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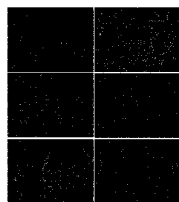
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(54) Title: INTRALUMINAL DEVICES COATED WITH SUBSTANCE P



(57) Abstract: The present invention relates to coated metal stents, to methods for coating or producing such coated metal stents, and to their use in medicine. In particular, the present invention relates to metal stents coated with Substance P, to methods for coating or producing such coated stents, and to their use as implants.



Description

Title of Invention: Intraluminal devices coated with Substance P

Technical Field

- [1] The present invention relates to coated Intraluminal devices such as coated metal stents, to methods for coating or producing coated Intraluminal devices such as coated metal stents, and to their use in medicine. In particular, the present invention relates to metal stents coated with Substance P., to methods for coating or producing such coated stents, and to their use as implants.

Background Art

- [2] A living being is continuously subjected to internal or external insults that cause continuous damage to organs and tissues. Through different homeostatic mechanisms such as inflammation, once tissue damage occurs the body begins a process of repair. This process attempts the recovery of the structure and functionality of the organ, although usually this repair is not perfect, and the generation of a scar is produced. The scar is a fibrous tissue of collagen that if deposited in excess can produce a fibrosis.
- [3] This fibrosis can occur in numerous organs and tissues, and in most cases, it is considered to generate secondary pathologies with the appearance of new structural and functional alterations. A second concern, in particular when vascular tissue is involved, as in the case of cardiac stents, is the thrombosis. Fibrosis and thrombosis generated in the vascular epithelia is of particular interest to the present invention.
- [4] The initial insults that can trigger the aberrant repair process can have an external origin as an infectious process, an internal origin as an autoimmune pathology, but we could also define an anthropic origin. We refer to an anthropic origin when it is an exacerbated biological response to the presence of a foreign body as a medical device. In this sense, the placement of a prosthetic material after the realization of a surgical wound determines a unique tissue environment in which the normal healing sequence (coagulation, inflammation, angiogenesis, epithelialization, fibroplasty and extra-cellular matrix formation) is in intimate contact with the foreign material. This material will determine the initiation of an inflammatory response, where the cellular components involved include platelets, monocytes, macrophages and polymorphonuclear leukocytes. In addition, there will be other cells such as fibroblasts, endothelial cells and smooth muscle cells.
- [5] When an inflammatory response occurs, it includes 4 phases: an acute inflammatory response, a chronic inflammatory response, the foreign body reaction, and finally, fibrosis.
- [6] - **Medical devices: fibrosis and thrombosis**

- [7] As already discussed, the presence of a foreign body as a medical device might initiate a fibrotic process, since the body shall attempt to encapsulate the medical device to isolate it, thus preventing it from performing its medical function properly. In this sense, joint prostheses, silicone prostheses, abdominal tights and metal stents, tend to produce such fibrosis leading to a new surgical process necessary to replace the implanted prosthesis.
- [8] A special case occurs when the growth of scar and fibrotic tissue is produced in tissues that form tubular structures or internal cavities. In this case, the scar generated will act by progressively closing the interior light of the cavity, even completely blinding it. Thus, depending on the affected organ, there may be vascular, digestive, airway, urological, neurological or gynaecological stenosis.
- [9] Current medical strategies to return functionality to the structure can be summarized as follows:
- [10] - Surgical processes to restore light to the duct or generate an alternative duct. For example, reconstructive surgeries to eliminate intestinal stenosis, or coronary bypass surgeries. These are very aggressive procedures for the patient.
- [11] - The use of balloons that, when expanded by inflating them inside the cavity, allow the light of the duct to be restored. Once the structure is recovered, and within the same surgical process, the balloon is deflated and removed. For example, the use of intestinal balloons that dilate the intestinal or oesophageal lumen, coronary balloons or tracheal balloons. Its efficiency rate is not high due to the temporary nature of the measure, requiring in some cases several expansion sessions.
- [12] - The implantation of spring type medical devices, which are often metallic (and more recently of re-absorbable materials) and when expanded they press the interior walls of the cavity, thus allowing the recovery of the light from the duct. These devices are permanently implanted. For example, coronary stents or tracheal stents. Their main disadvantage is the occurrence of restenosis. On many occasions, the presence of a foreign body such as a stent and the damage it induces to expand, generates a new insult that continues to favour the deposit of scar tissue and matrix. As a result, the problem is reproduced in an even more accentuated manner.
- [13] Other major concern is directly linked to the particular use of cardiac stents that often produce high rates of late and very late stent thrombosis, resulting in higher cardiac, non-cardiac and overall mortality. The increased risk of thrombosis can be explained by a double mechanism: firstly, the inhibition of cellular proliferation affects also the endothelial cells and delays the restoration of the endothelial continuity. This delayed or incomplete neointimal healing is the pathological substrate in cases of late stent thrombosis (>30 days, ≤365 days after implantation).
- [14] Secondly, a delayed type IVb hypersensitivity reaction, recruiting preferentially

eosinophils, has been described in cases of very late stent thrombosis (>365 days after implantation). This hypersensitivity reaction is believed to be triggered by the polymer used to carry the antiproliferative drug included in some stents, given the timing of onset (later than 90 days, when the drug is no longer detectable in the vessel wall) and the presence of polymer fragments surrounded by giant cells. In addition to the concerns about stent thrombosis, Drug Eluting Stent (DES) technology entails also some other drawbacks. The implantation of these devices elicits an inflammatory reaction in the vessel wall, presumably due to the polymeric coating, resulting in a torpid and irregular healing that might have a negative impact on both the thrombotic propensity and the incidence of restenosis. Indeed, although DES initially attenuate the neointimal response, this effect is not maintained in the long term, resulting in delayed thickening of the neointima and comparable restenosis rates to Bare Metal Stents (BMS).

- [15] Additionally, the endothelium of the neointimal layer submitted to the effect of the antiproliferative drug becomes dysfunctional and probably incompetent to prevent cholesterol accumulation, resulting in more frequent and earlier neo-atherosclerotic degeneration in DES than in BMS, another pathological substrate contributing to very late thrombosis and to late catch-up phenomena.

Disclosure of Invention

Technical Problem

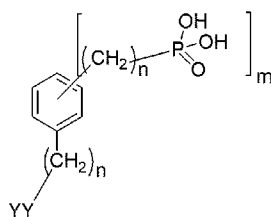
- [16] Thus, there is still a need to solve the problem of restenosis of medical devices, in particular of intraluminal devices such as metal stents, elicited by fibrosis and thrombosis.

Solution to Problem

- [17] The present invention generally provides for Substance P coated Intraluminal devices, preferably Substance P coated metal stents, capable of enhancing wound-healing after stenting, based on the local release of physiologic chemotactic mediators that mobilize and capture progenitor cells and circulating MSCs. Such coated Intraluminal devices, preferably coated metal stents, are described herein as having a twofold mechanism of action: a vasodilation effect and a call and homing effect.
- [18] Thus, an aspect of the invention refers to an Intraluminal device, such as a metal stent, coated with a peptide selected from the list consisting of substance P or an analogue thereof in an amount effective for inducing mobilization of endothelial precursor cells, wherein preferably, the peptide is substance P and wherein, more preferably, the peptide is coating the stent at a concentration of between 1 to 25 μM . Even more preferably, the concentration is between 1 and 10 μM .
- [19] In a preferred embodiment of this aspect of the invention, the peptide is linked to the

stent through an anchor and optionally a spacer molecule. Preferably, the anchor is selected from the group consisting of: -W, -V-W, -V-[V-W₂]₂, and -V-[V-(V-W₂)₂]₂, wherein W represents

[20]



[21]

and V represents lysine, aspartic acid or glutamic acid; m is 1, 2 or 3; and n each independently is 1, 2, 3, 4, 5, 6, 7 or 8; YY is an amino or carboxyl group.

[22]

In another preferred embodiment of this aspect of the invention, the anchor is selected from the group consisting of -CO-CH=CH₂, -CO-(CH)₁₋₂₀-CO-CH=CH₂, -CO-(CH₂)₁₋₂₀-SH, -CO-CH(NH₂)-CH₂-SH, -NH-(CH₂)₁₋₂₀-CO-CH=CH₂, -NH-(CH₂)₂₋₂₀-SH, -NH-CH(CO₂H)-CH₂-SH.

[23]

In another preferred embodiment of this aspect of the invention, the peptide is in combination with one or more therapeutic agents.

[24]

Preferably, from herein after references to Substance P or analogues thereof shall be referred to as "Peptides of the invention".

[25]

A further aspect of the present invention refers to a Peptide of the invention characterized in that said peptide is coating an Intraluminal device, such as a metal stent, for use as an implant. Preferably, such Peptide of the invention characterized in that said peptide is coating an Intraluminal device, such as a metal stent, is for use as an implant to promote blood vessel repair in an individual in need thereof.

[26]

More preferably, such Peptide of the invention characterized in that said peptide is coating an Intraluminal device, such as a metal stent, is for use as an implant to promote blood vessel repair in an individual in need thereof in a method that comprises the steps of introducing into a blood vessel in the individual the peptide coating the Intraluminal device, such as the metal stent. Preferably, the blood vessel is any artery or vein in the body, such as a coronary artery, a peripheral artery, an aorta, an intracerebral vessel, an aneurysm vessel, a renal vessel, a hepatic vessel, or a celiac vessel in the individual.

[27]

More preferably, such Peptide of the invention characterized in that said peptide is coating an Intraluminal device, such as a metal stent, is for use in a method of reducing restenosis in an individual in need thereof, comprising introducing into a blood vessel in the individual the peptide coating the Intraluminal device, such as a metal stent. Preferably, the blood vessel is any artery or vein in the body, such as a coronary artery, a peripheral artery, an aorta, an intracerebral vessel, an aneurysm vessel, a renal vessel, a hepatic vessel, or a celiac vessel in the individual.

[28]

[29] **Definitions**

[30] Unless specified otherwise herein, the term "Intraluminal device" means any medical device intended to keep opened any internal cavity of the body, optionally coupled with a substance that exerts a physiological effect. This includes temporary or permanent devices, like angioplasty balloons (made of polyvinyl chloride-PVC, cross-linked polyethylene, polyethylene terephthalate-PET or nylon) and stents or stent grafts (made of metal or any other polymer, bioabsorbable or not, with or without surface modification or surface activation).

[31] Unless specified otherwise, the term "endothelial precursor cells" as used herein refers to multiple different cell types that play roles in the regeneration of the endothelial lining of blood vessels. These cell types are preferably selected from Colony Forming Units (CFUs), Circulating Angiogenic Cells (CAC) and Endothelial Colony Forming Cells (ECFCs). Mesenchymal Stem Cells (MSCs) are also included within this category, because of their ability to differentiate into endothelial cells in the presence of specific molecules such as Vascular Endothelial Growth Factor (VEGF).

[32] Unless specified otherwise herein, the terms "Substance P (SP)" as used herein refers to an undecapeptide (a peptide composed of a chain of 11 amino acid residues) member of the tachykinin neuropeptide family. It is a neuropeptide, acting as a neurotransmitter and as a neuromodulator. Substance P and its closely related neurokinin A (NKA) are produced from a polypeptide precursor after differential splicing of the preprotachykinin A gene. The deduced amino acid sequence of substance P is as follows: [Campbell NA, Reece JB (2005) Biology (7th ed.). San Francisco: Pearson Benjamin Cummings. ISBN 9780805371468].

[33] - Arg Pro Lys Pro Gln Gln Phe Phe Gly Leu Met (RPKPQQFFGLM)

[34] with an amidation at the C-terminus. Substance P is released from the terminals of specific sensory nerves. It is found in the brain and spinal cord and is associated with inflammatory processes and pain.

[35] Unless specified otherwise herein, the term "amino acid" encompasses any organic compound comprising at least one amino group and at least one acidic group. The amino acid can be a naturally occurring compound or be of synthetic origin. Preferably, the amino acid contains at least one primary amino group and/or at least one carboxylic acid group. In the context of the present application, the term "amino acid" also refers to residues contained in larger molecules such as peptides and proteins, which are derived from such amino acids and which are bonded to the adjacent residues by means of peptide bonds or peptidomimetic bonds.

[36] Unless specified otherwise herein, the terms "naturally occurring amino acid" and "natural amino acid" encompass amino acid residues encoded by the standard genetic

code having the L-configuration and non-standard amino acids, e.g., amino acids having the D-configuration instead of the L-configuration, as well as those amino acids that can be formed by modification of such amino acids, for instance, but not limited thereto, pyroglutamic acid (Glp), norleucine(Nle) and ornithine (Orn).

- [37] Unless specified otherwise herein, the terms "unnaturally occurring amino acid" and "unnatural amino acid" encompass amino acid residues having the L- or D- configuration that have not been found in nature, but can be incorporated into a peptide chain. These include, but are not limited to, 4-aminobutyric acid (Abu), 6-aminohexanoic acid (Aha), p-benzoylphenylalanine (Bpa), 2,4-diaminobutyric acid (Dab), 2,3-Diaminopropionic acid (Dap), homo-cysteine (homo-Cys), homophenylalanine (homo-Phe), 2-(indole-3-yl)acetic acid (IAA), 4-(indol-3-yl)butyric acid (IAB), 3-(indol-3-yl)propionic acid (IPA), 1-naphthylalanine (1-Nal), 2-naphthylalanine (2-Nal), phenylglycine (Phg) and 4-halogen-phenylalanine (4-Hal-Phe).

[38] **Description**

- [39] The present invention refers to the medical field, in particular, to the development of proendothelialising coatings for implantable devices. The rationale for this approach, is moving into the opposite direction to the current standard of cellular inhibition, promoted for instance by drug eluting coronary stents.

- [40] In the present invention, this accelerated pro-endothelialization will be promoted thorough the mobilization of endothelial progenitors as well as the mobilization of hematopoietic, nonhematopoietic stem cells and mesenchymal stem cells (MSCs). For this purpose and as shown in the examples accompanying the present specification, we have employed MSCs with well-documented motility ability, to test their cell motion characteristics towards P Substance gradient concentrations. In this sense, the first method described in the accompanying examples employed a transwell cell migration and invasion assay that measured the capacity of cell motility toward a chemo-attractant gradient. The results of the transwell migration assay are illustrated in Figures 1 and 2 wherein percentages of migrated cells depending on different Substance P concentrations are shown.

- [41] The second employed method in the accompanying examples was the cell culture wound closure assay in which a scratch was generated on a confluent cell monolayer. The results of the wound assay are shown in Figure 3 wherein the scratch size can be observed after 33 hours of culture. Qualitative images of the effect of different concentrations of Substance P are shown.

- [42] That is, the above results make it plausible that a metal stent coated with substance P in an amount effective for inducing mobilization of endothelial precursor cells shall avoid the stenosis or re-stenosis of the cavity in a subject in need thereof.

[43] Thus, in a first aspect, the present invention relates to a coating whose use results in improved biocompatibility of Intraluminal devices, such as metal stents, implanted in the body (e.g., in any blood vessel, such as coronaries). Thus, the first aspect relates to the use of a coating in Intraluminal devices, such as metal stents, intended to be implanted in the body. The coating comprises (or consists essentially of or consists of) of substance P or an analogue thereof. In certain embodiments, the Substance P analogue is of

[44] Formula (I): $Z_1\text{-Xaa}^1\text{-Xaa}^2\text{-Xaa}^3\text{-Xaa}^4\text{-Xaa}^5\text{-Xaa}^6\text{-Xaa}^7\text{-Xaa}^8\text{-Xaa}^9\text{-Xaa}^{10}\text{-Xaa}^{11}\text{-Z}_2$ (I) (SEQ ID NO 11)

[45] or a pharmaceutically acceptable salt thereof, wherein:

[46] Xaa¹ is Arg, Lys, 6-N methyllysine or (6-N, 6-N) dimethyllysine;

[47] Xaa² is Pro or Ala;

[48] Xaa³ is Lys, Arg, 6-N-methyllysine or (6-N, 6-N) dimethyllysine;

[49] Xaa⁴ is Pro or Ala; Xaa⁵ is Gln or Asn;

[50] Xaa⁶ is Gln or Asn;

[51] Xaa⁷ is Phe or Phe substituted with chlorine at position 2, 3 or 4;

[52] Xaa⁸ is Tyr, Phe, or Phe substituted with chlorine at position 2, 3 or 4;

[53] Xaa⁹ is Gly, Pro, Ala or N-methylglycine;

[54] Xaa¹⁰ is Leu, Val, Ile, Norleucine, Met, Met sulfoxide, Met sulfone, N-methylleucine, or N-methylvaline;

[55] Xaa¹¹ is Met, Met sulfoxide, Met sulfone, or Norleucine;

[56] Z₁ is R₂N- or RC(O)NR-;

[57] Z₂ is -C(O)NR₂ or -C(O)OR or a salt thereof; each R is independently R is H, (C1-C6) alkyl, (C1-C6) alkenyl, (C1-C6) alkynyl, (C5-C20) aryl, (C6 -C26) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl; and each "-" between residues Xaa¹ through Xaa¹¹ independently designates an amide linkage, a substitute amide linkage or an isostere of an amide. In one embodiment, the Substance P analog can be of Formula (I) as described herein, wherein Xaa¹ is Arg; Xaa² is Pro; Xaa³ is Lys; Xaa⁴ is Pro; Xaa⁵ is Gln; Xaa⁶ is Gln; Xaa⁷ is Phe or Phe substituted with chlorine at position 4; Xaa⁸ is Tyr, Phe, or Phe substituted with chlorine at position 4; Xaa⁹ is Gly, Pro or N- methylglycine; Xaa¹⁰ is Leu; and Xaa¹¹ is Met, Met sulfoxide, Met sulfone or Norleucine.

[58] In a preferred embodiment, the Substance P analogue can be of Formula (I) as described herein wherein the "-" between residues Xaa¹ through Xaa¹¹ designates -C(O)NH-; Z₁ is H₂N-; and Z₂ is -C(O)NH₂.

[59] In another preferred embodiment, the Substance P analogue can be:

[60] RPKPQQFFGLM (SEQ ID NO 1);

[61] RPKPQQFFGLNIe (SEQ ID NO 2);

- [62] RPKPQQFFPLM (SEQ ID NO 3);
- [63] RPKPQQFFMeGlyLM (SEQ ID NO 4);
- [64] RPKPQQFTGLM (SEQ ID NO 5);
- [65] RPKPQQF(4-C1)F(4-C1)GLM (SEQ ID NO 6);
- [66] RPKPQQFFGLM(O) (SEQ ID NO 7);
- [67] RPKPQQFFMeGlyLM(O) (SEQ ID NO 8);
- [68] RPKPQQFFGLM(O₂) (SEQ ID NO 9); or
- [69] RPKPQQFFMeGlyLM(O₂) (SEQ ID NO 10).
- [70] In an even more preferred embodiment, the Substance P analogue can be Z₁ - RPKPQQFFMeGlyLM(O₂)-Z₂; wherein Z₁ is NH₂ and Z₂ is C(O)NH₂ (SEQ ID NO 12).
- [71] According to the invention, the coating can be applied to the surface of any Intraluminal device, such as in any part of a metal stent. Therefore, in a second aspect, the invention relates to a coated intraluminal device, wherein the coating comprises (or, alternatively, consists essentially of or consists of) of Substance P or an analogue thereof as defined in the first aspect. In one embodiment, the surface of the intraluminal device, preferably the metal stent, may be one selected from the group consisting of ABI alloy (palladium and silver), tantalum, niobium, tungsten, molybdenum, platinum, magnesium, cobalt chromium superalloy, cobalt alloys, titanium alloys, and elgiloy. In another embodiment, the surface of the intraluminal device, preferably the metal stent, is stainless steel. In another embodiment, the surface of the intraluminal device, preferably the metal stent, is Nitinol. Nitinol, a composition of nickel and titanium, is one of very few alloys that is both superelastic and biocompatible. Thus, nitinol is a material widely used for self-expanding stents.
- [72] According to the invention, the intraluminal device, preferably the metal stent, may receive a surface modification or activation prior to application of the coating. In certain embodiments, the surface of the stent is treated with an aminofunctionalized silane, providing a suitable anchoring surface for, e.g., acrylic acid functional groups, isothiocyanates (Kalina et al, 2008) (Kalinina, S., Gliemann, H., Lopez-Garcia, M., Auernheimer, J., Schimmel, T., Bruns, M., Schambony, A., Kessler, H., Wedlich, D., "Isothiocyanate-functionalized RGD-peptides as useful alternative in tailoring cell-adhesive surface patterns," *Biomaterials*, 2008; 29, p. 3004-3013) or an activated carboxylic group. In other embodiments, the surface is treated with an epoxyfunctionalized silane which allows coupling of a thiol group (under opening the oxirane ring) or other groups for opening the epoxy ring See e.g., Nanci, A. et al., *J Biomed Mat Res*, 1998, p. 324-335 or Saargeant, T.D. et al., *Biomaterials*, 2008; 29, p. 1085-1098.
- [73] According to the invention, the intraluminal device, preferably the metal stent, can be

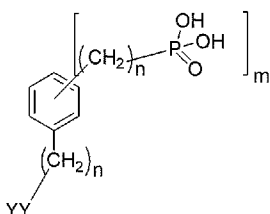
any form that is available and useful for the location in the body into which it will be introduced, such as any expandable wire form or perforated or non-perforated tube that can be inserted into the body.

[74] In a preferred embodiment of the second aspect of the invention, the peptide coating can be absorbed to the intraluminal device, preferably the metal stent, though an anchor and optionally a spacer. In this sense, a spacer can be optionally positioned between the substance P or an analogue thereof and the anchor. A spacer can be any molecule of sufficient length to allow the peptide inducing mobilization of endothelial precursor cells. In certain embodiments of the invention, the spacer is any organic molecule of sufficient length to allow inducing mobilization of endothelial precursor cells. The spacer is bonded to the peptide, for instance, by means of a covalent bond which can be connected to any atom of the peptide. In certain embodiments, the spacer is covalently bonded to one of the above-indicated "Xaa"-residues of the peptide analogues.

[75] Similarly, the spacer, if existent, is bonded to the anchor, for instance, by means of a covalent bond which is connected to any atom of the anchor (by substituting a hydrogen atom), excluding the atoms of the anchor involved in binding to the metal surface of the stent. In certain embodiments, the spacer has from 0 to 50 atoms in its backbone.

[76] The spacer should be inert or substantially inert under physiological conditions. It should in particular not be degraded by naturally occurring enzymes. In particular embodiments, the spacer is selected from the group consisting of $-\text{[CO-CH}_2\text{-(O-CH}_2\text{CH}_2\text{)}_y\text{-NH-]}_p\text{-}$; $-\text{[CO-(CH}_2\text{)}_z\text{CO-]}-$; $[\text{NH-(CH}_2\text{)}_z\text{-NH-}]$; $-\text{[CO-CH}_2\text{-(OCH}_2\text{CH}_2\text{)}_y\text{-O-CH}_2\text{-CO-]}-$; and $-\text{[NH-CH}_2\text{CH}_2\text{-(OCH}_2\text{CH}_2\text{)}_y\text{-NH-]}-$ as well as combinations thereof, wherein p each independently is from 1 to 20; x is from 1 to 12; y each independently is from 1 to 50; and z each independently is from 1 to 12. In certain embodiments, the spacer is one of the above moieties, wherein the value for p is from 1 to 8, the value for x is from 1 to 5, and the values for y and z are each from 1 to 6. It is also possible to employ spacers, wherein one or more of the hydrogen atoms of the above structural formulae is replaced by a substituent. Each substituent can be any chemical entity. In certain embodiments, the substituent can be independently selected from the group consisting of halogen atoms, C1-12 alkyl groups, C1-12 alkoxy groups, C2-12 alkene groups, C2-12 alkyne groups, C3-14 cycloalkyl groups, C3-14 aryl groups, saturated, unsaturated or aromatic 5 to 14-membered heterocyclic groups. The above alkyl groups, alkoxy groups, alkene groups and alkyne groups may be linear, branched or cyclic. They may themselves be substituted, for instance with fluorine atoms.

[77] The spacer itself should not be physiologically active. This is to be considered when choosing possible substituents.

- [78] In a specific embodiment, the spacer comprises at least one aminohexanoic acid, such as one, two or three aminohexanoic acids. In another specific embodiment, the spacer comprises at least three consecutive aminohexanoic acids. In another specific embodiment, the spacer is three consecutive aminohexanoic acids.
- [79] In another particular embodiment of the second aspect of the invention, if an anchor is used, the anchor can be derived from a molecule that comprises a component by which it is able to bind to the surface of the intraluminal device, preferably the metal stent. In those embodiments in which there is an anchor, a spacer can be present or absent. In the case that the spacer is present, the anchor is joined to the spacer, for instance, by means of a covalent bond which can be connected to any atom of the spacer (by substituting a hydrogen atom).
- [80] In certain embodiments, the anchor is the dopamine molecule.
- [81] In certain embodiments, the anchor, before coupling to the surface of the intraluminal device, preferably the metal stent, comprises at least one (one or more) phosphoric acid or phosphonic acid. In a specific embodiment, the anchor contains one or more phosphoric acid or phosphonic acid derived moiety. In other specific embodiments, the phosphonic acid derived moiety is an oligomer such as dimer, trimer, tetramer or any other oligomer. In a specific embodiment, the anchor molecule is a tetraphosphonate. In certain embodiments, the phosphonic acid derived moieties are linked to one another through a series of covalent bonds. In one embodiment, the anchor comprises four phosphonopropionic acids. In another embodiment, the anchor is bis-dibenzylphosphonic acid. In another embodiment, the anchor is based on aromatic phosphonic acids. Suitable anchors of this type may comprise one, two or more 3,5-bisphosphonomethyl-benzoyl (BPMP) moieties, as described in J. Auernheimer and H. Kessler, *Bioorg Med Chem Lett.* 2006 Jan 15;16(2): 271-3. Epub 2005 Oct 25.
- [82] In certain embodiments, the anchor is selected from the group consisting of -W, -V-W, -V-[VW₂]₂, and -V-[V-[V-W₂]₂]₂, wherein W represents
- [83]
- 
- [84] and V represents lysine, aspartic acid or glutamic acid; m is 1, 2 or 3; and n is each independently 1, 2, 3, 4, 5, 6, 7 or 8; YY is an amino or carboxyl group. In particular embodiments, the anchor is one of the group consisting of -Lys-(CO-CH₂-(CH₂)_n-PO₃H₂)₂, -Lys-[Lys-(CO-CH₂-(CH₂)_n-PO₃H₂)₂]₂ and -Lys-(Lys-[Lys-(CO-CH₂-(CH₂)_n-PO₃H₂)₂]₂)₂, wherein n each independently is 0, 1, 2 or 3.
- [85] In certain other embodiments, the anchor is selected from the group consisting of -

CO-CH=CH₂, -CO-(CH)₁₋₂₀-CO-CH=CH₂, -CO-(CH₂)₁₋₂₀-SH, -CO-CH(NH₂)-CH₂-SH, -NH-(CH₂)₁₋₂₀-CO-CH=CH₂, -NH-(CH₂)₂₋₂₀-SH, -NH-CH(CO₂H)-CH₂-SH. The thiol moiety of the anchor allows for the coupling of the integrin selective peptide to gold plated bare metal stents and Cobalt-chromium derived bare metal stents as well as to bare metal stents made of, but not limited thereto, stainless steel, titanium or titanium alloys.

- [86] In other certain embodiments, the anchor is based on acrylic acid functional groups, which allows for coupling to bare metal stents having received a surface modification or activation. Specifically, the acrylic acid functional group may undergo chemical reaction with a free amino group of the modified surface of the stent.
- [87] A third aspect of the invention refers to the use of the intraluminal device, preferably the metal stent, as defined in the second aspect of the invention (from hereinafter “coated intraluminal device of the invention”) in medicine, and in particular as an implant. In certain embodiments, the coated intraluminal device of the invention is for use as an implant in a blood vessel, the biliary tract, the urinary system, or the lymphatic system. In a particular embodiment, the coated intraluminal device of the invention is for use as an implant to promote blood vessel repair in an individual in need thereof. The blood vessel can be any artery or vein in the body such as a coronary artery, a peripheral artery, an aorta, an intracerebral vessel, an aneurysm vessel, a renal vessel, a hepatic vessel, or a celiac vessel. In a specific embodiment, the stent is for use as an implant in an artery.
- [88] The coated intraluminal device of the invention may also be used together with one or more therapeutic agents. The at least one therapeutic agent may either be provided as part of the stent coating or used (administered) separately to the coated metal stent. When administered separately, the therapeutic agent may be administered before or after insertion of the stent or simultaneously. The route of administration may be any appropriate route known in the art. In certain embodiments, the route of administration of the therapeutic agent is systemic, e.g., by the parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. In particular embodiments, the therapeutic agent is an antiproliferative agent. Examples for antiproliferative agents include, but are not limited to, paclitaxel, sirolimus or derivatives thereof (everolimus, zotarolimus, biolimus, pimecrolimus, tacrolimus). In particular embodiments, the coated metal stent of the invention is used together with paclitaxel, sirolimus or derivatives thereof. Regarding the other embodiments of the invention, pertaining to coated intraluminal devices of the invention that are coated with both Substance P or an analogue thereof as defined in the first aspect, and the at least one therapeutic agent, any way of binding the at least one therapeutic agent to the coated intraluminal device of the invention is conceivable. If the therapeutic agent is an antiproliferative agent, the

coupling to the surface of the coated intraluminal device of the invention should be such that the antiproliferative agent is released from the stent surface within a suitable period of time. This can be accomplished by employing chemical groups that are labile under physiological conditions.

[89] In other embodiments, the coated intraluminal device of the invention and the one or more therapeutic agents are arranged in kits, optionally with instructions for use.

[90] A fourth aspect of the invention relates to a method of coating a metal stent or producing a metal stent with a coating, wherein the coating is as defined in the first aspect of the invention. According to the invention, the method of coating a metal stent or producing a metal stent with a coating comprises the step of coupling the bare metal stent with the chemical entity as defined in the first aspect of the invention. The chemical entity may be coupled to the metal stent as a whole or coupled via attachment of the anchor, and optionally spacer in any appropriate order and timing (in the sense of a construction kit). In certain embodiments, the anchor and spacer are joined together and coupled first to the metal stent followed by attaching the peptide to the spacer. In certain other embodiments, the anchor is coupled first to the metal stent followed by attaching the spacer (if present) to the anchor and then attaching the peptide to either anchor or spacer (if present). The step of coupling may comprise the preparation of one or more coating mixtures for application by solubilizing the chemical entity as a whole or each of anchor, spacer and peptide, alone or in combination, in an appropriate solvent and contacting the metal stent with the thus obtained coating mixture(s).

[91] In certain embodiments, the solubilization is achieved by mixing the chemical entity as defined in the first aspect as a whole or each of anchor, spacer and peptide, alone or in combination, with the appropriate solvent by shaking or stirring. Shaking is carried out as needed such as from 3 to 24 hours or overnight. In certain embodiments, the contacting step is carried out under incubation conditions that result in application of the coating to the surface in such a manner that it remains on the surface under the conditions in which the metal stent is used. In certain embodiments, the contacting step is carried out at a temperature in the range from +4 to +37°C.

[92] In a specific embodiment, the contacting step is carried out at room temperature. In one embodiment, the solvent comprises water. In another embodiment, the solvent comprises PBS.

[93] In a specific embodiment, the solvent is a sterile PBS solution at room temperature.

[94] In other embodiments, the method of coating a metal stent or producing a metal stent with a coating further comprises sterilizing the coated bare metal stent without affecting the binding affinity. In certain embodiments, the sterilization step is carried out before the peptide is attached to either anchor or spacer (if present).

- [95] In other embodiments, the method of coating a metal stent or producing a metal stent with a coating further comprises drying the metal stent contacted with the appropriate coating mixture(s) for 1 to 24 hours. In a specific embodiment, the metal stent contacted with the respective coating mixture(s) is left to dry for 8 to 24 hours. In certain embodiments, the drying step is carried out at a temperature in the range from +4 to +37°C. In a specific embodiment, the drying step is carried out at room temperature. In certain embodiments, the metal stent is covered with the above-mentioned coating mixture at a concentration in the range from 5-100 µg/mL. In a particular embodiment, the concentration is 10 µg/mL. In one embodiment, the concentration of the selective peptide in the coating mixture is at least 10 µg/mL.

Brief Description of Drawings

- [96] Figure 1. **Transwell migration assay images.** Representative microphotographs showing the effect of substance-P concentration on Mesenchymal Stem Cells migration through transwell chamber A) Negative control, B) Positive control with 20% FBS, C) 0.1 µM, D) 10 µM, E) 25 µM and F) 50 µM.
- [97] Figure 2. **Transwell migration assay percentages.** Percentages of mesenchymal stem cells migrated through the transwell chamber. Graph A) shows the concentration ranges between 10 nM to 500 nM, while graph B) shows the concentration ranges between 1 µM and 50 µM. The asterisks show the statistical significance of the effect. Each of the concentrations is paired with the negative internal control of each experiment (C-). The comparisons between negative and positive internal controls (C-/C+) are also shown.
- [98] Figure 3. Representative images of wound healing assay after 33 hours of growth. A) Positive control, with 20% of FBS in culture media, B) Negative control without FBS, C) 1 µM, D) 10 µM, E) 25 µM and F) 50 µM of Substance P in the media. The overlapping dotted line represents the size of the scratch in the internal negative control of the experiment. The continuous line represents the size of the scratch after incubation with each of the concentrations of Substance P.

Best Mode for Carrying out the Invention

- [99] The following examples are for purposes of illustration only and are not meant to be limiting in any way.
- [100] Migration is a key property of live cells and critical for normal development, immune response, and disease processes.
- [101] We have employed MSC (mesenchymal stem cells), with well-documented motility ability, to test their cell motion characteristics towards P Substance gradient concentrations:
- [102] - The first employed method was the cell culture wound closure assay in which a

scratch was generated on a confluent cell monolayer. The speed of wound closure and cell migration was quantified by taking snapshot pictures with a regular inverted microscope at several time intervals.

- [103] - The second method employed was the transwell cell migration and invasion assay that measured the capacity of cell motility and invasiveness toward a chemo-attractant gradient.

[104] **Isolation and culture of mesenchymal stem cells (MSCs)**

- [105] Mesenchymal stem cells were obtained from fat samples, following standard methods with some adaptations. In brief, adipose tissue sample were digested with collagenases and elastases.

- [106] The stromal vascular fraction obtained after digestion was seeded in vented flask culture vessels, with DMEM culture medium (supplemented with 10% FBS and a 1X solution of penicillin, streptomycin and 2 mM glutamine).

- [107] The cells were incubated at 37°C, 95% humidity and 5% CO₂. At 24h, the medium was removed and washed with PBS 1X to remove the none adherent cell fraction and new media was added. When the cells were confluent, they were trypsinized with TripLE and seeded again. The process was repeated until reaching Passage 4.

[108] **Migration tests using inserts (transwell migration assay)**

- [109] Migration tests using permeable inserts allow *in vitro* chemotaxis experiments. For the migration tests, inserts with two types of membrane have been used: polycarbonate and polyester. Both types with a pore size of 8 µm, which allows the passage of MSCs (*Corning Inc, USA*).

- [110] To carry out the experiments, suspensions of MSCs (100,000 cells/ mL) were prepared in medium with 5% FBS. 1.5 mL of the suspension were added inside each insert. At the bottom of the wells, different concentrations of chemoattractants were added: positive control with 20% FBS, negative control with 5% FBS, and each of the eight tested concentrations of substance P.

- [111] Experiments were performed by duplicate in two groups, the first 10 nM concentrations, 50 nM, 200 nM and 500 nM were tested for substance P. In a second round of experiments, concentrations of 1 µM, 10 µM, 25 µM and 50 µM were tested.

- [112] The transwells were incubated *overnight* at 37°C and 5% CO₂. After this time, the non-migrated cells were removed and fixed and stained with crystal violet. For statistical analysis, cells were counted manually in 10 fields, using a visible light microscope at a magnification of 100X.

[113] **Healing tests (wound healing assay)**

- [114] The wound healing assay is based on migration of the cells in a "wound" made on a monolayer of cells This method mimics the proliferation of cells during a tissue repair process.

[115] We have employed a commercial kit: *CytoSelect™ 24 Well Wound kit Healing Assay* (CELL BIOLABS, INC).

[116] The inserts inside the culture chambers created a wound of a uniform width of 0.9 mm that allows to measure the migration and the degree of proliferation of the cells. Cell proliferation and migration degree were determined by microscopic observation over time. The experiment is satisfactory when migrated cells can invade and close the wound.

[117] 500 µL of the cell suspension was added to each well containing the insert and incubated overnight with 5% CO₂ and 37°C. After the first 24 hours of incubation, the medium was removed and new medium containing different concentrations of substance were added as follows: Negative control wells were filled with basal medium (0% FBS), the positive controls with complete medium (20% FBS) or alternatively with the concentration of Substance P to be tested (1 µM, 10 µM, 25 µM, 50 µM). Cells were observed at different timepoints to assess cell migration (2h, 4h, 24h, 28h and 33h).

[118] **Results**

[119] The first method employed was the transwell cell migration and invasion assay that measured the capacity of cell motility toward a chemo-attractant gradient. The cell culture was performed in presence of different concentrations of Substance P. The results of the transwell migration assay are shown in Figure 1 and 2 wherein percentages of migrated cells depending on different Substance P concentrations are shown. As a positive control, 20% FBS has been used, a stimulus that causes up to 70% of the cells in culture to migrate from the chamber.

[120] In comparison, when the concentration of Substance P is in the range between 10 and 500 nM, the number of cells migrated is higher than in the negative control, but this difference is not statistically significant. However, when the concentration of Substance P is between 1 and 50 µM, a migration similar to that of the positive control occurs.

[121] Furthermore, it seems that the percentage of migrated cells is independent of the concentration of Substance P in the medium, once a threshold concentration is exceeded. This threshold concentration is around 1 µM in the culture medium.

[122] *In vitro* migration assay using trans-well chambers has become a standard test in this science field to test the capacity of the eluted drug to induce or inhibit cell migration towards the stent surface. This was the method employed as proof of concept in the use of pro-healing stent coatings to facilitate reendothelialization and reduce the risk of neo-atherosclerosis inducing cell migration (doi.org/10.1038/s41598-020-64940-2, doi.org/10.1002/stem.2410). Also is the preferred method to test exactly the opposite in those stents that pursuit the cell migration inhibition and adhesion delay

(doi.org/10.1093/rb/rbx010, doi.org/10.1208/s12249-016-0501-7).

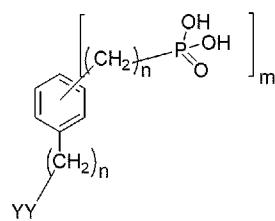
- [123] The second employed method was the cell culture wound closure assay in which a scratch was generated on a confluent cell monolayer. The speed of wound closure and cell growth and migration was quantified by taking snapshot pictures with a regular inverted microscope at several time intervals. The results of the wound assay are shown in Figure 3 wherein the scratch size can be observed after 33 hours of culture. Qualitative images of the effect of different concentrations of Substance P are shown. As a continuation of the previous experiments, only concentrations ranging from 1 to 50 μ M were used. All concentrations accelerate cell division and migration, reducing the size of the scratch when compared to the negative control in the same time interval. The concentration of 1 μ M seems to reduce the size of the scratch the most at 33 hours.
- [124] *In vitro* wound healing assay or scratch-wound assay, has become a standard test in this science field to test the capacity of the eluted drug to inhibit cell proliferation in the stent surface. This was the method employed as proof of concept in the use of drug eluting stent coatings that pursuit the inhibition of cell growth
(doi.org/10.1371/journal.pone.0094931, doi.org/10.1161/JAHA.119.014103,
doi.org/10.1371/journal.pone.0094931, doi.org/10.1016/j.msec.2020.111090,
doi.org/10.1093/rb/rbx010).

Sequence Listing Free Text

- [125] RPKPQQFFGLM (SEQ ID NO 1);
- [126] RPKPQQFFGLNIe (SEQ ID NO 2);
- [127] RPKPQQFFPLM (SEQ ID NO 3);
- [128] RPKPQQFFMeGlyLM (SEQ ID NO 4);
- [129] RPKPQQFTGLM (SEQ ID NO 5);
- [130] RPKPQQF(4-C1)F(4-C1)GLM (SEQ ID NO 6);
- [131] RPKPQQFFGLM(O) (SEQ ID NO 7);
- [132] RPKPQQFFMeGlyLM(O) (SEQ ID NO 8);
- [133] RPKPQQFFGLM(O₂) (SEQ ID NO 9);
- [134] RPKPQQFFMeGlyLM(O₂) (SEQ ID NO 10);
- [135] Z₁-Xaa¹-Xaa²-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa⁷-Xaa⁸-Xaa⁹-Xaa¹⁰-Xaa¹¹-Z₂ (SEQ ID NO 11); and
- [136] NH₂-RPKPQQFFMeGlyLM(O₂)-C(O)NH₂ (SEQ ID NO 12).

Claims

- [Claim 1] A metal stent coated with a peptide selected from the list consisting of substance P or an analogue thereof in an amount effective for inducing mobilization of endothelial precursor cells.
- [Claim 2] The metal stent of claim 1, wherein the peptide is substance P.
- [Claim 3] The metal stent of claim 2, wherein the peptide is coating the stent at a concentration of between 1 to 25 μ M.
- [Claim 4] The metal stent of claim 3, wherein the concentration is between 1 and 10 μ M.
- [Claim 5] The metal stent of any of claims 1 to 4, wherein the peptide is linked to the stent through an anchor and optionally a spacer molecule.
- [Claim 6] The metal stent according to claim 5, wherein the anchor is selected from the group consisting of: -W, -V-W, -V-[V-W₂]₂, and -V-[V-(V-W₂)₂]₂, wherein W represents



- and V represents lysine, aspartic acid or glutamic acid; m is 1, 2 or 3; and n each independently is 1, 2, 3, 4, 5, 6, 7 or 8; YY is an amino or carboxyl group.
- [Claim 7] The metal stent according to claim 6, wherein the anchor is selected from the group consisting of -CO-CH=CH₂, -CO-(CH)₁₋₂₀-CO-CH=CH₂, -CO-(CH₂)₁₋₂₀-SH, -CO-CH(NH₂)-CH₂-SH, -NH-(CH₂)₁₋₂₀-CO-CH=CH₂, -NH-(CH₂)₂₋₂₀-SH, -NH-CH(CO₂H)-CH₂-SH.
- [Claim 8] The metal stent according to any of claims 1 to 7, wherein the peptide is in combination with one or more therapeutic agents.
- [Claim 9] A peptide selected from the list consisting of Substance P. or an analogue thereof characterized in that said peptide is coating a metal stent as defined in any one of claims 1 to 8, for use as an implant.
- [Claim 10] A peptide selected from the list consisting of Substance P. or an analogue thereof characterized in that said peptide is coating a metal stent as defined in any one of claims 1 to 8, for use as an implant to promote blood vessel repair in an individual in need thereof.
- [Claim 11] A peptide selected from the list consisting of Substance P. or an analogue thereof characterized in that said peptide is coating a metal

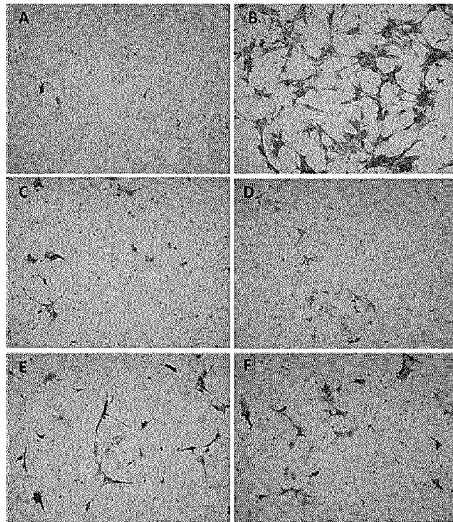
stent as defined in any one of claims 1 to 8, for use as an implant to promote blood vessel repair in an individual in need thereof in a method that comprises the steps of introducing into a blood vessel in the individual a coated metal stent of any one of claims 1 to 8.

[Claim 12] The peptide for use according to claim 11, wherein the blood vessel is any artery or vein in the body, such as a coronary artery, a peripheral artery, an aorta, an intracerebral vessel, an aneurysm vessel, a renal vessel, a hepatic vessel, or a celiac vessel in the individual.

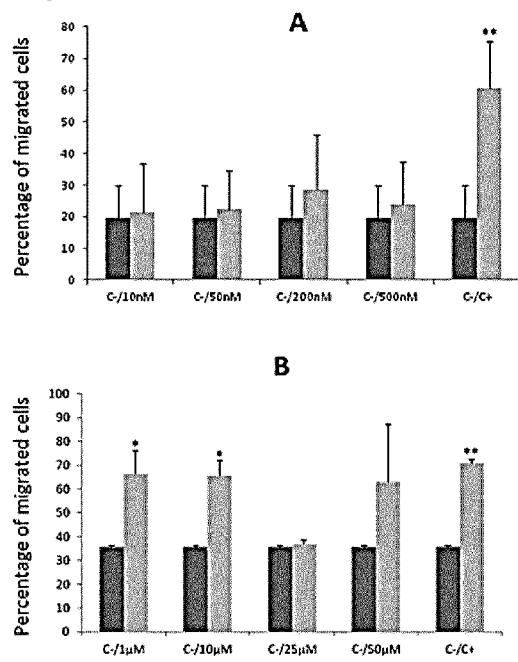
[Claim 13] A peptide selected from the list consisting of neurokinin, tachykinin or substance P characterized in that said peptide is coating a metal stent as defined in any one of claims 1 to 8, for use in a method of reducing restenosis in an individual in need thereof, comprising introducing into a blood vessel in the individual a coated metal stent of any one of claims 1 to 8.

[Claim 14] The peptide for use according to claim 13, wherein the blood vessel is any artery or vein in the body, such as a coronary artery, a peripheral artery, an aorta, an intracerebral vessel, an aneurysm vessel, a renal vessel, a hepatic vessel, or a celiac vessel in the individual.

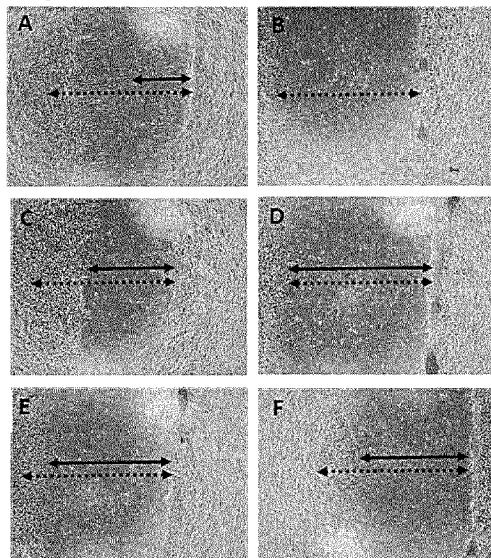
[Fig. 1]



[Fig. 2]



[Fig. 3]



INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR2023/009465

A. CLASSIFICATION OF SUBJECT MATTER

A61L 31/10(2006.01)i; A61L 31/02(2006.01)i; A61L 31/16(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61L 31/10(2006.01); A61K 38/19(2006.01); A61K 38/20(2006.01); A61L 31/16(2006.01)

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

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

eKOMPASS(Kipo internal), STN (Registry, Caplus), Google & Keywords: re-endothelialization, stents, substance P.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y A	KIM, D. et al., "The effect of Substance P/Heparin conjugated PLCL polymer coating of bioinert ePTFE vascular grafts on the recruitment of both ECs and SMCs for accelerated regeneration", Scientific reports, 2019, Vol. 9, 17083, pp. 1-13 abstract; page 2; figure 1	1-5 6,7
Y	BAE, I. -H. et al., "Mechanical and physio-biological properties of peptide-coated stent for re-endothelialization", Biomaterials research, 2020, Vol. 24, pp. 1-9 abstract; page 2	1-5
A	STONE, G. W., et al., "Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial", Jama, 2005, Vol. 294, pp. 1215-1223 the whole document	1-7
A	US 2007-0154448 A1 (REID, T. et al.) 05 July 2007 (2007-07-05) the whole document	1-7



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

01 April 2024

Date of mailing of the international search report

01 April 2024

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR2023/009465

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008-143933 A1 (CVPATH INSTITUTE, INC. et al.) 27 November 2008 (2008-11-27) the whole document	1-7

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR2023/009465

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: **12, 14**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 12, 14 refer to the multiple dependent claim which does not comply with PCT Rule 6.4(a).
3. ☒ Claims Nos.: **8-11, 13**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/KR2023/009465

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
US	2007-0154448	A1	05 July 2007	US	2010-0092561	A1	15 April 2010
				US	8222210	B2	17 July 2012
				WO	2007-062060	A2	31 May 2007
				WO	2007-062060	A3	30 April 2009
WO	2008-143933	A1	27 November 2008	US	2009-0053280	A1	26 February 2009