scope of the invention may be embodied in many other forms.

Summary

In the present disclosure, applicant has optimised its proprietary smart polymer, PNPHO, to bond with Thymosin beta-4 to form a cell-friendly medical filler material.

According to the present disclosure, there is provided a composition comprising a polymer and a natural or synthetic peptide or protein (NSPP), wherein the polymer comprises:

a first monomer for binding water;

a second monomer for imparting mechanical properties to said hydrogel;

a third monomer for binding to a natural or synthetic peptide or protein (NSPP); and

a fourth monomer for imparting phase-transition behaviour;

and wherein the natural or synthetic peptide or protein (NSPP) is Thymosin beta-4 or a functional homolog thereof.

According to one aspect of the present disclosure, there is provided a composition comprising a polymer at a concentration of 150 to 300 mg/mL of the composition and a natural or synthetic peptide or protein (NSPP), wherein the polymer comprises:

a first monomer for binding water;

a second monomer for imparting mechanical properties;

a third monomer in an amount of 7 to 13 mol. % for binding to a natural or synthetic peptide or protein (NSPP); and

a fourth monomer for imparting phase-transition behaviour;

and wherein the natural or synthetic peptide or protein (NSPP) is Thymosin beta-4 or a functional homolog thereof,

wherein binding of the natural or synthetic peptide or protein (NSPP) to the third monomer crosslinks the polymer, thereby forming a hydrogel with water, and

wherein the first monomer is oligo (ethylene) glycol monomethyl ether methacrylate (OEGMA); the second monomer is hydroxyethyl methacrylate poly(lactic acid) (HEMA-PLA); the third monomer is N-acryloxysuccinimide (NAS); and the fourth monomer is N-

isopropylacrylamide (NIPAAm).

In an example, the first monomer is selected from: polyethers, polyvinyl alcohol (PVA); poly(vinyl pyrrolidone) (PVP); poly(amino acids) and dextran.

In an example, the polyethers are selected from: polyethylene glycol (PEG), oligo(ethylene glycol) (OEG) or macromonomers thereof, polyethylene oxide (PEO), polyethylene oxide-co-propylene oxide (PPO), co-polyethylene oxide block or random copolymers thereof.

In an example, the first monomer is oligo (ethylene) glycol monomethyl ether methacrylate (OEGMA).

In an example, the second monomer is a methacrylate, or a random co-polymer comprising a methacrylate.

In an example, the second monomer is selected from: hydroxyethyl methacrylate (HEMA), a hydroxyethyl methacrylate poly(lactic acid) copolymer (HEMA-PLA), poly(lactic acid), poly(caprolactone), poly(glycolide), poly(glycolide-co-lactide) or poly(glycolide-co-caprolactone).

In an example, the second monomer is hydroxyethyl methacrylate poly(lactic acid) (HEMA-PLA).

In an example, the third monomer has electrophilic functional groups for

polymer is from about 100 mg/mL to about 300 mg/mL of the composition.

According to the present disclosure, there is provided a hydrogel comprising the composition as disclosed herein and water, wherein the binding of the NSPP to the third monomer crosslinks the polymer, thereby forming a hydrogel, with the water contained therein.

According to another aspect of the present disclosure there is provided a method of making a hydrogel, the method comprising adding water to the composition as disclosed herein.

According to another aspect of the present disclosure there is provided a method of making a hydrogel, the method comprising mixing an aqueous solution of the composition as disclosed herein with an aqueous solution of the natural or synthetic peptide or protein (NSPP).

In an example, the hydrogel is formed at body temperature. In an example, the hydrogel is formed following administration of the composition and the NSPP to a mammal by injection or by administering an aerosol.

According to another example of the present disclosure there is provided use of a composition as disclosed herein in the manufacture of a hydrogel for repair and/or restoration of both hard and soft tissue. Hard tissue (also termed calcified tissue) is tissue which is mineralised and has a firm intercellular matrix; the hard tissues of humans are bone, tooth enamel, dentin, and cementum. Soft tissue includes the tissues that connect, support, or surround other structures and organs of the body, not being hard tissue such as bone. Soft tissue includes tendons, ligaments, fascia, skin, fibrous tissues, fat, and synovial membranes (which are connective tissue), and muscles, nerves and blood vessels (which are not connective tissue).

According to another aspect of the present disclosure there is provided use of a composition as disclosed herein in the manufacture of a hydrogel for: repair and/or restoration of hard or soft body tissue; wound healing; temporary wrinkle reduction; temporarily lifting the base of a scar and promoting healing; supporting dermal connective tissue formation in scar tissue after a surgical intervention and promoting healing; supporting dermal connective tissue formation in scar management of post burn injuries; supporting vascular ingrowth in an acute dermal defect with bleeding and promoting

composition as disclosed herein for use in filling a prosthetic. In an example, the filler has no tissue-inductive properties. In an example, the administration step is made by injection or by administering an aerosol, thereby to form a hydrogel at the body temperature of a mammal.

According to another aspect of the present disclosure there is provided a composition as disclosed herein for use in supporting and repairing periodontal tissue after tooth extraction. In an example, the administration step is made by injection or by administering an aerosol, thereby to form a hydrogel at the body temperature of a mammal.

According to another aspect of the present disclosure there is provided a composition as disclosed herein for use in temporarily lifting a periodontal ligament tissue and/or supporting periodontal ligament tissue grafting. In an example, the administration step is made by injection or by administering an aerosol, thereby to form a hydrogel at the body temperature of a mammal.

According to another aspect of the present disclosure there is provided a hydrogel as disclosed herein for use in repair and/or restoration of tissue. In an example, an administration step is made by injection or by administering an aerosol, thereby to form a hydrogel at the body temperature of a mammal.

In all aspects and examples wherein the administration step is made by administering an aerosol, the aerosol may be applied to any opening of the body, such as but not limited to the nasal cavity, the mouth or an open wound.

According to the present disclosure, there is provided a kit for forming a hydrogel, the kit comprising: a polymer and a natural or synthetic peptide or protein (NSPP), wherein the polymer comprises: a first monomer for binding water; a second monomer for imparting mechanical properties to said hydrogel; a third monomer for binding to a natural or synthetic peptide or protein (NSPP); and a fourth monomer for imparting phase-transition behaviour; and wherein the natural or synthetic peptide or protein (NSPP) is Thymosin beta-4 or a functional homolog thereof. According to another aspect of the present disclosure, there is provided a kit for forming a hydrogel, the kit comprising: a polymer and a natural or synthetic peptide or protein (NSPP), wherein the polymer as disclosed herein; and wherein the natural or synthetic peptide or protein (NSPP) is Thymosin beta-4 or a functional homolog thereof. In an example, the kit further comprises water in a separate container.

According to the present disclosure, there is provided a kit for

forming a hydrogel, comprising in separate containers: a natural or synthetic peptide or protein (NSPP); and a composition, wherein the composition comprises: a first monomer for binding water; a second monomer for imparting mechanical properties to said hydrogel;

a third monomer for binding to a natural or synthetic peptide or protein (NSPP); and a fourth monomer for imparting phase-transition behaviour; wherein the natural or synthetic peptide or protein (NSPP) is Thymosin beta-4 or a functional homolog thereof; and wherein the NSPP and the second monomer are crosslinked, thereby enabling formation of the hydrogel when the composition is contacted with water.

According to another aspect of the present disclosure, there is provided a kit for forming a hydrogel, comprising in separate containers: a natural or synthetic peptide or protein (NSPP); and a polymer as disclosed herein; wherein the natural or synthetic peptide or protein (NSPP) is Thymosin beta-4 or a functional homolog thereof; and wherein the NSPP and the second monomer are crosslinked, thereby enabling formation of the hydrogel when the composition is contacted with water.

In an example, one or both of the NSPP and the composition are in solid form. In an example, the kit further comprises water in a separate container. In an example, the kit further comprises instructions for the sequential or simultaneous administration of the components of the kit. In an example, the kit is configured such that the composition, the NSPP and water are mixed together when dispensed.

In an example, the NSPP and the composition are used as a filler to deliver bone graft substitutes *in situ* in a patient in need of treatment with such. The filler keeps BGS in place (adhesive) for at least 6 weeks (degradation) and provides scaffolds for cell ingrowth (bone osteoblasts).

In another example, to form an aerosol for topical administration, the concentration of the polymer in the composition is from about 5 mg/mL to about 70 mg/mL. For instance, the concentration of the polymer in the composition is from about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69 or 70 mg/mL. The polymer can therefore be delivered via aerosol in very low concentrations, can be adhered to the surgical site and used accordingly.

Definitions and nomenclature

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments of the

invention only and is not intended to be limiting. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one having ordinary skill in the art to which the invention pertains.

Unless the context clearly requires otherwise, throughout the description and the claims, the words “comprise”, “comprising”, and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A composition comprising a polymer at a concentration of 150 to 300 mg/mL of the composition and a natural or synthetic peptide or protein (NSPP), wherein the polymer comprises:

a first monomer for binding water;

a second monomer for imparting mechanical properties;

a third monomer in an amount of 7 to 13 mol. % for binding to a natural or synthetic peptide or protein (NSPP); and

a fourth monomer for imparting phase-transition behaviour;

and wherein the natural or synthetic peptide or protein (NSPP) is Thymosin beta-4 or a functional homolog thereof,

wherein binding of the natural or synthetic peptide or protein (NSPP) to the third monomer crosslinks the polymer, thereby forming a hydrogel with water, and

wherein the first monomer is oligo (ethylene) glycol monomethyl ether methacrylate (OEGMA); the second monomer is hydroxyethyl methacrylate poly(lactic acid) (HEMA-PLA); the third monomer is N-acryloxysuccinimide (NAS); and the fourth monomer is N-isopropylacrylamide (NIPAAm).

2. The composition according to claim 1, wherein the polymer comprises the first monomer in an amount of from 3 to 8 mol%, preferably 5 mol%.

3. The composition according to any one of the preceding claims, wherein the polymer comprises the second monomer in an amount of from 5 to 9 mol%, preferably 7 mol%.

4. The composition according to any one of the preceding claims, wherein the polymer comprises:

the first monomer in an amount of from 3 to 8 mol%,

the second monomer in an amount of from 5 to 9 mol%,

and

the fourth monomer in an amount which makes up the remainder to 100% of the polymer composition.

5. The composition according to any one of the preceding claims, wherein the polymer comprises the fourth monomer in an amount from 60 to 85 mol%.

6. The composition according to any one of the preceding claims, wherein the polymer comprises:

OEGMA in an amount of 5 mol%,

HEMA-PLA in an amount of from 7 mol%,

and

NIPAAm in an amount of up to 81 mol%.

7. The composition according to any one of the preceding claims, wherein the natural or synthetic peptide or protein (NSPP) is Thymosin beta-4.

8. The composition according to any one of the preceding claims, comprising equimolar amounts of the polymer and Thymosin beta-4.

9. A method of making a hydrogel, the method comprising adding water to the composition of any one of claims 1 to 8.

10. A method of making a hydrogel, the method comprising mixing an aqueous solution of the composition of any one of claims 1 to 8 with an aqueous solution of the natural or synthetic peptide or protein (NSPP).

11. A method according to claim 10, wherein the hydrogel is formed at body temperature.

12. A method according to claim 10 or claim 11, wherein the hydrogel is to be formed after the composition and the NSPP are administered to a mammal by injection.

13. Use of a composition according to any one of claims 1 to 8 in the manufacture of a hydrogel for: repair and/or restoration of hard or soft body tissue; wound healing; temporary wrinkle reduction; temporarily lifting the base of a scar and promoting healing; supporting dermal connective tissue formation in scar tissue after a surgical intervention and promoting healing; supporting dermal connective tissue formation in scar management of post burn injuries; supporting vascular ingrowth in an acute dermal defect with bleeding and promoting healing; filling a surgically generated dermal cavity; supporting a skin grafting operation; physically delivering bone graft substitutes; filling a prosthetic; use as a filler with no tissue-inductive properties; supporting and repairing periodontal tissue after tooth extraction; or temporarily lifting a periodontal ligament tissue and/or supporting periodontal ligament tissue grafting.

14. Use of a hydrogel according to claim 13 in the manufacture of a medicament for repair and/or restoration of tissue.

15. The use according to claim 13 or 14, wherein:
    - the composition as defined in claim 13 is to be injected to a mammal to form a hydrogel at the body temperature of the mammal;
    - the hydrogel as defined in claim 14 is to be injected to the mammal; or
    - an aerosol is to be administered to the mammal to form a hydrogel at the body temperature of the mammal.

16. A composition according to any one of claims 1 to 8 for use in: the repair and/or restoration of tissue; wound healing; temporary wrinkle reduction; temporarily lifting the base of a scar and promoting healing; supporting dermal connective tissue formation in scar tissue after a surgical intervention and promoting healing; supporting dermal connective tissue formation in scar management of post burn injuries; supporting vascular ingrowth in an acute dermal defect with bleeding and promoting healing; filling a surgically generated dermal cavity; supporting a skin grafting operation; physically delivering bone graft substitutes; filling a prosthetic; use as a filler with no

tissue-inductive properties; supporting and repairing periodontal tissue after tooth extraction; or temporarily lifting a periodontal ligament tissue and/or supporting periodontal ligament tissue grafting.

17. A composition for use according to claim 16, wherein the filler has no tissue-inductive properties.

18. A composition according to any one of claims 1 to 8 for use in supporting and repairing periodontal tissue after tooth extraction.

19. A composition according to any one of claims 1 to 8 for use in temporarily lifting a periodontal ligament tissue and/or supporting periodontal ligament tissue grafting.

20. A hydrogel according to claim 1 for use in repair and/or restoration of tissue.

21. A composition for use according to any one of claims 16 to 20 wherein:
- the composition as defined in any one of claims 16 to 19 is to be injected to a mammal to form a hydrogel at the body temperature of the mammal;
- the hydrogel as defined in claim 20 is to be injected to the mammal; or
- an aerosol is to be administered to the mammal to form a hydrogel at the body temperature of the mammal.

22. A hydrogel for use according to claim 20, wherein:
- the hydrogel as defined in claim 20 is to be injected to the mammal; or
- an aerosol is to be administered to the mammal to form a hydrogel at the body temperature of the mammal.

23. A kit for forming a hydrogel, the kit comprising:

a polymer and a natural or synthetic peptide or protein (NSPP), wherein the polymer is as defined according to claim 1;

and wherein the natural or synthetic peptide or protein (NSPP) is Thymosin beta-4 or a functional homolog thereof.

24. The kit according to claim 23, further comprising water in a separate container.

25. A kit for forming a hydrogel, comprising in separate containers:

a natural or synthetic peptide or protein (NSPP); and

a polymer as defined according to claim 1;

wherein the natural or synthetic peptide or protein (NSPP) is Thymosin beta-4 or a functional homolog thereof;

and wherein the NSPP and the second monomer are crosslinked, thereby enabling formation of the hydrogel when the composition is contacted with water.

26. The kit according to claim 25 wherein one or both of the NSPP and the composition are in solid form.

27. The kit according to claim 25 or claim 26 further comprising water in a separate container.

28. The kit according to any one of claims 25 to 27 further comprising instructions for the sequential or simultaneous administration of the components of the kit.

29. The kit according to any one of claims 25 to 28, configured such that the composition, the NSPP and water are mixed together when dispensed.