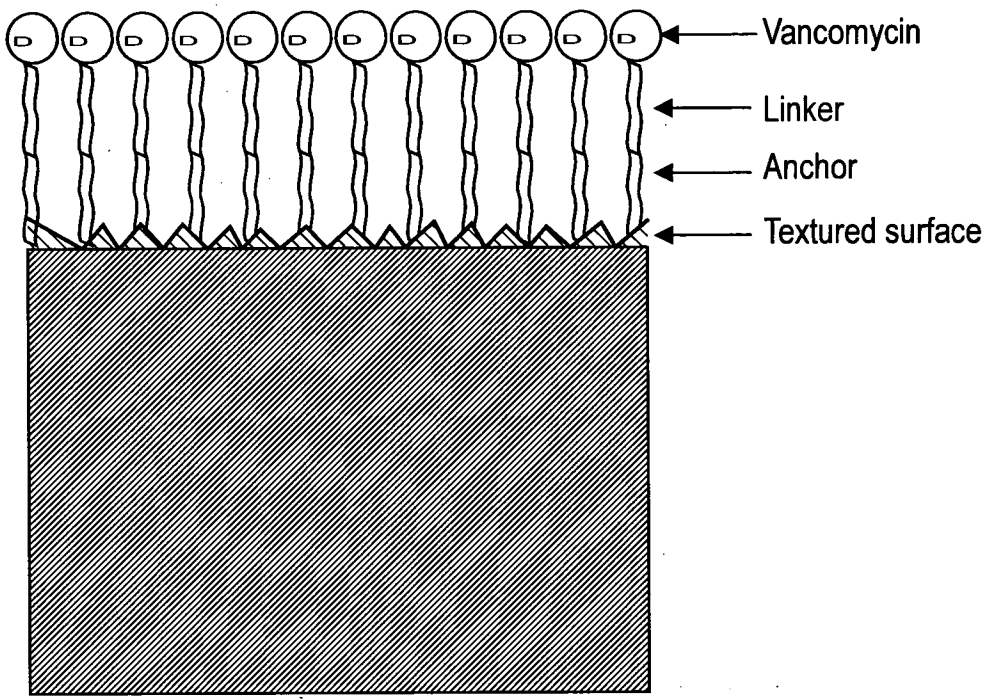

FIG. 5

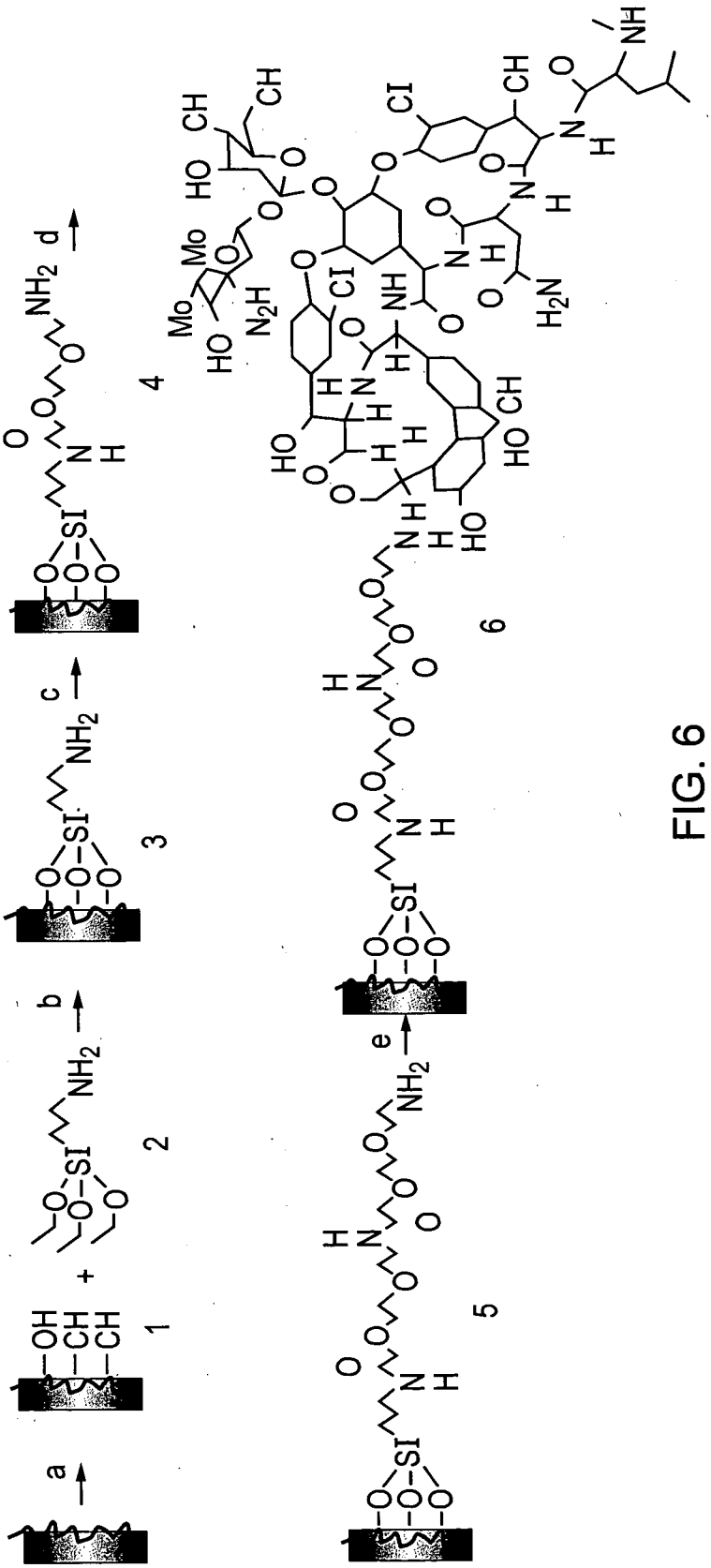

FIG. 6

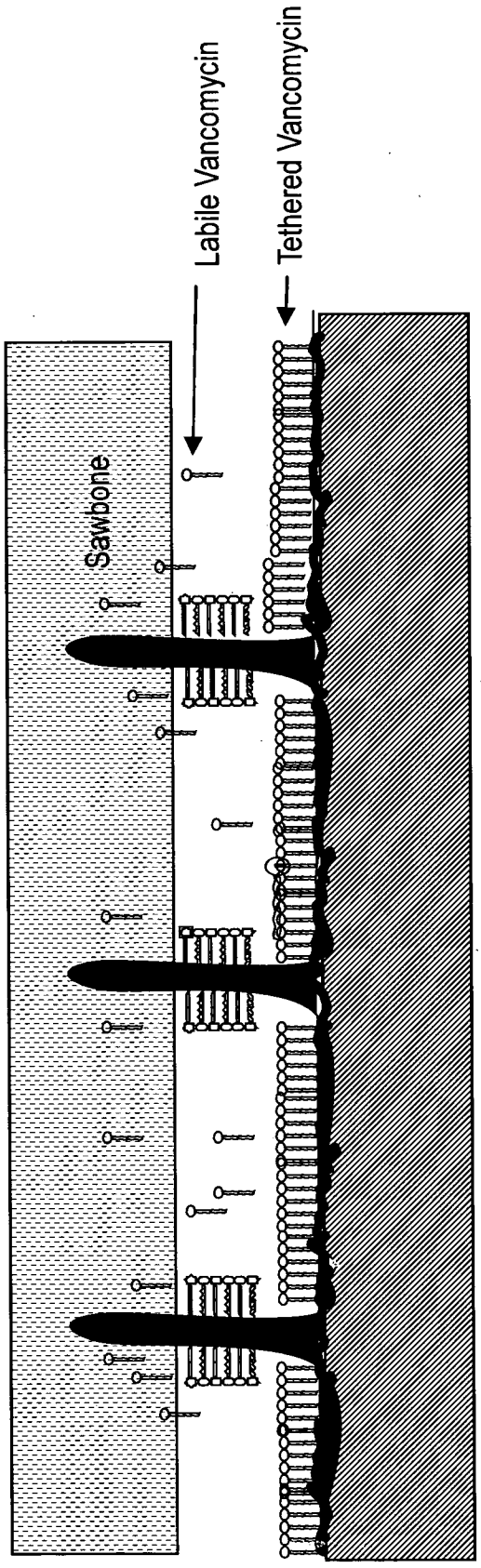

FIG. 7

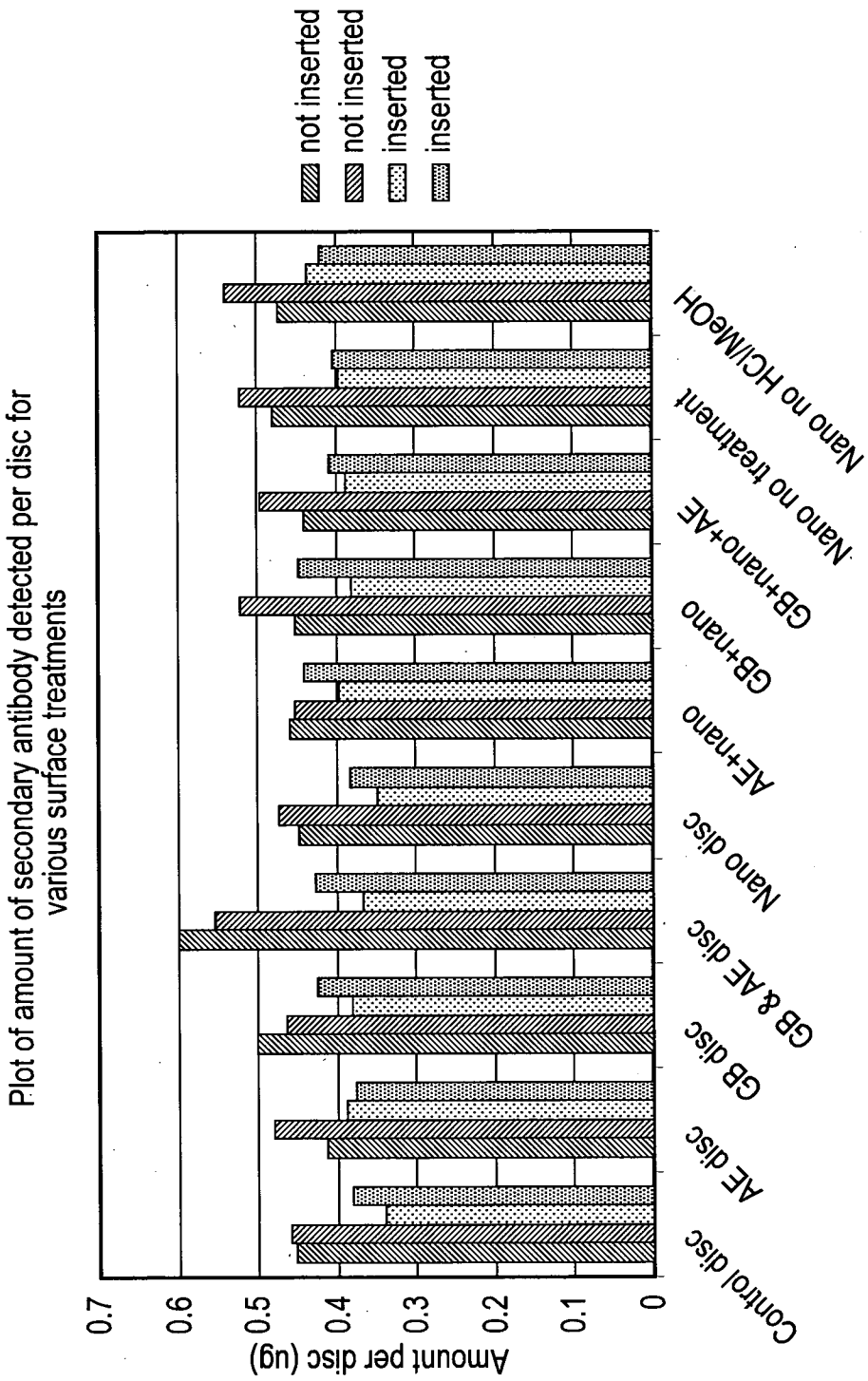
Plot of amount of secondary antibody detected per disc for various surface treatments
not inserted
not inserted
inserted
inserted
Amount per disc (ug)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Control disc
AE disc
GB disc
GB & AE disc
Nano disc
AE+nano
GB+nano
GB+nano+AE
Nano no treatment
Nano no HCl/MeOH
sample

FIG. 8

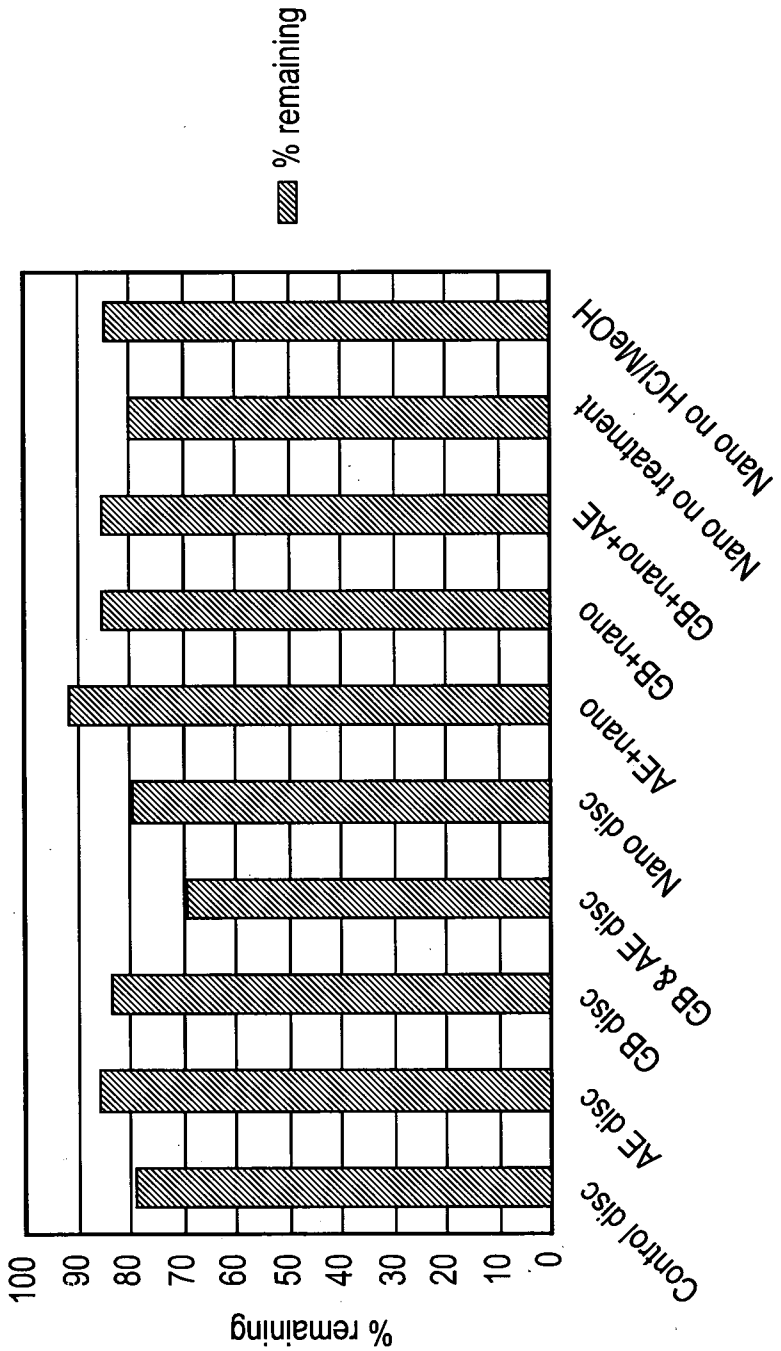
% remaining
Control disc
AE disc
GB disc
GB & AE disc
Nano disc
AE+nano
GB+nano
GB+nano+AE
Nano no treatment
Nano no HCl/MeOH
sample
100
90
80
70
60
50
40
30
20
10
0
% remaining

FIG. 9