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(54) Title: PEPTIDES FOR THE TREATMENT OF OSTEOARTHRITIS

(57) Abstract: The present invention relates to peptides comprising a sequence SEQ ID NO: 1 for use in the treatment of osteoarthritis.



WO 2017/212057 A1

PEPTIDES FOR THE TREATMENT OF OSTEOARTHRITIS

FIELD OF INVENTION

The present invention relates to the treatment of osteoarthritis. In particular, the present
5 invention relates to peptides for use in the treatment of osteoarthritis.

BACKGROUND OF INVENTION

Osteoarthritis is commonly related to a type of degenerative joint disease afflicting
millions of individuals, and resulting in the breakdown of joint cartilage and of underlying
10 bone, provoking in concerned subjects, joint pain, joint swelling, stiffness and decreased
range of motion. Though it was previously thought to be a normal consequence of aging,
it is now realized that osteoarthritis results from a complex interplay of multiple factors,
including joint integrity, genetic predisposition, local inflammation, mechanical forces,
and cellular and biochemical processes. In more than 10 % of the cases, injuries can also
15 cause post-traumatic osteoarthritis to develop and thus, affect individuals at any age.

Current treatments and researches are directed towards reduction of symptoms and
prevention of disabilities, but no efficient and long-lasting pharmacologic therapies have
been proven to prevent the progression of joint damage due to osteoarthritis. Among these
treatments currently available, physical activity is considered an important part of the
20 treatment plan. Studies show that simple activities and/or stretching exercises can reduce
pain by maintaining a healthy weight and improving flexibility. Excess weight indeed
adds additional stress to weight-bearing joints, such as the hips, knees, feet and back.
Losing weight can help people with osteoarthritis reduce pain and limit further joint
damage. Pain and anti-inflammatory medications, including analgesics, nonsteroidal anti-
25 inflammatory drugs or corticosteroids, are also often considered in the treatment plan to
alleviate osteoarthritis symptoms. These are available as creams, tablets or intra-articular
injections. Finally, more severely suffering patients can consider the surgery option like
arthroplasty, arthrodesis or osteotomy, to repair or replace damaged joints.

More recently, cell-based and biological therapies for osteoarthritis have been developed. For example, autologous chondrocyte implantation has been used for treatment of osteoarticular lesions for several decades. Chondrocyte-based therapy has shown its capacity to slow down the progression of osteoarthritis and delay joint replacement surgery, but numerous complications remain associated with like hypertrophy, disturbed fusion, delamination, and graft failure.

Finally, gene therapy has attracted the attention of scientists, to target the disease process rather than the symptoms. Both viral and non-viral vectors have been developed to carry the therapeutic genes to autologous chondrocytes, raising serious concerns about the immunogenicity of viral vectors; and the low and short-term efficiency of non-viral vectors. These gene therapies aim at inhibiting inflammatory and catabolic pathways, stimulating anabolic pathways to rebuild the matrix, impeding cell senescence, avoiding the pathological formation of osteophytes and/or preventing apoptosis. Numerous candidates for osteoarthritis gene therapy have been identified to date, like cytokines Interleukin-1 (IL-1), Tumor necrosis factor receptor (TNFR) and Interleukin-4 (IL-4) and their respective antagonists; matrix breakdown inhibitors Tissue inhibitor of metalloproteinases (TIMPs), Plasminogen activator inhibitors (PAIs) or serpins; apoptosis inhibitor B-cell lymphoma 2 (Bcl-2); cartilage growth factors; etc.

However, no effective, safe and easy-to-implement treatment is currently available. According to the World Health Organization, an estimated 10 % to 15 % of all adults have some degree of osteoarthritis. This prevalence is increasing due to population ageing and an increase in related factors such as obesity. According to the United Nations, by 2050, 130 million people worldwide will suffer from osteoarthritis, of whom 40 million will be severely disabled by the disease. These figures shed the light on the urgent need to develop a new treatment, easy to administrate and capable of curing instead of alleviating the symptoms.

Willing to develop peptides for treating osteoarthritis, the Applicant surprisingly showed that chimeric peptides comprising an amino acid sequence derived from growth hormone linked at its C-terminal extremity with an amino acid sequence derived from somatostatin

may efficiently induce chondrocytes proliferation and differentiation, and may therefore be used for treating osteoarthritis.

The present invention thus relates to peptides for treating osteoarthritis.

5 SUMMARY

The invention thus relates to a peptide comprising an amino acids sequence SEQ ID NO: 1, or a fragment or variant thereof, wherein SEQ ID NO: 1 is the following:

X₁-Tyr-X₂-Leu-X₃-Ala-Gly-X₄-Lys-Asn-Phe-Phe-X₅ (SEQ ID NO: 1)

wherein:

- 10 - X₁ is vacant or is valine or a sequence selected from:

Z₁-Val

Asp-Z₁-Val

Ser-Asp-Z₁-Val (SEQ ID NO: 5)

Z₂-Ser-Asp-Z₁-Val (SEQ ID NO: 6) and

- 15 Gly-Z₂-Ser-Asp-Z₁-Val (SEQ ID NO: 7)

wherein Z₁ is arginine and Z₂ threonine, or Z₁ is Ser-Asp or Ser-Asn and Z₂ is alanine;

- X₂ is a sequence selected from Glu-Lys, Glu-Ser and Asp-Leu;

- X₃ is vacant or is lysine or a sequence selected from:

Lys-Asp

- 20 Lys-Asp-Leu

Lys-Asp-Leu-Glu (SEQ ID NO: 8)

Lys-Asp-Leu-Glu-Glu (SEQ ID NO: 9)

Lys-Asp-Leu-Glu-Glu-Gly (SEQ ID NO: 10)

Lys-Asp-Leu-Glu-Glu-Gly-Ile (SEQ ID NO: 11)

- 25 Lys-Asp-Leu-Glu-Glu-Gly-Ile-Gln (SEQ ID NO: 12)

Lys-Asp-Leu-Glu-Glu-Gly-Ile-Gln-Z₃ (SEQ ID NO: 13) and

Lys-Asp-Leu-Glu-Glu-Gly-Ile-Gln-Z₃-Leu (SEQ ID NO: 14)

wherein Z₃ is alanine or threonine;

- X₄ is an amino acid residue selected from cysteine, serine, tyrosine, phenylalanine, aspartic acid, glutamic acid, alanine and glycine; and
- X₅ is vacant or is a tryptophan residue or a sequence selected from:

Trp-Lys

5 Trp-Lys-Thr

Trp-Lys-Thr-Phe (SEQ ID NO: 15)

Trp-Lys-Thr-Phe-Thr (SEQ ID NO: 16)

Trp-Lys-Thr-Phe-Thr-Ser (SEQ ID NO: 17)

Trp-Lys-Thr-Phe-Thr-Ser-X₆ (SEQ ID NO: 18) and

10 Trp-Lys-Thr-Phe-Thr-Ser-X₆-Lys-Gln-Ala (SEQ ID NO: 19)

wherein X₆ is an amino acid residue selected from cysteine, serine, tyrosine, phenylalanine, aspartic acid, glutamic acid, alanine and glycine;

for use in the treatment of osteoarthritis in a subject.

In one embodiment, the peptide consists in an amino acid sequence ranging from 11 to
15 50 amino acids residues, preferably ranging from 20 and 30 amino acid residues.

In one embodiment, X₁ is Gly-Z₂-Ser-Asp-Z₁-Val; and X₅ is Trp-Lys-Thr-Phe-Thr-Ser-X₆.

In one embodiment, the peptide comprises a sequence SEQ ID NO: 2, 3, 4 or 20:

- Gly-Ala-Ser-Asp-Ser-Asp-Val-Tyr-Asp-Leu-Leu-Ala-Gly-Ser-Lys-Asn-Phe-
20 Phe-Trp-Lys-Thr-Phe-Thr-Ser-Ser (SEQ ID NO: 2)
- Gly-Ala-Ser-Asp-Ser-Asp-Val-Tyr-Asp-Leu-Leu-Lys-Ala-Gly-Ser-Lys-Asn-
Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Ser (SEQ ID NO: 3)
- Gly-Thr-Ser-Asp-Arg-Val-Tyr-Glu-Lys-Leu-Ala-Gly-Ser-Lys-Asn-Phe-Phe-
Trp-Lys-Thr-Phe-Thr-Ser-Ser (SEQ ID NO: 4)
- 25 - Gly-Ala-Ser-Asp-Ser-Asn-Val-Tyr-Asp-Leu-Leu-Lys-Ala-Gly-Ser-Lys-Asn-
Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Ser (SEQ ID NO: 20).

In one embodiment, said peptide is to be administrated by intra-articular injection in the joint to be treated.

In one embodiment, said peptide is to be administrated at a final concentration in the joint ranging from 10^{-3} M to 10^{-7} M or from 10^{-4} M to 10^{-7} M.

The present invention further relates to a pharmaceutical composition containing at least one peptide for use as described in the present invention and one or more
5 pharmaceutically acceptable excipient.

The present invention further relates to a medicament containing at least one peptide for use as described in the present invention.

The present invention further relates to a pharmaceutical unit dosage form containing at least one peptide for use as described in the present invention.

10 In one embodiment, the unit dosage form is a single use pre-filled, pre-dosed syringe, for local injection in the joint to be treated.

The present invention further relates to a pharmaceutical composition, a medicament, or a pharmaceutical unit dosage form as described hereinabove, wherein said pharmaceutical composition, medicament or pharmaceutical unit dosage for further
15 contains at least one viscosupplementation agent.

In one embodiment, the at least one viscosupplementation agent is hyaluronic acid, preferably wherein hyaluronic acid is at a concentration ranging from 0.1 % to 10 %.

DEFINITIONS

20 In the present invention, the following terms have the following meanings:

The term “**subject**” refers to a mammal, preferably a human. In one embodiment of the invention, a subject may also refer to a horse, a cow or a pet, such as, for example, a dog, a cat, a guinea pig, a hamster, a rat, a mouse, a ferret, a rabbit and the like. In one embodiment, a subject may be a “patient”.

The term “**patient**” refers to a subject, who/which is awaiting the receipt of, or is receiving medical care or was/is/will be the object of a medical procedure, or is monitored for the development of a disease.

5 The term “**elderly**” refers to a human subject or patient past 30 years-old (such as, for example, past about 40, 50, 60, 70, 80, 90 years-old or more), or to a non-human animal with equivalent age according to the specie.

The terms “**treating**”, “**treatment**” or “**alleviation**” refer to both therapeutic treatment and prophylactic or preventative measures; wherein the object is to prevent or slow down (lessen) osteoarthritis. Those in need of treatment include those already with osteoarthritis as well as those prone to have osteoarthritis or those in whom osteoarthritis is to be prevented. A subject or mammal is successfully “treated” for osteoarthritis if, after receiving a therapeutic amount of a peptide according to the present invention, the patient shows observable and/or measurable reduction in or absence of one or more of the following: reduction or slow-down of the degradation of cartilage structure, maintenance or increase in cartilage thickness, relief to some extent of one or more of the symptoms associated with osteoarthritis; reduced morbidity, and/or improvement in quality of life issues. The above parameters for assessing successful treatment and improvement in osteoarthritis are readily measurable by routine procedures familiar to a physician.

20 The term “**therapeutically effective amount**” means level or amount of agent that is aimed at, without causing significant negative or adverse side effects to the target, (1) delaying or preventing the onset of osteoarthritis; (2) slowing down or stopping the progression, aggravation, or deterioration of one or more symptoms of osteoarthritis; (3) bringing about ameliorations of the symptoms of osteoarthritis; (4) reducing the severity or incidence of osteoarthritis; or (5) curing osteoarthritis. A therapeutically effective amount may be administered prior to the onset of osteoarthritis, for a prophylactic or preventive action. Alternatively or additionally, the therapeutically effective amount may be administered after initiation of osteoarthritis, for a therapeutic action.

30 The term “**pharmaceutically acceptable excipient**” refers to an excipient that does not produce an adverse, allergic or other untoward reaction when administered to an animal, preferably a human. It includes any and all solvents, dispersion media, coatings,

antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. For human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by regulatory offices, such as, for example, FDA Office or EMA.

- 5 The term “**about**” preceding a figure means plus or less 10 % of the value of said figure.

DETAILED DESCRIPTION

The present invention relates to a peptide for use in the treatment of osteoarthritis. Indeed, the Applicant surprisingly demonstrated that the peptides of the invention are capable of
10 inducing a local acceleration of chondrocytes proliferation and differentiation, and may therefore be used for treating osteoarthritis.

In one embodiment, the peptide of the invention is a synthetic peptide comprising a fragment of growth hormone (GH) sequence (such as, for example, human GH sequence in particular in an embodiment where the subject to be treated is a human) linked via an
15 amino bond to a fragment of somatostatin sequence (such as, for example, human somatostatin sequence, in particular in an embodiment where the subject to be treated is a human).

In one embodiment, the peptide of the invention comprises or consists in SEQ ID NO: 1 or a fragment or variant thereof, wherein SEQ ID NO: 1 is the following:

20 **X₁-Tyr-X₂-Leu-X₃-Ala-Gly-X₄-Lys-Asn-Phe-Phe-X₅** (SEQ ID NO: 1)

wherein:

- X₁ is vacant or is valine or a sequence selected from:
Z₁-Val
Asp-Z₁-Val
25 Ser-Asp-Z₁-Val (SEQ ID NO: 5)
Z₂-Ser-Asp-Z₁-Val (SEQ ID NO: 6) and
Gly-Z₂-Ser-Asp-Z₁-Val (SEQ ID NO: 7)

wherein Z₁ is arginine and Z₂ threonine, or Z₁ is Ser-Asp or Ser-Asn and Z₂ is alanine;

- X₂ is a sequence selected from Glu-Lys, Glu-Ser and Asp-Leu;
 - X₃ is vacant or is lysine or a sequence selected from:
 - Lys-Asp
 - Lys-Asp-Leu
 - 5 Lys-Asp-Leu-Glu (SEQ ID NO: 8)
 - Lys-Asp-Leu-Glu-Glu (SEQ ID NO: 9)
 - Lys-Asp-Leu-Glu-Glu-Gly (SEQ ID NO: 10)
 - Lys-Asp-Leu-Glu-Glu-Gly-Ile (SEQ ID NO: 11)
 - Lys-Asp-Leu-Glu-Glu-Gly-Ile-Gln (SEQ ID NO: 12)
 - 10 Lys-Asp-Leu-Glu-Glu-Gly-Ile-Gln-Z₃ (SEQ ID NO: 13) and
 - Lys-Asp-Leu-Glu-Glu-Gly-Ile-Gln-Z₃-Leu (SEQ ID NO: 14)
- wherein Z₃ is alanine or threonine;
- X₄ is an amino acid residue selected from cysteine, serine, tyrosine, phenylalanine, aspartic acid, glutamic acid, alanine and glycine; and
 - 15 - X₅ is vacant or is a tryptophan residue or a sequence selected from:
 - Trp-Lys
 - Trp-Lys-Thr
 - Trp-Lys-Thr-Phe (SEQ ID NO: 15)
 - Trp-Lys-Thr-Phe-Thr (SEQ ID NO: 16)
 - 20 Trp-Lys-Thr-Phe-Thr-Ser (SEQ ID NO: 17)
 - Trp-Lys-Thr-Phe-Thr-Ser-X₆ (SEQ ID NO: 18) and
 - Trp-Lys-Thr-Phe-Thr-Ser-X₆-Lys-Gln-Ala (SEQ ID NO: 19)
- wherein X₆ is an amino acid residue selected from cysteine, serine, tyrosine, phenylalanine, aspartic acid, glutamic acid, alanine and glycine.
- 25 In one embodiment, X₁ is Gly-Z₂-Ser-Asp-Z₁-Val (SEQ ID NO: 7) wherein Z₁ and Z₂ are as described above; X₂, X₃ and X₄ are as described above; X₅ is Trp-Lys-Thr-Phe-Thr-Ser-X₆ (SEQ ID NO: 18), wherein X₆ is as described above.
- In one embodiment, X₁ is Gly-Z₂-Ser-Asp-Z₁-Val (SEQ ID NO: 7) wherein Z₁ is Ser-Asp and Z₂ is alanine; X₂ is Asp-Leu; X₃ is vacant; X₄ is serine; X₅ is Trp-Lys-Thr-Phe-Thr-
- 30 Ser-X₆ (SEQ ID NO: 18), wherein X₆ is serine. According to this embodiment, the peptide

of the invention comprises or consists of SEQ ID NO: 2, a fragment or a variant thereof, wherein SEQ ID NO: 2 is the following:

Gly-Ala-Ser-Asp-Ser-Asp-Val-Tyr-Asp-Leu-Leu-Ala-Gly-Ser-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Ser (SEQ ID NO: 2)

- 5 In another embodiment, X₁ is Gly-Z₂-Ser-Asp-Z₁-Val (SEQ ID NO: 7) wherein Z₁ is Ser-Asp and Z₂ is alanine; X₂ is Asp-Leu; X₃ is lysine; X₄ is serine; X₅ is Trp-Lys-Thr-Phe-Thr-Ser-X₆ (SEQ ID NO: 18), wherein X₆ is serine. According to this embodiment, the peptide of the invention comprises or consists of SEQ ID NO: 3, a fragment or a variant thereof, wherein SEQ ID NO: 3 is the following:

- 10 **Gly-Ala-Ser-Asp-Ser-Asp-Val-Tyr-Asp-Leu-Leu-Lys-Ala-Gly-Ser-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Ser** (SEQ ID NO: 3)

- In another embodiment, X₁ is Gly-Z₂-Ser-Asp-Z₁-Val (SEQ ID NO: 7) wherein Z₁ is arginine and Z₂ is threonine; X₂ is Glu-Lys; X₃ is vacant; X₄ is serine; X₅ is Trp-Lys-Thr-Phe-Thr-Ser-X₆ (SEQ ID NO: 18), wherein X₆ is serine. According to this embodiment,
- 15 the peptide of the invention comprises or consists of SEQ ID NO: 4, a fragment or a variant thereof, wherein SEQ ID NO: 4 is the following:

Gly-Thr-Ser-Asp-Arg-Val-Tyr-Glu-Lys-Leu-Ala-Gly-Ser-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Ser (SEQ ID NO: 4)

- In another embodiment, X₁ is Gly-Z₂-Ser-Asp-Z₁-Val (SEQ ID NO: 7) wherein Z₁ is Ser-Asn and Z₂ is alanine; X₂ is Asp-Leu; X₃ is lysine; X₄ is serine; X₅ is Trp-Lys-Thr-Phe-Thr-Ser-X₆ (SEQ ID NO: 18), wherein X₆ is serine. According to this embodiment, the peptide of the invention comprises or consists of SEQ ID NO: 20, a fragment or a variant thereof, wherein SEQ ID NO: 20 is the following:
- 20

- Gly-Ala-Ser-Asp-Ser-Asn-Val-Tyr-Asp-Leu-Leu-Lys-Ala-Gly-Ser-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Ser** (SEQ ID NO: 20)
- 25

In one embodiment, the peptide of the invention consists in an amino acid sequence ranging from about 11 to about 50 amino acids residue, preferably ranging from 14 to about 40 amino acid residues, more preferably from about 20 to about 30 amino acid

residues. In one embodiment, the peptide of the invention consists in 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 or 50 amino acids.

As used herein, “amino acids” are represented by their full name, their three letter code
5 or their one letter code as well known in the art. Amino acid residues in peptides are abbreviated as follows: Phenylalanine is Phe or F; Leucine is Leu or L; Isoleucine is Ile or I; Methionine is Met or M; Valine is Val or V; Serine is Ser or S; Proline is Pro or P; Threonine is Thr or T; Alanine is Ala or A; Tyrosine is Tyr or Y; Histidine is His or H; Glutamine is Gln or Q; Asparagine is Asn or N; Lysine is Lys or K; Aspartic Acid is Asp
10 or D; Glutamic Acid is Glu or E; Cysteine is Cys or C; Tryptophan is Trp or W; Arginine is Arg or R; and Glycine is Gly or G.

As used herein, the term “amino acids” includes both natural and synthetic amino acids, and both D and L amino acids. “Standard amino acid” or “naturally occurring amino acid” means any of the twenty standard L-amino acids commonly found in naturally occurring
15 peptides. “Nonstandard amino acid residue” means any amino acid, other than the standard amino acids, regardless of whether it is prepared synthetically or derived from a natural source. For example, naphthylalanine can be substituted for tryptophan to facilitate synthesis. Other synthetic amino acids that can be substituted include, but are not limited to, L-hydroxypropyl, L-3,4-dihydroxyphenylalanyl, alpha-amino acids such as L-alpha-hydroxylysyl and D-alpha-methylalanyl, L-alpha-methylalanyl, beta-amino acids, and
20 isoquinolyl. Also, threonine, alanine, tryptophan and phenylalanine residues can belong to the D-form, for the peptide to be more resistant to peptidases.

As used herein, “amino acid” also encompasses chemically modified amino acids, including but not limited to salts, amino acid derivatives (such as amides), and
25 substitutions. Amino acids contained within the peptides of the present invention, and particularly at the carboxy- or amino-terminus, can be modified by methylation, amidation, acetylation or substitution with other chemical groups which can change the peptide's circulating half-life without adversely affecting their activity. Additionally, a disulfide linkage may be present or absent in the peptides of the invention.

The peptides useful in the present invention may comprise naturally standard amino acids or non-standard amino acids. Peptide mimetics include peptides having the following modifications: i) peptides wherein one or more of the peptidyl -C(O)NR- linkages (bonds) have been replaced by a non-peptidyl linkage such as a -CH₂-carbamate linkage
 5 (-CH₂OC(O)NR-), a phosphonate linkage, a -CH₂-sulfonamide (-CH₂-S(O)₂NR-) linkage, a urea (-NHC(O)NH-) linkage, a -CH₂-secondary amine linkage, or with an alkylated peptidyl linkage (-C(O)NR-) wherein R is C₁-C₄ alkyl; ii) peptides wherein the N-terminus is derivatized to a -NRR¹ group, to a -NRC(O)R group, to a -NRC(O)OR group, to a -NRS(O)₂R group, to a -NHC(O)NHR group where R and R¹ are hydrogen or
 10 C₁-C₄ alkyl with the proviso that R and R¹ are not both hydrogen; iii) peptides wherein the C terminus is derivatized to -C(O)R² where R² is selected from the group consisting of C₁-C₄ alkoxy, and -NR³R⁴ where R³ and R⁴ are independently selected from the group consisting of hydrogen and C₁-C₄ alkyl.

In one embodiment, the N- and C-termini of the peptides useful in the present invention
 15 may be optionally protected against proteolysis. For instance, the N-terminus may be in the form of an acetyl group, and/or the C-terminus may be in the form of an amide group.

Therefore, in one embodiment, the peptide of the invention comprises or consists in the following amino acid sequence:

Ac-Gly-Ala-Ser-Asp-Ser-Asp-Val-Tyr-Asp-Leu-Leu-Ala-Gly-Ser-Lys-Asn-Phe-Phe-
 20 Trp-Lys-Thr-Phe-Thr-Ser-Ser-NH₂ (SEQ ID NO: 2 protected with an acetyl group in N-term and with an amide group in C-term); or

Ac-Gly-Ala-Ser-Asp-Ser-Asp-Val-Tyr-Asp-Leu-Leu-Lys-Ala-Gly-Ser-Lys-Asn-Phe-
 Phe-Trp-Lys-Thr-Phe-Thr-Ser-Ser-NH₂ (SEQ ID NO: 3 protected with an acetyl group
 in N-term and with an amide group in C-term); or

25 Ac-Gly-Thr-Ser-Asp-Arg-Val-Tyr-Glu-Lys-Leu-Ala-Gly-Ser-Lys-Asn-Phe-Phe-Trp-
 Lys-Thr-Phe-Thr-Ser-Ser-NH₂ (SEQ ID NO: 4 protected with an acetyl group in N-term
 and with an amide group in C-term); or

Ac-Gly-Ala-Ser-Asp-Ser-Asn-Val-Tyr-Asp-Leu-Leu-Lys-Ala-Gly-Ser-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Ser-NH₂ (SEQ ID NO: 20 protected with an acetyl group in N-term and with an amide group in C-term).

Internal modifications of the peptides to be resistant to proteolysis are also envisioned,
5 e.g. wherein at least a -CONH- peptide bond is modified and replaced by a (CH₂NH) reduced bond, a (NHCO) retro-inverso bond, a (CH₂-O) methylene-oxy bond, a (CH₂-S) thiomethylene bond, a (CH₂CH₂) carba bond, a (CO-CH₂) cetomethylene bond, a (CHOH-CH₂) hydroxyethylene bond), a (N-N) bound, a E-alcene bond or also a -CH=CH-bond.

10 In one embodiment of the invention, the polypeptides as described here above are modified by means well-known in the art, for instance by the addition of one or more functional group such as a phosphate, acetate, lipid or carbohydrate group, and/or by the addition of one or more protecting group.

For example, the polypeptides can be modified by the addition of one or more functional
15 groups such as phosphate, acetate, or various lipids and carbohydrates. The polypeptides of the invention can also exist as polypeptide derivatives. The term "polypeptide derivative" refers to compound having an amino group (--NH--), and more particularly, a peptide bond. Polypeptides may be regarded as substituted amides. Like the amide group, the peptide bond shows a high degree of resonance stabilization. The C--N single
20 bond in the peptide linkage has typically about 40 percent double-bond character and the C=O double bond about 40 percent single-bond character. "Protecting groups" are those groups that prevent undesirable reactions (such as proteolysis) involving unprotected functional groups. Specific examples of amino protecting groups include formyl; trifluoroacetyl; benzyloxycarbonyl; substituted benzyloxycarbonyl such as (ortho- or
25 para-) chlorobenzyloxycarbonyl and (ortho- or para-) bromobenzyloxycarbonyl; and aliphatic oxycarbonyl such as t-butoxycarbonyl and t-amiloxycarbonyl. The carboxyl groups of amino acids can be protected through conversion into ester groups. The ester groups include benzyl esters, substituted benzyl esters such as methoxybenzyl ester; alkyl esters such as cyclohexyl ester, cycloheptyl ester or t-butyl ester. The guanidino moiety
30 may be protected by nitro; or arylsulfonyl such as tosyl, methoxybenzensulfonyl or

mesitylenesulfonyl, even though it does not need a protecting group. The protecting groups of imidazole include tosy, benzyl and dinitrophenyl. The indole group of tryptophan may be protected by formyl or may not be protected.

- Peptides useful in the present invention can also be covalently bound to a polyethylene glycol (PEG) molecule by their C-terminal terminus or a lysine residue, notably a PEG of 1500 MW or 4000 MW, for a decrease in urinary clearance and in therapeutic doses used and for an increase of water solubility, mobility in solution and half-life in blood plasma, all with a low immunogenicity. The binding of PEG is as described by Abuchowski et al., (J. Biol. Chenu., 1977, 252: 3582-3586). In a further aspect of the invention, two or more PEG molecules are bound in each anchorage site. In yet another embodiment, peptide half-life is increased by including the peptide in a biodegradable and biocompatible polymer material for drug delivery system forming microspheres. Polymers and copolymers are, for instance, poly(D,L-lactide-co-glycolide) (PLGA) (as illustrated in US2007/0184015, SoonKap Hahn et al.,).
- Other examples of modifications used to prevent degradation of the polypeptides by endopeptidases or exopeptidases include N-terminal modifications such as acetylation or glycosylation, C-terminal modifications such as amidation and use of unnatural amino acids (β -amino and α -trifluoromethyl amino acids) at particular sites within the polypeptides.
- Another alternative to increase polypeptide molecular size is the genetic fusion of the polypeptides to the Fc domain of human gamma immunoglobulin or the fusion of the polypeptides to albumin.

In one embodiment, the peptide of the invention is a variant of SEQ ID NO: 1, preferably a variant of SEQ ID NO: 2, 3, 4 or 20.

- A peptide "variant" as the term is used herein, is a peptide that typically differs from a peptide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions. Such variants may be naturally occurring or may be synthetically generated, for example, by modifying one or more of the above peptide sequences and evaluating one or more biological activities of the peptide as described herein and/or using

any of a number of techniques well known in the art. Modifications may be made in the structure of peptides and still obtain a functional molecule that encodes a variant or derivative peptide with desirable characteristics.

When it is desired to alter the amino acid sequence of a peptide to create an equivalent,
5 or even an improved, variant or portion of a ligand of the invention, one skilled in the art will typically change one or more of the codons of the encoding DNA sequence. For example, certain amino acids may be substituted by other amino acids in a protein structure without appreciable loss of its ability to bind cell surface receptor, preferably cell surface nutrient transporters. Since it is the binding capacity and nature of a protein
10 that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with similar properties. It is thus contemplated that various changes may be made in the peptide sequences, or corresponding DNA sequences that encode said peptides without appreciable loss of their
15 biological utility or activity. In many instances, a peptide variant will contain one or more conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted by another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the peptide to be substantially unchanged. As outlined above, amino acid substitutions
20 are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing characteristics into consideration are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine,
25 leucine and isoleucine. Amino acid substitutions may further be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include histidine, lysine and arginine; and amino acids with uncharged polar head groups having similar
30 hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other

groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

As used herein, the term “conservative amino acid substitution” may further be defined as an amino acid exchange within one of the following five groups:

- I. Small aliphatic, nonpolar or slightly polar residues: Ala, Ser, Thr, Pro, Gly;
- II. Polar, negatively charged residues and their amides: Asp, Asn, Glu, Gln;
- III. Polar, positively charged residues: His, Arg, Lys;
- IV. Large, aliphatic, nonpolar residues: Met, Leu, Ile, Val, Cys;
- 10 V. Large, aromatic residues: Phe, Tyr, Trp.

A variant may also, or alternatively, contain non-conservative changes. In a preferred embodiment, variant peptides differ from a native sequence by substitution, deletion or addition of 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal
15 influence on the immunogenicity, secondary structure and hydrophobic nature of the peptide. Therefore, in one embodiment, a variant of SEQ ID NO: 1, 2, 3, 4 or 20 is a peptide wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids from the sequence of SEQ ID NO: 1, 2, 3, 4 or 20 respectively is/are absent, or substituted by any amino acid, or wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids (either contiguous or not) is/are added.

20 In one embodiment, a variant of SEQ ID NO: 1, 2, 3, 4 or 20 is a peptide having the sequence of SEQ ID NO: 1, 2, 3, 4 or 20 and 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 additional amino acids in C-term and/or in N-term.

In one embodiment, a variant of SEQ ID NO: 1, 2, 3 4 or 20 is a peptide showing at least about 70% identity with SEQ ID NO: 1, 2, 3, 4 or 20 respectively, preferably at least
25 about 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99% identity or more.

The term “identity”, when used in a relationship between the sequences of two or more polypeptides, refers to the degree of sequence relatedness between polypeptides, as determined by the number of matches between strings of two or more amino acid residues. “Identity” measures the percent of identical matches between the smaller of two or more

sequences with gap alignments (if any) addressed by a particular mathematical model or computer program (i.e., “algorithms”). Identity of related polypeptides can be readily calculated by known methods. Such methods include, but are not limited to, those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part 1, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M. Stockton Press, New York, 1991; and Carillo et al., SIAM J. Applied Math. 48, 1073 (1988). Preferred methods for determining identity are designed to give the largest match between the sequences tested. Methods of determining identity are described in publicly available computer programs. Preferred computer program methods for determining identity between two sequences include the GCG program package, including GAP (Devereux et al., Nucl. Acid. Res. 12, 387 (1984); Genetics Computer Group, University of Wisconsin, Madison, Wis.), BLASTP, BLASTN, and FASTA (Altschul et al., J. Mol. Biol. 215, 403-410 (1990)). The BLASTX program is publicly available from the National Center for Biotechnology Information (NCBI) and other sources (BLAST Manual, Altschul et al. NCB/NLM/NIH Bethesda, Md. 20894; Altschul et al., supra). The well-known Smith Waterman algorithm may also be used to determine identity.

In one embodiment, tryptophan residue of the peptides can be linked to a C₁-C₃ alkyl group (methyl, ethyl, propyl, isopropyl) for the peptides to resist to oxidation. A tryptophan residue may for example be present when X₅ is in sequence set forth as SEQ ID NO: 1, thus being in position 19 in sequence set forth as SEQ ID NO: 2; in position 20 in sequence set forth as SEQ ID NO: 3 or SEQ ID NO: 20; in position 18 in sequence set forth as SEQ ID NO: 4.

The peptides described herein can be produced synthetically by chemical synthesis or enzymatic synthesis as it is well known in the art. Alternatively, nucleotide sequences encoding the peptides of the invention can be introduced into a protein expression vector and produced in a suitable host organism (e.g., bacteria, insect cells, etc), then purified.

In a preferred embodiment, peptides are obtained by stepwise condensation of amino acids residue, either by condensation of a preformed fragment already containing an amino acid sequence in appropriate order, or by condensation of several fragments previously prepared, while protecting the amino acid functional groups except those
5 involved in peptide bond during condensation. In particular, the peptides can be synthesized according to the method originally described by Merrifield.

An additional polypeptide ("tag") can be added on for the purpose of purifying or identifying or purifying the peptides. Protein tags make it possible, for example, for the peptides to be adsorbed, with high affinity, to a matrix, and for the matrix then to be
10 washed stringently with suitable buffers without the complex being eluted to any significant extent, and for the adsorbed complex subsequently to be eluted selectively. Examples of protein tags which are known to the skilled person are a (His)₆ tag, a Myc tag, a FLAG tag, a hemagglutinin tag, a glutathione transferase (GST) tag, intein having an affinity chitin-binding tag or maltose-binding protein (MBP) tag. These protein tags
15 can be located N- terminally, C -terminally and/or internally.

Advantageously, even when administered in an iterate way, peptides described herein do not induce anti-peptide or anti-GH antibody production, in contrast with immunogenic peptides of the art, which cause antibody production leading to endogenous GH neutralization and thus, to biological activity neutralization.

20 The present invention also relates to a composition comprising or consisting or consisting essentially of at least one peptide comprising SEQ ID NO: 1 (in particular a peptide having a sequence SEQ ID NO: 2-4 or 20) as described hereinabove or a fragment or variant thereof.

The invention also relates to a pharmaceutical composition comprising or consisting or
25 consisting essentially of at least one peptide comprising SEQ ID NO: 1 in particular a peptide having a sequence SEQ ID NO: 2-4 or 20) as described hereinabove or a fragment or variant thereof and at least one pharmaceutically acceptable excipient.

The invention also relates to a medicament comprising or consisting or consisting essentially of at least one peptide comprising SEQ ID NO: 1 as described hereinabove or a fragment or variant thereof.

In one embodiment, the composition, pharmaceutical composition or medicament of the invention is for use for treating osteoarthritis in a subject in need thereof.

As used herein, the term “consisting essentially of”, with reference to a composition, pharmaceutical composition or medicament of the invention, means that the at least one peptide of the invention is the only one therapeutic agent or agent with a biologic activity within said composition, pharmaceutical composition or medicament.

Examples of suitable excipients include, but are not limited to, water, saline, Ringer's solution, dextrose solution, and solutions of ethanol, glucose, sucrose, dextran, mannose, mannitol, sorbitol, polyethylene glycol (PEG), phosphate, acetate, gelatin, collagen, Carbopol®, vegetable oils, and the like. One may additionally include suitable preservatives, stabilizers, antioxidants, antimicrobials, and buffering agents, such as, for example, BHA, BHT, citric acid, ascorbic acid, tetracycline, and the like.

Other examples of pharmaceutically acceptable excipients that may be used in the composition of the invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene- polyoxypropylene- block polymers, polyethylene glycol and wool fat.

In one embodiment, the composition, pharmaceutical composition or medicament of the invention may comprise some excipients, such as, for example, surfactants (e.g. hydroxypropylcellulose); suitable carriers, such as, for example, solvents and dispersion media containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils,

such as, for example, peanut oil and sesame oil; isotonic agents, such as, for example, sugars or sodium chloride; coating agents, such as, for example, lecithin; agents delaying absorption, such as, for example, aluminum monostearate and gelatin; preservatives, such as, for example, benzalkonium chloride, benzethonium chloride, chlorobutanol, thimerosal and the like; buffers, such as, for example, boric acid, sodium and potassium bicarbonate, sodium and potassium borates, sodium and potassium carbonate, sodium acetate, sodium biphosphate and the like; tonicity agents, such as, for example, dextran 40, dextran 70, dextrose, glycerin, potassium chloride, propylene glycol, sodium chloride; antioxidants and stabilizers, such as, for example, sodium bisulfite, sodium metabisulfite, sodium thiosulfite, thiourea and the like; nonionic wetting or clarifying agents, such as, for example, polysorbate 80, polysorbate 20, poloxamer 282 and tyloxapol; viscosity modifying agents, such as, for example dextran 40, dextran 70, gelatin, glycerin, hydroxyethylcellulose, hydroxymethylpropylcellulose, lanolin, methylcellulose, petrolatum, polyethylene glycol, polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose; and the like.

In one embodiment, the composition, pharmaceutical composition or medicament may comprise a pharmaceutically acceptable salt of the peptide of the invention.

Examples of the pharmaceutically acceptable salt include salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, salts with basic or acidic amino acids and the like. Examples of salts with an inorganic base include, but are not limited to, alkali metal salts, such as a sodium salt and a potassium salt; an alkaline earth metal salt such as a calcium salt and a magnesium salt; an aluminum salt; and an ammonium salt. Examples of salts with an organic base include, but are not limited to, salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine and N,N'-dibenzylethylenediamine. Examples of salts with an inorganic acid include, but are not limited to, salts with hydrochloric acid, boric acid, nitric acid, sulfuric acid and phosphoric acid. Examples of salts with an organic acid include, but are not limited to, salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid,

benzenesulfonic acid and p-toluenesulfonic acid. Examples of salts with a basic amino acid include, but are not limited to, salts with arginine, lysine and ornithine. Examples of salts with an acidic amino acid include, but are not limited to, salts with aspartic acid and glutamic acid. The list of suitable salts is disclosed in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., p 1418, 1985, the entire disclosure of which is incorporated herein by reference.

In one embodiment, the amount of peptide of the invention within the composition, pharmaceutical composition or medicament of the invention is a therapeutically effective amount and ranges from about 0.01 to 90 % in volume, preferably from 0.1 % to 10 % in volume, more preferably from 1 % to 5 % in volume to the total volume of the composition, pharmaceutical composition or medicament of the invention. In another embodiment, the therapeutically effective amount ranges from about 10^{-9} M to about 10^{-1} M, preferably from about 10^{-8} M to about 10^{-2} M, and more preferably from about 10^{-7} M to about 10^{-3} M. These amounts are routinely adaptable by the skilled artisan, who is able to choose the best quantity to administer to a patient to achieve recovery.

According to one embodiment, peptides described herein are to be administrated together with at least one viscosupplementation agent. Therefore, in one embodiment, the composition, pharmaceutical composition or medicament of the invention further comprises at least one viscosupplementation agent.

Examples of viscosupplementation agents include, but are not limited to, a glycosaminoglycan, most commonly a non-sulfated glycosaminoglycan including hyaluronic acid, hylan, hyaluronan and related.

In a preferred embodiment, the at least one viscosupplementation agent is hyaluronic acid, preferably non-reticulated hyaluronic acid. In one embodiment, the viscosupplementation agent is hyaluronic acid with a molecular weight ranging from about 100 to about 5000 kDa, preferably from about 400 to about 1000 kDa, preferably non-reticulated hyaluronic acid with a molecular weight ranging from about 100 to about 5000 kDa, preferably from about 400 to about 1000 kDa. In one embodiment, the viscosupplementation agent is hyaluronic acid with a molecular weight ranging from

about 600 to about 1000 kDa, preferably non-reticulated hyaluronic acid with a molecular weight ranging from about 600 to about 1000 kDa.

In another embodiment, the viscosupplementation agent, preferably hyaluronic acid, is present in the composition, pharmaceutical composition or medicament of the invention
5 at a concentration ranging from about 0.1 % to about 10 %, preferably about 0.25 % to about 5 %, preferably about 0.25 % to about 2 %, preferably about 1 % (percentages are in weight to the total volume of the composition, i.e. 1 % corresponds to a concentration of 10 mg/ml).

Indeed, the applicant shows that hyaluronic acid induces a significant stabilization of the
10 chimeric peptide in water solution (see Examples). Raman spectroscopy experiments have indeed shown an unstable structure in water of peptides with sequence set forth as SEQ ID NO: 1, reflected by the presence of four different conformations among which, three are quantitatively equivalent; whereas peptide with sequence set forth as SEQ ID NO: 1 in presence of hyaluronic acid have a stabilized β -hairpin conformation. Without
15 willing to be bound to a theory, the Applicant suggests that this conformation allows somatostatin residues to be exposed for their specific and high-affinity binding to their receptors.

The present invention further relates to the use of peptides described herein, optionally combined with a viscosupplementation agent, for the treatment of osteoarthritis in a
20 subject in need thereof. Indeed, the Applicant demonstrated that the peptides described herein act directly on chondrocytes, allowing them to differentiate, multiply, spread and produce a better quality cartilaginous matrix. These peptides show a long-term efficiency (up to 5 months after injection) on the thickness of the joint as well as the quality of the cartilaginous matrix (see Examples).

25 In one embodiment, the subject is affected, preferably is diagnosed, with osteoarthritis. In a first aspect, the subject is an elderly individual (such as, for example, an individual of more than 30, 40, 50, 60, 70, 80, 90 or more year-old) suffering from osteoarthritis. In a second aspect, the subject is an injured individual suffering from post-traumatic osteoarthritis.

In one embodiment, the subject is affected by grade 0, 1, 2, 3, or 4 osteoarthritis, according to the Kellgren–Lawrence grade (or K-L system). According to this scoring tool, grade 0 corresponds to the absence of radiographic features of osteoarthritis; grade 1 corresponds to possible joint space narrowing and osteophyte formation; grade 2 corresponds to definite osteophyte formation with possible joint space narrowing; grade 3 corresponds to multiple osteophytes, definite joint space narrowing, sclerosis and possible bony deformity; and grade 4 corresponds to large osteophytes, marked joint space narrowing, severe sclerosis and definite bony deformity.

In one embodiment, the subject is affected by grade 0, 1 or 2 osteoarthritis. In another embodiment, the subject is affected by grade 0 or 1 osteoarthritis.

In one embodiment, the peptide, composition, pharmaceutical composition or medicament of the invention is for preventing osteoarthritis, preferably in a subject at risk of developing osteoarthritis.

In another embodiment, the subject is at risk of developing osteoarthritis. Examples of risk factors include, but are not limited to, genetic factors, familial history of osteoarthritis, misalignments of bones caused by congenital or pathogenic causes, trauma, mechanical injury, excess body weight and obesity, loss of strength in the muscles supporting a joint, impairment of peripheral nerves leading to sudden or uncoordinated movements, alkaptonuria, congenital disorders of joints, diabetes, Ehlers-Danlos Syndrome, hemochromatosis and Wilson's disease, injury to joints or ligaments, ligamentous deterioration or instability, Marfan syndrome, joint infection and the like.

In one embodiment, the peptide, composition, pharmaceutical composition or medicament of the invention is for curing osteoarthritis in a subject already affected with osteoarthritis.

In one embodiment, the peptide, composition, pharmaceutical composition or medicament of the invention is for preventing aggravation of osteoarthritis in a subject already affected with osteoarthritis, such as, for example, in a subject with grade 0, 1 or 2 osteoarthritis according to the K-L system.

In one embodiment, the at least one peptide of the invention is, or is to be administrated by intra-articular injection in the joint to be treated.

In one embodiment, the targeted concentration of the peptide of the invention within the joint after administration ranges from about 10^{-9} M to about 10^{-2} M, preferably from about 10^{-8} M to about 10^{-3} M, and more preferably from about 10^{-7} M to about 10^{-3} M. In one embodiment, the targeted concentration of the peptide of the invention within the joint after administration ranges from about 10^{-7} M to about 10^{-4} M. The concentration of therapeutically effective amount of peptide to be administrated to reach such intra-articular concentration depends on the size of the joint and the volume of synovial fluid inside it. These factors vary according to the nature of the joint, the age and the species of the subject to be treated. These parameters are well-known from those skilled in the art, in particular medical practitioners and veterinarians. For example, the volume of synovial fluid within a knee is usually of about 6-7 mL in human, about 500 μ L for rabbit, and about 240 μ L for dog.

Therefore, in one embodiment, for treating osteoarthritis in a human knee, 2 mL of a composition comprising a peptide of the invention (preferably a peptide as set forth as SEQ ID NO: 2 or SEQ ID NO: 3 or SEQ ID NO: 20), and optionally hyaluronic acid, can be injected in the joint. In veterinarian cases, this volume can be adjusted depending on the species.

In one embodiment, the composition, pharmaceutical composition or medicament is administered once, twice, three times or more, such as, for example, 4, 5, 6, 7, 8, 9, or 10 times, or until complete treatment of osteoarthritis.

In one embodiment, when the composition, pharmaceutical composition or medicament is administered several times, the interval between two administrations is of about 1, 2, 3, 4, 5, 6, 7 days, or of about 1, 2, 3, 4 weeks or of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or more.

In one embodiment, the composition, pharmaceutical composition or medicament of the invention is administered three times with a one-week-interval.

In one embodiment, before use, the peptide of the invention is sterilized, preferably by filtration or autoclaving. In another embodiment, before use, the composition of the invention comprising a peptide and a viscosupplementation agent is sterilized, preferably by filtration or autoclaving. In another embodiment, the peptide and the viscosupplementation agents are separately sterilized before mixing and use.

In one embodiment, peptides described herein are contained in a pharmaceutical unit dosage form. Preferably, this dosage unit is a single use pre-filled, pre-dosed syringe, for local injection in the joint to be treated. The present invention thus further relates to a unit dosage form (such as, for example, a pre-filled syringe) comprising a peptide of the invention, and optionally a viscosupplementation agent, such as, for example, hyaluronic acid. In one embodiment, the pharmaceutical unit dosage form is sterilized, preferably by filtration.

The concentration of peptide in the pharmaceutical unit dosage form depends on the size of the joint and the volume of synovial fluid inside it. These factors vary according to the nature of the joint, the age and the species of the subject to be treated.

In one embodiment, the pharmaceutical unit dosage form contains 2 mL of a composition, pharmaceutical composition or medicament comprising a peptide of the invention at a concentration suitable for administration of the peptide with a final concentration in the joint ranging from about 10^{-7} M to about 10^{-3} M or from about 10^{-7} M to about 10^{-4} M, and optionally a viscosupplementation agent, preferably hyaluronic acid.

The present invention further relates to a kit of part comprising a first pharmaceutical unit dosage form comprising a peptide of the invention, and a second pharmaceutical unit dosage form comprising a viscosupplementation agent.

In one embodiment, both dosage units of the kit of part are a single use pre-filled, pre-dosed syringe.

In another embodiment, in the kit of part, the pharmaceutical unit dosage form comprising the viscosupplementaion agent is a single use pre-filled, pre-dosed syringe, wherein the viscosupplementation agent is preferably sterilized by autoclaving, and the

pharmaceutical unit dosage form comprising the peptide of the invention is a vial, wherein preferably the peptide is sterilized by filtration.

The present invention further relates to a method for treating osteoarthritis in a subject in need thereof, wherein said method comprises administering a peptide of the present invention to the subject, and optionally a viscosupplementation agent (preferably hyaluronic acid). Preferably, a therapeutically effective amount of the peptide of the invention is administered to the subject.

Indeed, peptides described herein act directly on chondrocytes in the joint. As shown in the Examples, *in vivo* data obtained from Guinea Pig show a long term (5 months) efficiency on the thickness of the joint as well as the quality of the cartilaginous matrix. Moreover, *in vivo* data obtained from rabbit show a short term efficiency for reducing osteoarthritis lesions severity and size.

The present invention thus further relates to a method to differentiate chondrocytes and/or to multiply chondrocytes and/or to spread chondrocytes and/or to produce cartilaginous matrix, wherein said method comprises administering a peptide of the invention, and optionally a viscosupplementation agent (preferably hyaluronic acid).

The present invention further relates to a method for slowing-down or preventing cartilage degradation in a subject, wherein said method comprises administering a peptide of the present invention to the subject, and optionally a viscosupplementation agent (preferably hyaluronic acid). In one embodiment, said subject is affected with osteoarthritis, preferably with grade 0, 1 or 2 osteoarthritis.

The present invention further relates to a method for maintaining or increasing cartilage thickness in a subject, wherein said method comprises administering a peptide of the present invention to the subject, and optionally a viscosupplementation agent (preferably hyaluronic acid). In one embodiment, said subject is affected with osteoarthritis, preferably with grade 0, 1 or 2 osteoarthritis.

The present invention further relates to a method for decreasing the severity or size of osteoarthritis lesions, or for preventing an increase in severity or size of osteoarthritis

lesions in a subject, wherein said method comprises administering a peptide of the present invention to the subject, and optionally a viscosupplementation agent (preferably hyaluronic acid).

5 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a combination of graphs showing *in vivo* efficiency tests carried out in Guinea Pig for hyaluronic acid versus peptide with sequence set forth as SEQ ID NO: 4 (“peptide”). (A) the histogram illustrates the sum of the scores representing the degradation of several structures in the joint, in particular the presence of osteophytes, the degradation of matrix proteoglycans, the degradation of the synovial membrane, the presence of abnormal cells, etc. It shows a significantly decreased degradation of cartilage structure in presence of peptide with sequence set forth as SEQ ID NO: 4 as compared to both control and hyaluronic acid alone. (B) the histogram shows an increased cartilage thickness in presence of both hyaluronic acid or peptide with sequence set forth as SEQ ID NO: 4. * $p < 0.05$. (C) the histogram shows a decreased osteophytes scoring. ** $p < 0.001$.

Figure 2 is a Raman spectra showing the stabilization of peptide with sequence set forth as SEQ ID NO: 4 (“peptide”) in presence of hyaluronic acid. Peptides described herein differ from endogenous somatostatin or from peptides known in the art and exhibit a β -hairpin molecular conformation which stability depends of physiological medium and hydrophobic medium used. This figure illustrates the Raman data obtained for peptide with sequence set forth as SEQ ID NO: 4 alone, hyaluronic acid alone and a mix of peptide with sequence set forth as SEQ ID NO: 4 and hyaluronic acid. Peptide with sequence set forth as SEQ ID NO: 4 has an unstable structure in water, reflected by the presence of four different conformations among which, three are quantitatively equivalent; whereas peptide with sequence set forth as SEQ ID NO: 4 together with hyaluronic acid has a stabilized β -hairpin conformation. This conformation may allow somatostatin residues to be exposed for their specific and high-affinity binding to their receptors.

Figure 3 is a graph showing *in vivo* efficiency tests carried out in rabbits for hyaluronic acid (“HA”) versus peptide with sequence set forth as SEQ ID NO: 4 combined with HA (“peptide + HA”). (A) the histogram illustrates the sum of the global macroscopic score grade representing the lesion severity on macroscopic aspect for the low score subpopulation (animals with the less severe lesions). It shows a significant decrease of the score grade in presence of the peptide with sequence set forth as SEQ ID NO: 4 combined with HA as compared to both control and hyaluronic acid (HA) alone. (B) the histogram shows a decrease of the sum of the global macroscopic score size in presence of the peptide with sequence set forth as SEQ ID NO: 4. ** = p -value < 0.01.

10

EXAMPLES

The present invention is further illustrated by the following examples.

Example 1: In vivo effect of the peptide of the invention

Sample Preparation

15 Peptide of the invention (corresponding to SEQ ID NO: 4) was dissolved at 2.5 mg/ml in water for injection (CDM Lavoisier) to make a stock solution conserved at -20°C. The syringe was prepared by aspiration of 50 µl of peptide work solution prepared just before use at 10^{-7} M (other concentrations are tested) in NaCl 0.9 % and kept on ice until use.

Animal IA injection

20 The study was performed on male Duncan-Hartley guinea pigs (Harlan), whose particularity is to be affected with age of spontaneous and progressive degeneration of the knee that closely resembles knee osteoarthritis (OA) in humans. Seven 5-month-old animals (weighing 879 g. +/- 58.1) were injected per group. Animals were treated in accordance with institutional animal care guidelines. Animals were anesthetized with an
25 anesthesia module (Minerva) with a rapid induction device (4 % isoflurane) and anesthesia was maintained using a specific device mask in guinea coaxial (2.5 % isoflurane). 50 µl of the peptide of the invention or control - salt solution or Hyalgan®

(10 mg/ml solution of MW 500-730 kDa hyaluronic - Laboratoire Expanscience, available in the market) - were injected on each hind legs of the animal into the joint space from the lateral side using a 29 G needle. This was followed by passive knee joint movements to facilitate the intra-articular distribution of the solution.

5 *Histological analysis*

Five month after injection, the two knee joints from each animal were fixed for 36 to 48 hours in 10 % buffered formalin then kept in 70 % ethanol and followed by decalcification in 15 % EDTA in phosphate buffer. Paraffin sections (3-4 µm) of the central region of the joint were stained with haematoxylin and eosin for histological analyses of cartilage structure, namely: loss of cartilage matrix, cellular abnormalities, appearance of articular cartilage mineralization front, formation of osteophytes and synovial membrane (microscopy: Nikon 80i). A semi-quantitative modified Mankin histological grading system was used to evaluate OA severity (Kraus et al., The OARSI histopathology initiative recommendations for histological assessments of osteoarthritis in the Guinea Pig. *Osteoarthritis Cartilage*, 2010 (18 S3) S35-S52). The articular cartilage area was analyzed quantitatively by immunohistochemistry (Pastoureau et al., *Cartilage, bone and synovial histomorphometry in animal models of osteoarthritis. Osteoarthritis Cartilage*. 2010 Oct; 18 Suppl 3:S106-12). Sections of guinea pig knees were stained with monoclonal antibody (monoclonal anti-chicken mouse collagen II, 6B3 clone - reference MAB887 / 250, Millipore). The measurement of the total area of articular cartilage was performed with Color deconvolution H DAB and Siox and the measurement of joint height by ImageJ ("Fit Ellipse" module). Statistical analyzes of scoring and quantification results were performed using a Kruskal-Wallis test followed by Dunn's test using PRISM software.

25 *Results*

Various histomorphometric parameters are then introduced, all of them expressing the OA pathology at the cartilage, bone and synovium levels. The greatest severity of both cartilage structural damage and loss of proteoglycan was evident for the medial tibial surface of the knee.

Results are shown in **Figure 1**.

Comparing “sham” and “HA” groups, there were no significant differences in cartilage structure scoring as well proteoglycan and type II Collagen content, although the thickness of cartilage is highest for HA group.

- 5 Comparing the “peptide” group to “sham” and “HA”, it was found in animals injected with the peptide of the invention a lowest severity of both cartilage structural damage and proteoglycan loss onto the medial tibial surface of the knee, as well as a decreased osteophytes scoring. Finally, the total scoring of degradation parameters are lowest for knee articulation of animals injected with the peptide of the invention. Moreover, in the
- 10 guinea pigs administered with the peptide of the invention, there is a more sustained staining which highlights greater synthesis of type II collagen and an increase in the thickness of the cartilage. In resume, animals injected with a peptide of the invention have a highest thickness and a better cartilage quality than sham and HA injected animals.

Example 2: Stability of the peptide of the invention

15 ***Sample Preparation***

Peptide alone, at a concentration of 0.9 mM (2.5 mg/ml), was dissolved in a Millipore filter treated water. Peptide + HA solution consists of peptide dissolved at 0.9 mM in a solution of HA (1.8 MDa) at 1 % (10 mg/ml) in water.

Raman Scattering Measurements

- 20 Samples were placed in a suprasil quartz cell (5 mm path length) and excited by the 488 nm line of an Ar⁺ laser (Spectra Physics, CA, USA) with a ~200 mW power at the sample. Scattered light at right angle was analyzed on a Jobin-Yvon T64000 (HORIBA Jobin-Yvon, France) in a single spectrograph configuration with a 1200 grooves per mm holographic grating and a holographic notch filter. Stokes Raman data were collected by
- 25 means of a liquid nitrogen cooled CCD detection system (Spectrum One, Jobin- Yvon, France). The effective spectral slit width was set to ~5 cm⁻¹. Each recorded spectrum corresponds to a total acquisition time of 1200 s. Buffer subtraction and smoothing of the

observed Raman spectra could be performed using the GRAMS/AI package (Thermoage Galactic, MA, USA). The final presentation of these spectra was performed by means of SigmaPlot package (Systat Software Inc., CA, USA).

Results

5 Results are shown in **Figure 2**.

Figure 2A shows a Raman spectra, obtained from the aqueous solution of a mix with peptide and hyaluronic acid (HA). Peptide spectra are distinct of HA spectra. The beta-marker Raman band at 1669 cm^{-1} is the major component observed in this region and assigned to H-bonded beta-strands of peptide.

10 **Figure 2A1** shows a focus on the spectral region 1646 cm^{-1} of the Raman spectra recorded at 0.9 mM peptide – 1 % HA in water. It is observed the secondary peptide conformation belonging to the antiparallel beta sheet structure of the peptide.

Figure 2B1 shows a decomposition of the Raman spectra of peptide alone observed in the spectral region between 1686 and 1645. Several (4) secondary conformations of peptide belonging to beta-form structures can be evidenced by band decomposition : beta-strand residues implying the presence of inter-strand hydrogen bonds (marker at ca. 1660 cm^{-1}) and antiparallel beta sheet (a doublet in the frequency intervals at ca. 1686-1674 cm^{-1} and one at ca. 1645 cm^{-1}).

15 **Figure 2B2** shows a schematic result of Raman spectra of somatostatin in phosphate buffer. The existence of the beta-marker Raman band at 1668 cm^{-1} as the unique component observed in this region and assigned to H-bonded beta-strand.

20 Therefore, unlike the conformations adopted by the peptide alone in water (4 major bands), peptide HA kept a single secondary conformation as the beta sheet conformation of typical somatostatin.

Example 3: Effect of the peptide of the invention on the osteoarticular cartilage quality and quantity

Sample Preparation

Peptide of the invention (corresponding to SEQ ID NO: 4) was dissolved at 74.6 µg/ml
5 in a solution of NaCl 0.9 % containing 1 % (10 mg/ml) of hyaluronic acid.

Animal IA injection

The study was performed on males New-Zealand rabbits. Osteoarthritis is induced through the surgical transection of the anterior cruciate ligament of the right knee joint (this animal model, named ACLT model, is a well validated model of traumatic
10 osteoarthritis). Ten 28-weeks old animals were injected per group. Rabbits were transected by ACLT of the right knee joint. 300 µl of the mix peptide of the invention/HA (“Peptide + HA group”, corresponding to a peptide concentration within the joint after injection of about 10^{-5} M) or saline solution (“Control” group) or a commercially available hyaluronic acid having a molecular weight of 600 kDa (HA600, “HA” group) were
15 administered through intra-articular injection into the right knee after total recovery from ACLT surgery (i.e. 14 days), repeated 3 times one week apart. Animals were euthanized 8 weeks after ACLT surgery.

Macroscopic evaluation of articular structure

A macroscopic evaluation was performed on the four compartments of the joint: medial
20 and lateral femoral condyles and medial and lateral tibial plateaus. Each lesion was evaluated for its grade (severity, score ranging from 0 to 4) and its size (score ranging from 0 to 7). The global macroscopic score corresponds to the sum of the score obtained for all the lesions in all compartments of the joint. The score can be considered as size x grade or size and grade separately. The four compartments are considered independent
25 for the purpose of statistical analysis.

Results

The global macroscopic score (size x grade) in the whole population and in the low subpopulation (with the less severe lesions) of each group was analyzed. In the whole population, the administration of the combination of the peptide of the invention with
5 hyaluronic acid leads to a decrease of the severity of the lesions as well as of the size of the lesion, whereas HA alone did not show any effect.

In the low subpopulation of rabbit, there was no significant differences in the global macroscopic scores grade and size in “Control” and “HA” groups. However, comparing the “peptide + HA” group to “control” and “HA” groups, it was found in animals injected
10 with the peptide of the invention combined with HA a significant decrease of the global macroscopic score grade (**Figure 3A**). Moreover, in rabbits administered with the peptide of the invention combined with HA, it was also found a slight decrease of the global macroscopic score size, close to zero for some animals (**Figure 3B**).

These results thus demonstrate the therapeutic potential of the combination of a peptide
15 of the invention and hyaluronic acid in a model of traumatic osteoarthritis.

Example 4: Effect of the combination of peptides of the invention and hyaluronic acid on chondrogenesis

Material and methods

Normal human articular chondrocytes from knee (NHAC-kn) were seeded into a culture
20 chamber (8 wells) at 0.22×10^6 cells per well. NHAC-kn cells were expanded using the Chondrocyte Growth Medium containing fetal bovine serum 5 %, gentamicin/amphotericin-B 0.1 %, human recombinant Fibroblast Growth Factor-beta 0.5 %, R3-Insulin-like Growth Factor-1 0.2 %, insulin 0.2 %, transferrin 0.1 % in the presence of peptides of the invention with or without hyaluronic acid (HA) at a
25 concentration of 10 μ M. Medium was changed every 2 days. After 4 days of incubation, cells were fixed with formaldehyde and stained with alcian blue.

Results

The alcian blue staining revealed an increase of cell clusters for cells treated with the tested peptides alone indicating a stimulation of the chondrogenesis. The addition of hyaluronic acid induces a slight increase in cell proliferation, but no cluster formation.

- 5 The addition of hyaluronic acid (HA) in combination with the peptide as set forth in SEQ ID NO: 2 induced more proliferation with a later effect on cluster formation than the peptide alone. Thus, the addition of hyaluronic acid in combination with the peptide allowed a better proliferation of cells and a better long term effect than the peptides tested alone.

CLAIMS

1. A peptide comprising an amino acids sequence SEQ ID NO: 1, or a fragment or variant thereof, wherein SEQ ID NO: 1 is the following:

5 **X₁-Tyr-X₂-Leu-X₃-Ala-Gly-X₄-Lys-Asn-Phe-Phe-X₅ (SEQ ID NO: 1)**

wherein:

- X₁ is vacant or is valine or a sequence selected from:

Z₁-Val

Asp-Z₁-Val

10 Ser-Asp-Z₁-Val (SEQ ID NO: 5)

Z₂-Ser-Asp-Z₁-Val (SEQ ID NO: 6) and

Gly-Z₂-Ser-Asp-Z₁-Val (SEQ ID NO: 7)

wherein Z₁ is arginine and Z₂ threonine, or Z₁ is Ser-Asp or Ser-Asn and Z₂ is alanine;

15 - X₂ is a sequence selected from Glu-Lys, Glu-Ser and Asp-Leu;

- X₃ is vacant or is lysine or a sequence selected from:

Lys-Asp

Lys-Asp-Leu

Lys-Asp-Leu-Glu (SEQ ID NO: 8)

20 Lys-Asp-Leu-Glu-Glu (SEQ ID NO: 9)

Lys-Asp-Leu-Glu-Glu-Gly (SEQ ID NO: 10)

Lys-Asp-Leu-Glu-Glu-Gly-Ile (SEQ ID NO: 11)

Lys-Asp-Leu-Glu-Glu-Gly-Ile-Gln (SEQ ID NO: 12)

Lys-Asp-Leu-Glu-Glu-Gly-Ile-Gln-Z₃ (SEQ ID NO: 13) and

25 Lys-Asp-Leu-Glu-Glu-Gly-Ile-Gln-Z₃-Leu (SEQ ID NO: 14)

wherein Z₃ is alanine or threonine;

- X₄ is an amino acid residue selected from cysteine, serine, tyrosine, phenylalanine, aspartic acid, glutamic acid, alanine and glycine; and
- X₅ is vacant or is a tryptophan residue or a sequence selected from:

30 Trp-Lys

Trp-Lys-Thr

Trp-Lys-Thr-Phe (SEQ ID NO: 15)

Trp-Lys-Thr-Phe-Thr (SEQ ID NO: 16)

Trp-Lys-Thr-Phe-Thr-Ser (SEQ ID NO: 17)

5 Trp-Lys-Thr-Phe-Thr-Ser-X₆ (SEQ ID NO: 18) and

Trp-Lys-Thr-Phe-Thr-Ser-X₆-Lys-Gln-Ala (SEQ ID NO: 19)

wherein X₆ is an amino acid residue selected from cysteine, serine, tyrosine, phenylalanine, aspartic acid, glutamic acid, alanine and glycine;

for use in the treatment of osteoarthritis in a subject.

10 2. The peptide for use according to claim 1, wherein the peptide consists in an amino acid sequence ranging from 11 to 50 amino acids residues, preferably ranging from 20 and 30 amino acid residues.

3. The peptide for use according to any one of claims 1-2, wherein:

- X₁ is Gly-Z₂-Ser-Asp-Z₁-Val; and

15 - X₅ is Trp-Lys-Thr-Phe-Thr-Ser-X₆.

4. The peptide for use according to any one of claims 1-3, wherein the peptide comprises a sequence SEQ ID NO: 2, 3 4 or 20:

- Gly-Ala-Ser-Asp-Ser-Asp-Val-Tyr-Asp-Leu-Leu-Ala-Gly-Ser-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Ser (SEQ ID NO: 2)

20 - Gly-Ala-Ser-Asp-Ser-Asp-Val-Tyr-Asp-Leu-Leu-Lys-Ala-Gly-Ser-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Ser (SEQ ID NO: 3)

- Gly-Thr-Ser-Asp-Arg-Val-Tyr-Glu-Lys-Leu-Ala-Gly-Ser-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Ser (SEQ ID NO: 4)

25 - Gly-Ala-Ser-Asp-Ser-Asn-Val-Tyr-Asp-Leu-Leu-Lys-Ala-Gly-Ser-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Ser (SEQ ID NO: 20).

5. The peptide for use according to any one of claims 1-4, wherein said peptide is to be administrated by intra-articular injection in the joint to be treated.

6. The peptide for use according to any one of claims **1-5**, wherein said peptide is to be administrated at a final concentration in the joint ranging from 10^{-3} M to 10^{-7} M.
7. A pharmaceutical composition containing at least one peptide for use according to any one of claims **1-6** and one or more pharmaceutically acceptable excipient.
- 5 8. A medicament containing at least one peptide for use according to any one of claims **1-6**.
9. A pharmaceutical unit dosage form containing at least one peptide for use according to any one of claims **1-6**.
- 10 10. The pharmaceutical unit dosage form for use according to claim **9**, wherein the unit dosage form is a single use pre-filled, pre-dosed syringe, for local injection in the joint to be treated.
11. A pharmaceutical composition according to claim **7**, a medicament according to claim **8**, or a pharmaceutical unit dosage form according to any one of claims **9-10** further containing at least one viscosupplementation agent.
- 15 12. The pharmaceutical composition, medicament or pharmaceutical unit dosage form according to claim **11**, wherein the at least one viscosupplementation agent is hyaluronic acid, preferably wherein hyaluronic acid is at a concentration ranging from 0.1 % to 10 %.

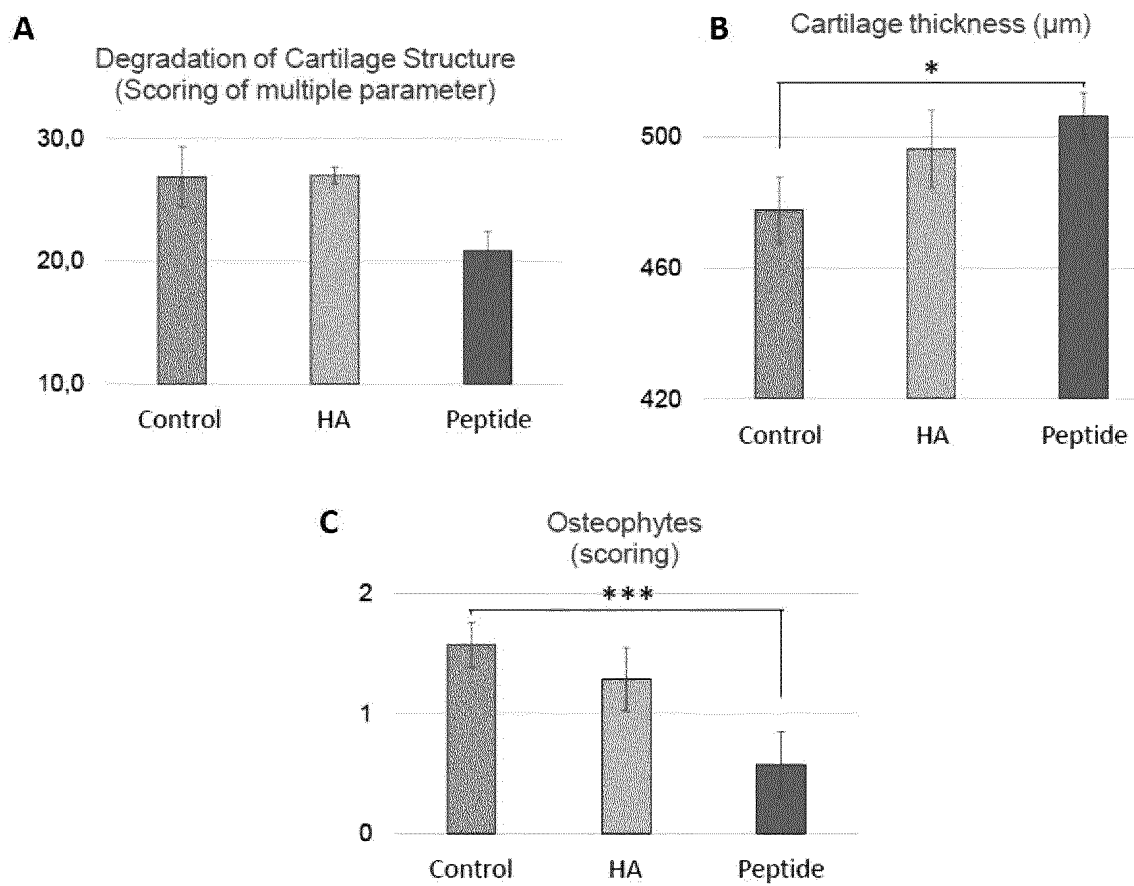


FIG. 1

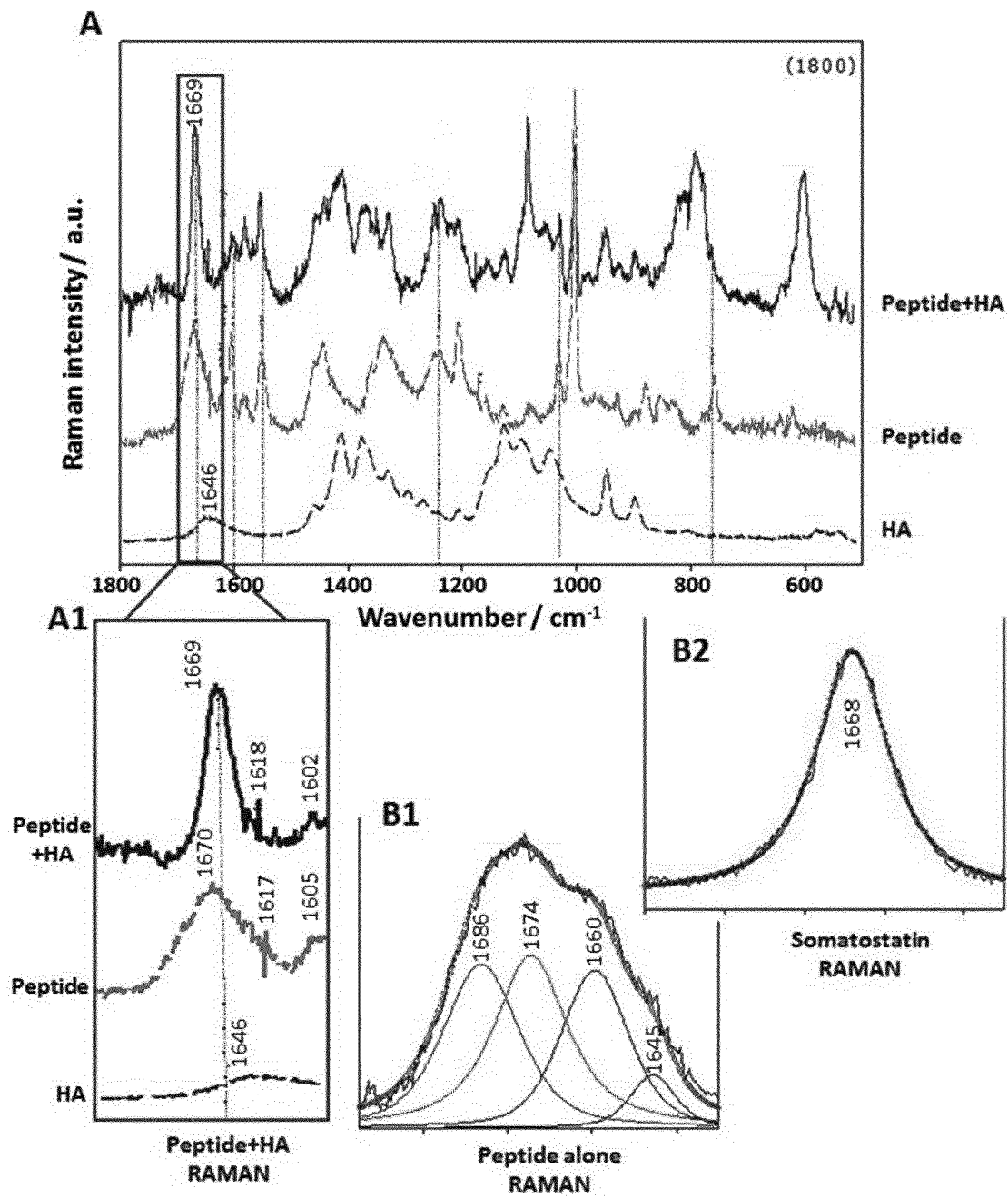


FIG. 2

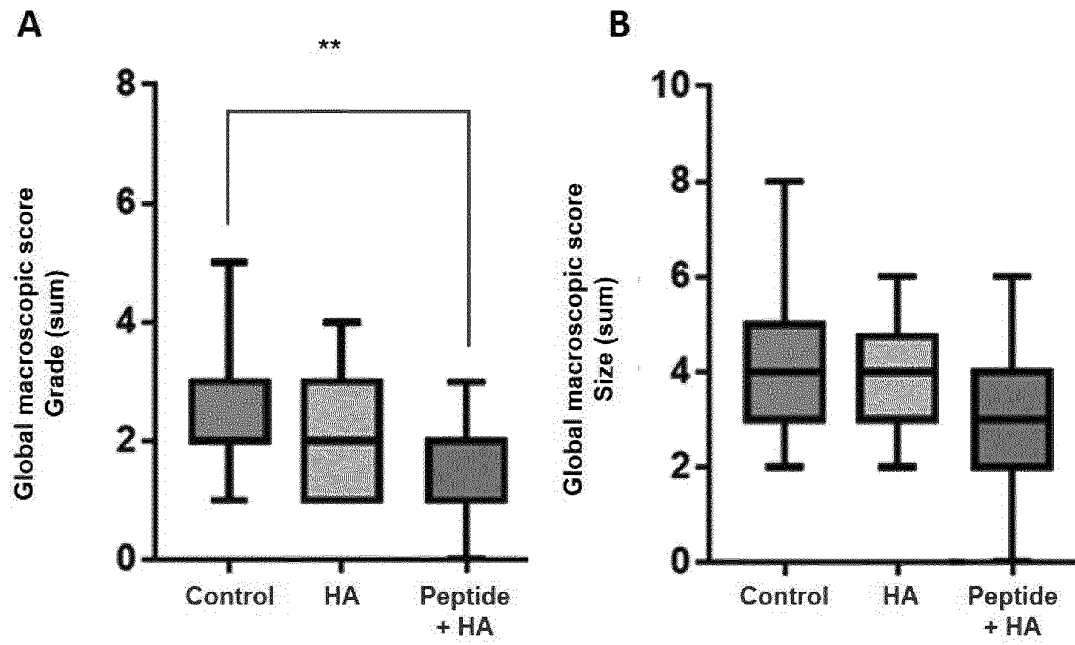


FIG. 3

SEQUENCE LISTING

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 CARELLI Claude
 VÊTU Christelle
 PAOLINI Raffaello

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