

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
15 November 2007 (15.11.2007)

PCT

(10) International Publication Number
WO 2007/128973 A2

(51) International Patent Classification:

A61L 31/04 (2006.01) A61L 31/16 (2006.01)
A61L 31/10 (2006.01)

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(21) International Application Number:

PCT/GB2007/001271

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(22) International Filing Date: 5 April 2007 (05.04.2007)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

0607189.8 10 April 2006 (10.04.2006) GB

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, 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, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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(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, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INTERLEUKIN 1-RECEPTOR ANTAGONIST COMPOSITION TO TREAT RESTENOSIS

(57) Abstract: A coating composition comprising a polymer and Interleukin I-Receptor Antagonst (IL- 1ra) which allows (IL- 1ra) to be eluted in vivo from a medical device whilst retaining its activity to treat restenosis.



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Interleukin 1- receptor antagonist composition to treat restenosis

The present invention relates to a composition comprising Interleukin 1ra ("IL-1ra") and a vehicle therefor. In particular, it relates to a composition which can be coated onto a metal surface (such as a stent) and from which IL-1ra can be released whilst retaining its bioactivity.

The interleukins are naturally occurring proteins which play an important part in the development of the immune system by their regulation of lymphocyte cells. The interleukin-1 receptor antagonist (IL-1ra) is a member of the IL-1 family that binds to IL-1 receptors but does not induce any intracellular response. It is thought to be useful in the treatment of arthritis, colitis, and granulomatous pulmonary disease (Arend *et al.*, Annu Rev Immunol. 1998; 16:27-55).

The current inventors have shown that IL-1ra is associated with a sustained, significant reduction in neointima after vessel wall injury as long as it is given systemically for at least 28 days (Morton A.C. et al. Cardiovascular Research 68 (2005) 493-501).

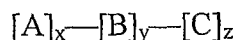
It would be useful to be able to treat patients with IL-1ra by coating a medical implant (such as a metal stent) with a composition comprising IL-1ra and then releasing it *in vivo* at the desired locus for at least 28 days. However, up till now, it has been thought that this mode of preparation (in organic solvents) and delivery would result in a loss of bioactivity of IL-1ra.

The present applicants have surprisingly found that IL-1ra retains its bioactivity after it has been released from such a polymer coated metallic surface. This has been shown through the binding affinity of eluted Interleukin IL-1 Receptor Antagonist from polymer-coated stainless steel plates, towards the signaling receptor, IL-1r1. The polymeric coating compositions which result in this beneficial effect are preferably those

disclosed in PCT/GB2004/003547 (PolyBioMed Limited), the contents of which are incorporated herein by reference.

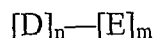
According to a first aspect of the present invention, there is provided a coating
5 composition for an implantable medical device comprising a combination of IL-1ra protein and a vehicle therefore, wherein the vehicle comprises a biostable or biodegradable polymer.

In a preferred embodiment the vehicle comprises either a first compound which is a
10 random copolymer of Formula 1:



wherein A is a vinyl acetal group, B is a vinyl alcohol group and C is a vinyl acetate
15 group and wherein $x > 0$ and $x + y + z = 1$,

or a second compound which is a random copolymer of Formula 2:



20 wherein D is a vinyl pyrrolidone group and E is a vinyl acetate group and wherein $0 \leq m \leq 1$ and $n + m = 1$,

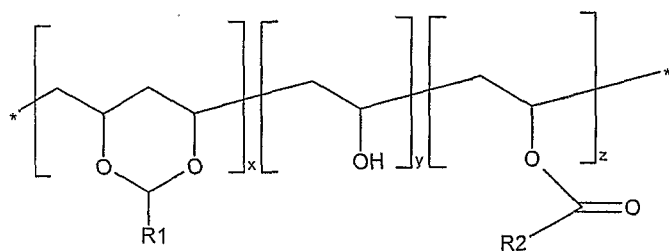
or a combination of both the first and second compounds.

25 Preferably, x is greater than zero. More preferably, x is from 0.8 to 0.9, y is from 0.1 to 0.2 and z is from 0 to 0.025.

It has been found that a useful composition results from employing only vinyl pyrrolidone as the second compound, and therefore m can be zero in Formula 2 above. Preferably, however, n is from 0.3 to 0.7 and m is from 0.3 to 0.7.

- 5 The proportion of the second compound may be over 50% by weight of the coating composition.

In a preferred embodiment, $[A]_x-[B]_y-[C]_z$ is a compound of Formula 1A:



10

- wherein R_1 and R_2 are independently H or an alkyl, alkenyl, alkynyl or aryl group and wherein optionally an alkyl, alkenyl, alkynyl or aryl group may be substituted for any pendent hydrogen atom. More preferably, R_1 and R_2 are independently C1-C6 alkyl.

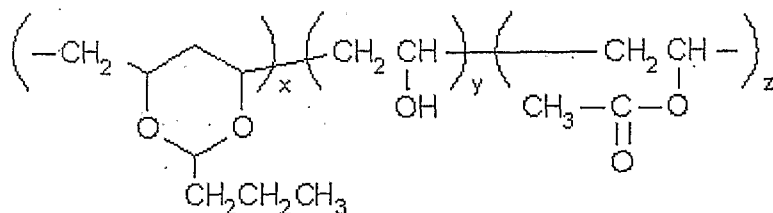
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Although the first compound can be bought "off the shelf", it can also be synthesised from vinylacetate ($\text{CH}_2\text{CHOCOCH}_3$). This is hydrolysed to form one of the co-polymers (polyvinylalcohol), reacts with an aldehyde (butyl-1-al in the preferred embodiment) to form the co-polyvinylacetal co-polymer and itself forms the co-vinylacetate co-polymer.

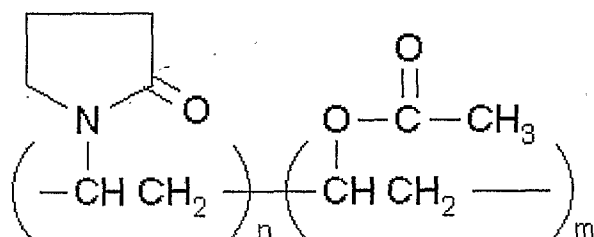
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In the particularly preferred embodiment, the first compound is a polymer which is poly(vinylbutyral-co-vinyl alcohol-co-vinyl acetate) with an average M_w from 50,000 to 80,000 and with 88 wt% vinyl butyral groups:

25



which is commercially available from Solutia under the trade mark Butvar® and the second compound is a polymer which is poly(vinyl pyrrolidone-co-vinyl acetate) with an average M_w of 50,000;



The present applicant has discovered that employing a copolymer of Formula 1 provides an effective vehicle for Interleukin 1ra to be released from a medical device such as a stent. In particular, the exemplary copolymer PVB combines hydrophobicity with good adhesion properties.

The applicant has further discovered that an especially effective vehicle can be provided by combining the copolymer of Formula 1 with the copolymer of Formula 2 as defined above. These two classes of copolymers have been found to be particularly compatible and therefore suitable for use together in the inventive coating composition.

In a particularly preferred embodiment, the vehicle for IL-1Ra comprises 60wt% Poly(vinyl butyral-co-vinyl alcohol-co-vinyl acetate) and 40wt% Poly (1-vinylpyrrolidone-co-vinyl acetate).

The good compatibility of the preferred copolymer combination is in contrast to other combinations that have been tried such as PVB and polyethylene glycol or PVB with a combination of polyethylene glycol and polypropylene glycol, both of which result in compatibility problems.

A further advantage of the inventive composition is that it allows greater control and selectivity of the drug release than prior art compositions. For example, many prior art compositions release the drug too quickly for it to have the required effect, and therefore drug release is controlled by the use of polymer-only top coatings or variations in the polymer:drug ratio of the coating. In particular, the latter can lead to a requirement for coating thicknesses which may compromise coating integrity.

According to a second aspect of the present invention, there is provided a method for coating a medical device comprising the step of:

(a) applying to at least a part of the device a first coating composition as defined above.

In a particularly preferred embodiment, the method additionally comprising the step of:

(b) applying a second coating composition as defined above

wherein said first and said second coating composition are the same or different.

Both first and second coatings may have vehicles comprising said first component and said second component in ratios which may range from 50:50 to 100:0. The compositions can be the same or different.

The first coating preferably has a vehicle comprising said first compound and said second compound in a ratio from 80:20 to 100:0 (most preferably 98:2) and the second coating preferably has a vehicle comprising said first compound and said second compound in a ratio from 60:40 to 94:6 (most preferably 80:20) .

5

The proportion of Interleukin 1ra to vehicle may be typically from 1:9 to 1:1 and is preferably from 1:4 to 1:2.

10 The coatings are preferably applied by spraying or dipping, and the second coating is preferably applied over part or all of the first coating.

The method preferably includes the step of applying a primer layer to the device before applying the first composition, wherein the primer layer comprises either said first compound or said second compound or a combination thereof in the absence of IL-1ra.

15

According to a third aspect of the present invention, there is provided a medical device (such as a stent or graft-stent) which has been coated with a coating composition by means of a method as defined above. The stent is preferably formed of a metal but the inventive compositions can adhere to many other materials such as PET, PTFE, nylon,
20 polycarbonate, polypropylene and polyurethane.

According to a fourth aspect of the present invention, there is provided a method of using said device comprising implanting the device in an animal or human body.

25 According to a fifth aspect of the present invention, there is provided method of treating restenosis comprising administering to a patient a composition comprising Interleukin 1-receptor antagonist. Preferably this is delivered *in vivo* by elution from an implanted medical device.

A preferred embodiment of the present invention will now be described with reference to the following worked Examples and with reference to the drawings, in which:

Figure 1 is a graph showing the percentage of protein released by weight with time (Example 1) via Biacore Assay; and

Figure 2 is a graph showing the percentage of IL-1ra released (by weight) with time (Example 1) via ELISA Assay.

Example 1

Stent samples were prepared with PEP / IL-1ra coating to determine elution profile and activity for the IL-1ra protein.

Sample Preparation

Stents (15mm long, Vascular Concept, Prolinks) were placed on a holder and cleaned with a series washes with ultrasonication: 7.5%w/w aqueous sodium hydrogen carbonate solution, deionised water, 2-propanol, and deionised water. The samples were dried at 100°C overnight.

The stents were functionalised to give a reactive surface.

Stents were reacted by immersion in a solution of N-[3-(trimethoxysilyl) propyl] ethylenediamine at 1% by weight in toluene with a small amount (0.012%w/w) of glacial acetic acid present for 5 minutes, followed by drying in an oven at 50°C for 20 hours. Next the stents were rinsed in a series of solvents (toluene, methanol, deionised water, methanol, deionised water) each for 15 minutes with rotation and finally dried at 50°C for two hours to produce an amine functionalised surface.

The surface was further reacted by rotation in a solution of 3-(triethoxysilyl) propyl isocyanate at 2%, by volume, in anhydrous toluene, under a nitrogen blanket for 15 minutes. This was followed by rotation in anhydrous toluene rinse for 15 minutes under a nitrogen blanket. The stents were vacuum dried to produce a triethoxysilylated surface.

5

Functionalised stents were spray coated with a primer solution of PEP100 polymer at 0.5% by weight in chloroform with conditions optimised to apply an even coating. The stents were dried at 100°C for 20 hours. The amount of polymer applied to each stent was around 60 micrograms.

10

Functionalised and primed stents were spray coated with a 1%w/w PEP80/ IL-1ra in a solvent mixture of 75% dimethylsulfoxide/15% 1-methyl-2-pyrrolidinone/10% acetone by weight, using conditions to give an even coating on each stent. The stents were dried at 40°C under high vacuum with the chamber let down to air and re-evacuated a number of times.

15

The final coating weights of the stents were in a range of 620 to 680 micrograms.

The solids content of the PEP80/IL-1ra solution was such that on drying the composition of the coating was 75% PEP80 to 25% IL-1ra.

20

Materials

PEP100 – Butvar B79 supplied by Solutia Inc.

25

PEP80 - a blend of 80% Butvar B79 as supplied by Solutia Inc and 20% Plasdane S630 polymer supplied by ISP (Switzerland) AG. Plasdane S630 is a random copolymer of vinyl pyrrolidone and vinyl acetate in a 60:40 ratio.

PEP80/IL-1ra – A blend of 3 parts PEP80 to 1 part IL-1ra protein to result in 25% IL-1ra protein, 60% Butvar B79 polymer and 15% Plasdane S630 polymer by solids in solution (with the solution formulated to give this composition in the dry coating).

- 5 IL-1ra protein – A freeze dried solid produced from a solution supplied by Amgen Inc, USA.

Sodium hydrogen carbonate -40 to +140 mesh – as supplied by the Sigma – Aldrich Company Ltd.

10

2-propanol, 99% – as supplied by the Sigma – Aldrich Company Ltd.

Deionised water – Prepared by treatment of mains water through an ELGA micromeg MC:DS cartridge.

15

N-[3-(trimethoxysilyl) propyl] ethylenediamine, 97% supplied by the Sigma – Aldrich Company Ltd.

3-(triethoxysilyl) propyl isocyanate, as supplied by the Sigma – Aldrich Company Ltd.

20

Toluene 99+% as supplied by the Sigma – Aldrich Company Ltd.

Anhydrous toluene 99.8%, as supplied by the Sigma – Aldrich Company Ltd.

- 25 Chloroform 99.8% as supplied by the Sigma – Aldrich Company Ltd.

Glacial acetic acid as supplied by the Sigma –Aldrich Company ltd

Methylsulfoxide 99.8% ACS - as supplied by the Sigma –Aldrich Company ltd

Acetone 99%+ - as supplied by the Sigma –Aldrich Company ltd

1-methyl-2-pyrrolidinone 99% - as supplied by the Sigma –Aldrich Company ltd

5

Protein Elution

The two stents were set up to elute the protein and determine the elution profile for the PEP80/ IL-1ra coating over 28 days.

10

Method

For elution each stent was suspended in 8mls of release eluant and incubated at 37.5°C with agitation.

15

At regular periods the release eluant was changed for fresh and the used eluant stored for analysis. After 28 days the final eluant sample was collected and the stent completely stripped into 8mls of chloroform. This was dried down at 40°C under vacuum and the residue taken up in 8mls of release eluant. This was kept for analysis.

20

Protein Analysis

The amount of IL-1ra was determined by two methods: one using a protein staining reagent with UV/Vis spectrometry, and ELISA analysis. The activity of the released protein was determined by BiaCore analysis.

25

Coomassie Protein Reagent Analysis – Bradford Method Determination Of Protein (IL-1ra) Concentration.

5 The amount of protein in the release eluant was assessed by UV/Vis spectrophotometry using Coomassie Protein Reagent to give an absorbance shift from addition of the protein.

10 The absorbance values obtained were converted into micrograms of protein released using a standard calibration curve constructed from readings from solutions of known concentrations of protein.

These values were used to construct a cumulative release profile for each stent sample. This was expressed a percentage release of total protein loaded. See Figure 1 (Graph.1).

15 ELISA Analysis.

The sampled release eluant was analysed by ELISA to determine the amount of protein present. Standards of known concentration were used for calibration.

20 The values obtained from ELISA analysis were used to calculate the total amount of loaded protein released from the stent with time, expressed as a percentage. The values are shown in Graph 2 as an elution profile.

IL-1ra Activity

25

Interaction between any eluted drug and the chemically-bound receptor ligand was measured using surface plasmon resonance detection (which exploits differences in the refractive index of the sensor chip coated with ligand and the chip coated with ligand-drug) as the drug solution was passed over the chip.

The sampled eluant was analysed by Biacore assay to assess the activity of the eluted protein. A CM5 chip (from Biacore AB) was used for the protein analysis.

- 5 The results showed that the IL-1ra protein was still active after elution from the stents.

Materials

Coomassie Protein Reagent – as supplied by the Sigma –Aldrich Company Ltd

10

Chloroform 99.8% as supplied by the Sigma – Aldrich Company Ltd.

Deionised water – Prepared by treatment of mains water through an ELGA micromeg MC:DS cartridge.

15

Release eluant – 150mMol sodium chloride, 10mmol sodium phosphate, 3mmol EDTA, & 0.05%v/v surfactant P20 in deionised water at pH 7.4. sodium chloride as supplied by Fisher Scientific UK ltd, sodium phosphate (S7909) as supplied by the Sigma-Aldrich company Ltd, EDTA (ED2SS) as supplied by the Sigma-Aldrich company Ltd,

- 20 Surfactant P20 (BR1000-54) as supplied by Biacore AB.

Example 2

- 25 Samples were prepared to examine if ethylene oxide (EtO) sterilisation affected the bioactivity of the IL-1ra protein.

Method

Two stents were prepared following the method described in Example 1.

One of the prepared stents and 12mg of the lyophilised protein were EtO sterilised using a soft cycle (50°C temperature, shallow vacuum, 2hours exposure) process.

- 5 The sterilised and un-sterilised stents were set up for protein elution as in Example 1 with the elution run over 5 days, sampling the eluant on each day. The 10 release eluant samples, the sterilised and un-sterilised solid protein were analysed for protein activity as in Example 1.
- 10 The Biacore assay results showed that the activity of the IL-1ra eluted from the sterilised stent had not been affected by the process.

The solid IL-1ra sample that had been sterilised also remained bioactive.

15 Example 3

Preparation of Interleukin IL 1ra / polymer matrix PEP60

- PEP60 is a proprietary polymer composition of PolyBioMed Limited containing 60wt%
20 Poly(vinyl butyral-covinyl alcohol-co-vinyl acetate) and 40wt% Poly (1-vinylpyrrolidone-co-vinyl acetate).

- 20 µl (approx 30 mg) of PEP 60 polymer solution was added to 10 µg IL-1ra (supplied by R&D Systems, Inc.). The resulting polymer/drug solution contains approx 0.15% total
25 solids, 18% of which is IL-Ra. The solution was coated onto a small area of stainless steel plate (316L, approx 0.5 cm²). Curing time was 24 h at 40°C.

Drug Release

The drug/polymer-coated steel plate was immersed into Biacore buffer solution (0.5 ml HBS-EP) at 37°C for 24 hours. HBS-EP buffer contains 0.01 M HEPES pH 7.4, 0.15 M NaCl, 3 mM EDTA, and 0.005% surfactant P20.

Preparation of Biacore chip

Receptor ligand IL-1r1 (supplied by R&D Systems, Inc.) was chemically bound to a Biacore sensor chip (series S chip, CM5) using a conventional method which is based on an amide-bond coupling reagent.

Measuring Drug – Ligand Activity Of Eluted Drug

Interaction between any eluted drug and the chemically-bound receptor ligand was measured using surface plasmon resonance detection (which exploits differences in the refractive index of the sensor chip coated with ligand and the chip coated with ligand-drug) as the drug solution was passed over the chip.

The result was a qualitative measurement, i.e., binding affinities were not measured, but just to see if there was any actual binding. As a control, pure polymer solution was passed over the bound ligand and no binding was observed.

This experiment shows that Interleukin IL-1ra retains its bioactivity when released from metallic surface (such as a stent) coated with 60:40 ratio of Poly(vinyl butyral-co-vinyl alcohol-co-vinyl acetate to Poly (1-vinylpyrrolidone-co-vinyl acetate) copolymers.

CLAIMS

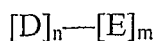
1. A composition for coating an implantable medical device comprising a combination of IL-1ra protein and a vehicle therefore, wherein the vehicle comprises a biostable or biodegradable polymer and the IL-1ra remains bioactive.

2. A composition as claimed in claim 1, wherein the vehicle comprises either a first compound which is a random copolymer of Formula 1:



wherein A is a vinyl acetal group, B is a vinyl alcohol group and C is a vinyl acetate group and wherein $x > 0$ and $x + y + z = 1$,

or a second compound which is a random copolymer of Formula 2:



wherein D is a vinyl pyrrolidone group and E is a vinyl acetate group and wherein $0 \leq m \leq 1$ and $n + m = 1$,

or a combination of both the first and second compounds.

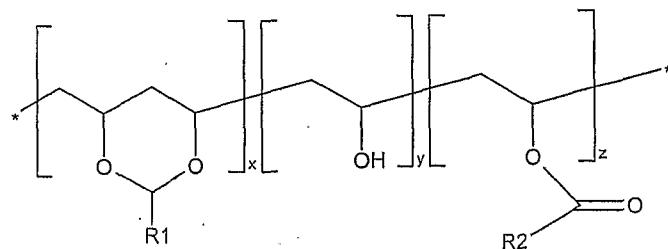
3. A composition as claimed in claim 2, wherein the proportion of said second compound is up to 80% by weight of the coating composition.

4. A composition as claimed in claim 2 or 3, wherein n is from 0.3 to 0.7 and m is from 0.3 to 0.7.

5. A composition as claimed in any of claims 2 to 4, wherein said second compound is

poly(vinyl pyrrolidone-co-vinyl acetate) with an average Mw of 50,000.

6. A composition as claimed in any of claims 2 to 5, wherein $[A]_x-[B]_y-[C]_z$ is a compound of Formula 1A:



wherein R1 and R2 are independently H or an alkyl, alkenyl, alkynyl or aryl group and wherein optionally an alkyl, alkenyl, alkynyl or aryl group may be substituted for any pendent hydrogen atom.

7. A composition as claimed in claim 6, wherein x is from 0.8 to 0.9, y is from 0.1 to 0.2 and z is from 0 to 0.025.

8. A composition as claimed in claim 6 or 7, wherein said first compound is poly(vinylbutyral-co-vinyl alcohol-co-vinyl acetate) with an average Mw from 50,000 to 80,000 and with 88 wt% vinyl butyral groups.

9. A composition as claimed in any preceding claim, wherein the implantable medical device is formed of a metal.

10. A composition as claimed in any preceding claim, wherein the proportion of IL-1ra to vehicle is from 1:9 to 1:1.

11. A method for coating a medical device comprising the step of:

(a) applying to at least a part of the device a first composition as claimed in any of claims 1 to 10.

5 12. A method as claimed in claim 11 additionally comprising the step of:

(b) applying a second composition as claimed in any of claims 1 to 10

wherein said first and said second compositions are the same or different.

10

13. A method as claimed in claim 12, wherein the first coating has a vehicle comprising said first compound and said second compound in a ratio from 80:20 to 100:0 and wherein the second coating has a vehicle comprising said first compound and said second compound in a ratio from 60:40 to 94:6.

15

14. A method as claimed in claim 12, wherein the ratio of said first compound to said second compound is 98:2 in the first coating and 80:20 in the second.

20

15. A method as claimed in any of claims 12 to 14, additionally comprising a step of applying a primer layer to the device before applying the first composition, wherein the primer layer comprises either said first compound or said second compound or a combination thereof in the absence of IL-1ra.

25

16. A medical device having a first coating of a composition as claimed in any of claims 1 to 10, wherein the first coating is applied directly to the device.

17. A device as claimed in claim 16 having a second coating (which is the same as or different to the first coating) as claimed in any of claims 1 to 10, wherein the second coating is applied to at least a part of the first coating.

18. A device as claimed in claim 17 wherein the first coating has a vehicle comprising said first compound and said second compound in a ratio from 80:20 to 100:0 and wherein the second coating has a vehicle comprising said first compound and said second compound in a ratio from 60:40 to 94:6.

19. A device as claimed in claim 18, wherein the ratio of said first compound to said second compound is 98:2 in the first coating and 80:20 in the second.

20. A device as claimed in any of claims 16 to 19 which is a stent or graft-stent.

21. A method of using a device as claimed in any of claims 16 to 20 comprising implanting the device in an animal or human body.

22. A method of treating restenosis comprising administering to a patient a composition comprising Interleukin 1- receptor antagonist.

23. A method as claimed in claim 22 wherein the composition is delivered *in vivo* by elution from an implanted medical device.

24. A method as claimed in claim 23 wherein the medical device is a stent or stent graft formed of metal.

25. A method as claimed in any of claims 22 to 24 wherein the composition is as claimed in any of claims 1 to 10.

26. Interleukin 1- receptor antagonist for use in the treatment of restenosis.

27. A composition as claimed in any of claims 1 to 10 for use in the treatment of restenosis.

28: The use of Interleukin 1- receptor antagonist in the manufacture of a medicament for
5 the treatment of restenosis.

29. The use of a composition as claimed in any of claims 1 to 10 in the manufacture of a medicament for the treatment of restenosis.

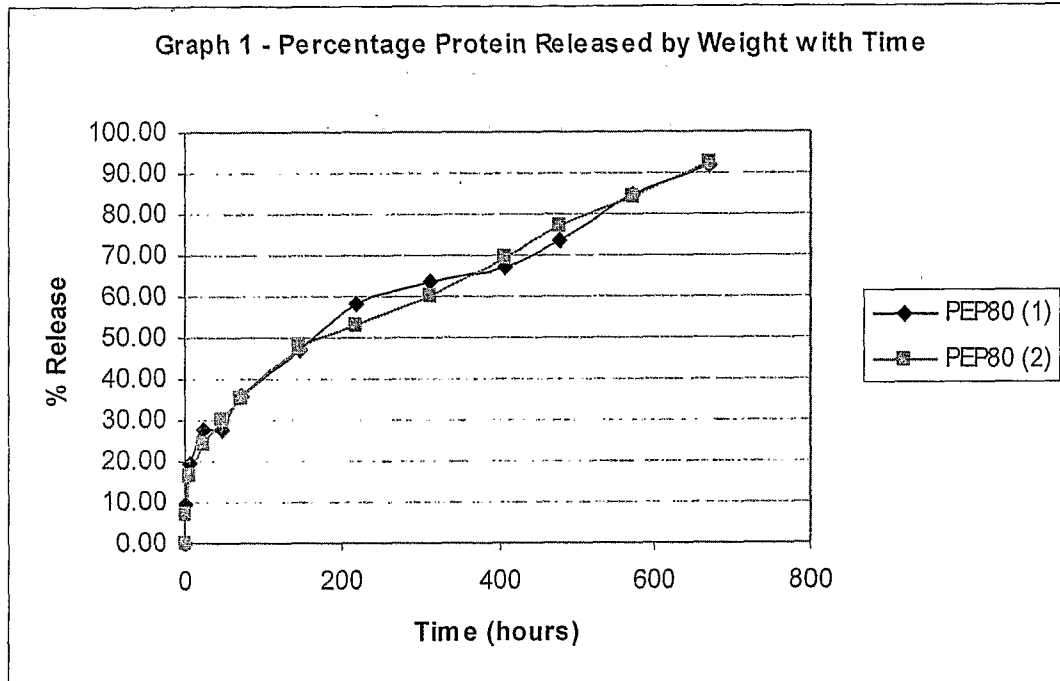
Figure 1

Figure 2