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(54) Title: HEPARIN COFACTOR II FRAGMENTS WITH ANTI-INFLAMMATORY AND ANTI-COAGULANT ACTIVITY

(57) Abstract: The present invention provides polypeptides comprising or consisting of an amino acid sequence derived from a naturally occurring protein which modulates blood coagulation, or a fragment, variant, fusion or derivative thereof, or a fusion of said fragment, variant or derivative thereof, for use in the treatment or prevention of inflammation and/or excessive coagulation of the blood. Related aspects of the invention provide isolated polypeptides comprising or consisting of an amino acid sequence of SEQ ID NOS: 1 to 3, or a fragment, variant, fusion or derivative thereof, or a fusion of said fragment, variant or derivative thereof, which exhibit an anti- inflammatory activity, together with isolated nucleic acid molecules, vectors and host cells for making the same. Additionally provided are pharmaceutical compositions comprising a polypeptide of the invention, as well as methods of use of the same in the treatment and/or prevention of inflammation and/or excessive coagulation.

AMENDED CLAIMS

received by the International Bureau on 11 April 2011 (11.04.2011)

1. A polypeptide comprising or consisting of an amino acid sequence derived from heparin cofactor II, or a fragment, variant or derivative thereof,

   for use in the treatment or prevention of inflammation and/or excessive coagulation of the blood

   wherein the fragment, variant or derivative exhibits an anti-inflammatory and/or anticoagulant activity

   wherein the polypeptide is between 15 and 100 amino acids in length.

2. A polypeptide according to Claim 1 wherein the polypeptide is not a naturally occurring protein.

3. A polypeptide according to Claim 1 or 2 wherein the heparin cofactor II is human heparin cofactor II

4. A polypeptide according to Claim 3 wherein the heparin cofactor II is Swiss Port Accession No. P05546.

5. A polypeptide according to any one of the preceding claims comprising or consisting of the amino acid sequence of any one of SEQ ID NOS:1 to 3:

"*KYE28*":	KYEITTIHNLFRKLTHRLFRRNFGYTLR	**[SEQ ID NO:1]**
"*KYE21*":	KYEITTIHNLFRKLTHRLFRR	**[SEQ ID NO:2]**
"*NLF20*":	NLFRKLTHRLFRRNFGYTLR	**[SEQ ID NO:3]**

   or a fragment, variant or derivative thereof, which retains an anti-inflammatory activity of any one of SEQ ID NOS:1 to 3.

6. A polypeptide according to Claim 5 comprising or consisting of the amino acid sequence of any one of SEQ ID NOS:1 to 3.

7. A polypeptide according to any one of the preceding claims wherein the polypeptide, or fragment, variant or derivative thereof, comprises or consists of L-amino acids.

8. A polypeptide according to any one of the preceding claims wherein the polypeptide, or fragment, variant or derivative thereof, comprises one or more amino acids that are modified or derivatised.

9. A polypeptide according to Claim 8 wherein the one or more amino acids are modified or derivatised by PEGylation, amidation, esterification, acylation, acetylation and/or alkylation.

10. A polypeptide according to any one of the preceding claims wherein the polypeptide comprises or consists of a fragment of the amino acid sequence of SEQ ID NO: 3.

11. A polypeptide according to Claim 10 wherein the fragment comprises or consists of at least 5 contiguous amino acids of SEQ ID NO: 3, for example at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26 or 27 contiguous amino acids.

12. A polypeptide according to any one of the preceding claims wherein the polypeptide comprises or consists of a variant of the amino acid sequence of any one of SEQ ID NOs: 1 to 3.

13. A polypeptide according to Claim 12 wherein the variant has at least 50% identity with the amino acid sequence amino acid sequence of any one of SEQ ID NOS: 1 to 3, for example at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or at least 99% identity.

14. A polypeptide according to any one of the preceding claims wherein the polypeptide is between 15 and 50amino acids in length, for example between 15 and 30, 17 and 30, or 17 and 28 amino acids in length.

15. A polypeptide according to Claim 14 wherein the polypeptide is at least 20 amino acids in length.

16. A polypeptide according to any one of the preceding claims wherein the polypeptide is linear.

17. A polypeptide according to any one of the preceding claims wherein the polypeptide is a recombinant polypeptide.

18. A polypeptide according to any one of the preceding claims wherein the polypeptide is capable of inhibiting the release of one or more pro-inflammatory cytokines from human monocyte-derived macrophages.

19. A polypeptide according to Claim 18 wherein the pro-inflammatory cytokines are selected from the group consisting of macrophage inhibitory factor, TNF-alpha, HMGB1, C5a, IL-17, IL-8, MCP-1, IFN-gamma, Il-6, IL-1b, IL-12.

20. A polypeptide according to any one of the preceding claims wherein the polypeptide is capable of blocking platelet activation.

21. A polypeptide according to any one of the preceding claims wherein the polypeptide is capable of interfering with Toll-like receptor (TLR)-signalling in leukocytes, epithelial cells (including keratinocytes) and/or mesenchymal cells (including fibroblasts).

22. A polypeptide according to any one of the preceding claims wherein the polypeptide exhibits anti-inflammatory activity in one or more of the following models:

(a) *in vitro* macrophage models using LPS, LTA, zymosan, flagellin, dust mites, viral or bacterial DNA or RNA, or peptidoglycan as stimulants; and/or

(b) *in vivo* mouse models of endotoxin shock;

(c) *in vivo* infection models, either in combination with antimicrobial therapy, or given alone.

23. A polypeptide according to any one of the preceding claims wherein the polypeptide exhibits anticoagulant activity.

24. A polypeptide according to Claim 23 for use in the concomitant treatment or prevention of inflammation and coagulation.

25. A polypeptide according to any one of the preceding claims wherein the polypeptide exhibits Toll-like receptor (TLR) blocking activity.

26. A polypeptide according to any one of the preceding claims for use in the treatment or prevention of inflammation associated with an infection.

27. A polypeptide according to any one of the preceding claims for use in the treatment or prevention of a disease, condition or indication selected from the following:

i) Acute systemic inflammatory disease, with or without an infective component, such as systemic inflammatory response syndrome (SIRS), ARDS, sepsis, severe sepsis, and septic shock. Other generalized or localized invasive infective and inflammatory disease, including erysipelas, meningitis, arthritis, toxic shock syndrome, diverticulitis, appendicitis, pancreatitis, cholecystitis, colitis, cellulitis, burn wound infections, pneumonia, urinary tract infections, postoperative infections, and peritonitis.

ii) Chronic inflammatory and or infective diseases, including cystic fibrosis, COPD and other pulmonary diseases, gastrointestinal disease including chronic skin and stomach ulcerations, other epithelial inflammatory and or infective disease such as atopic dermatitis, oral ulcerations (aphtous ulcers), genital ulcerations and inflammatory changes, parodontitis, eye inflammations including conjunctivitis and keratitis, external otitis, mediaotitis, genitourinary inflammations.

iii) Postoperative inflammation. Inflammatory and coagulative disorders including thrombosis, DIC, postoperative coagulation disorders, and coagulative disorders related to contact with foreign material, including extracorporeal circulation, and use of biomaterials. Furthermore,

vasculitis related inflammatory disease, as well as allergy, including allergic rhinitis and asthma.

iv) Excessive contact activation and/or coagulation in relation to, but not limited to, stroke.

v) Excessive inflammation in combination with antimicrobial treatment. The antimicrobial agents used may be administred by various routes; intravenous (iv), intraarterial, intravitreal, subcutaneous (sc), intramuscular (im), intraperitoneal (ip), intravesical, intratechal, epidural, enteral (including oral, rectal, gastric, and other enteral routes), or topically, (including dermal, nasal application, application in the eye or ear, eg by drops, and pulmonary inhalation). Examples of agents are penicillins, cephalosporins, carbacephems, cephamycins, carbapenems, monobactams, aminoglycosides, glycopeptides, quinolones, tetracyclines, macrolides, and fluoroquinolones. Antiseptic agents include iodine, silver, copper, clorhexidine, polyhexanide and other biguanides, chitosan, acetic acid, and hydrogen peroxide.

28. A polypeptide according to any one of the preceding claims for use in the treatment or prevention of acute inflammation, sepsis, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), cystic fibrosis, asthma, allergic and other types of rhinitis, cutaneous and systemic vasculitis, thrombosis and disseminated intravascular coagulation (DIC).

29. A polypeptide according to Claim 28 for use in the treatment or prevention of sepsis.

30. A polypeptide according to Claim 28 for use in the treatment or prevention of chronic obstructive pulmonary disease (COPD).

31. A polypeptide according to any one of the preceding claims for use in combination with one or more additional therapeutic agent.

32. A polypeptide according to Claim 31 wherein the additional therapeutic agent is selected from the group consisting of antibiotic agents, anti-fungal agents,

antiseptic agents, anti-inflammatory agents, immunosuppressive agents, vasoactive agents, receptor blockers, receptor agonists and antiseptic agents.

33. A polypeptide according to Claim 32 wherein the antibiotic agents are selected from the groups consisting of anti-bacterial agents, anti-fungicides, anti-viral agents and anti-parasitic agents.

34. An isolated polypeptide comprising or consisting of an amino acid sequence derived from heparin cofactor II, or a fragment, variant or derivative thereof, which polypeptide exhibits an anti-inflammatory and/or anti-microbial and/or anti-coagulant activity,

wherein the polypeptide is between 15 and 100 amino acids in length

with the proviso that the polypeptide is not a naturally occurring protein.

35. A polypeptide according to Claim 34 wherein the heparin cofactor II is a human heparin cofactor II.

36. A polypeptide according to any one of Claims 34 to 35 wherein the heparin cofactor II (HCII) corresponds to Swiss-Prot Accession No. P05546.

37. A polypeptide according to any one of Claims 34 to 36 comprising or consisting of the amino acid sequence of any one of SEQ ID NOS:1 to 3:

"*KYE28*":	KYEITTIHNLFRKLTHRLFRRNFGYTLR	**[SEQ ID NO:1]**
"*KYE21*":	KYEITTIHNLFRKLTHRLFRR	**[SEQ ID NO:2]**
"*NLF20*":	NLFRKLTHRLFRRNFGYTLR	**[SEQ ID NO:3]**

or a fragment, variant, or derivative thereof, which retains an anti-inflammatory and/or anti-microbial and/or anti-coagulant activity of any one of SEQ ID NOS:1 to 3.

38. A polypeptide according to Claim 37 comprising or consisting of the amino acid sequence of any one of SEQ ID NOS:1 to 3.

39. A polypeptide according to any one of Claims 34 to 38 wherein the polypeptide, or fragment, variant or derivative thereof, comprises or consists of L-amino acids.

40. A polypeptide according to any one of Claims 34 to 39 wherein the polypeptide, or fragment, variant or derivative thereof, comprises one or more amino acids are modified or derivatised.

41. A polypeptide according to Claim 40 wherein the one or more amino acids are modified or derivatised by PEGylation, amidation, esterification, acylation, acetylation and/or alkylation.

42. A polypeptide according to any one of Claims 34 to 41 wherein the polypeptide is between 15 and 50, 15 and 30, 17 and 30, or 17 and 28 amino acids in length.

43. A polypeptide according to Claim 42 wherein the polypeptide is at least 20 amino acids in length.

44. A polypeptide according to any one of Claims 34 to 43 wherein the polypeptide is linear.

45. A polypeptide according to any one of Claims 34 to 44 wherein the polypeptide is a recombinant polypeptide.

46. A polypeptide according to any one of Claims 30 to 42 wherein the polypeptide is capable of inhibiting the release of one or more pro-inflammatory cytokines from human monocyte-derived macrophages.

47. A polypeptide according to Claim 46 wherein the pro-inflammatory cytokines are selected from the group consisting of macrophage inhibitory factor, TNF-alpha, HMGB1, C5a, IL-17, IL-8, MCP-1, IFN-gamma, Il-6, IL-1b, IL-12.

48. A polypeptide according to any one of Claims 34 to 47 wherein the polypeptide is capable of blocking platelet activation.

49. A polypeptide according to any one of Claims 34 to 48 wherein the polypeptide is capable of interfering with Toll-like receptor (TLR)-signalling in leukocytes, epithelial cells (including keratinocytes) and/or mesenchymal cells (including fibroblasts).

50. A polypeptide according to any one of Claims 30 to 46 wherein the polypeptide exhibits anti-inflammatory activity in one or more of the following models:

(a) *in vitro* macrophage models using LPS, LTA, zymosan, flagellin, dust mites, viral or bacterial DNA or RNA, or peptidoglycan as stimulants;

(b) *in vivo* mouse models of endotoxin shock; and/or

(c) *in vivo* infection models, either in combination with antimicrobial therapy, or given alone.

51. A polypeptide according to any one of Claims 34 to 50 wherein the polypeptide exhibits anticoagulant activity.

52. A polypeptide according to any one of Claims 34 to 51 wherein the polypeptide exhibits Toll-like receptor (TLR) blocking activity.

53. An isolated nucleic acid molecule which encodes a polypeptide according to any one of Claims 34 to 52.

54. A vector comprising a nucleic acid molecule according to Claim 53.

55. A vector according to Claim 54 wherein the vector is an expression vector.

56. A host cell comprising a nucleic acid molecule according to Claim 53 or a vector according to Claim 54 or 55.

57. A method of making a polypeptide according to any one of Claims 34 to 52 comprising culturing a population of host cells according to Claim 56 under conditions in which said polypeptide is expressed, and isolating the polypeptide therefrom.

58. A method of making a polypeptide according to any one of Claims 34 to 52 comprising liquid-phase or solid-phase synthesis of the polypeptide.

59. A pharmaceutical composition comprising a polypeptide according to any one of Claims 34 to 52 together with a pharmaceutically acceptable excipient, diluent, carrier, buffer or adjuvant.

60. A pharmaceutical composition according to Claim 59 suitable for administration via a route selected from the group consisting of topical, ocular, nasal, pulmonar, buccal, parenteral (intravenous, subcutaneous, intratechal and intramuscular), oral, vaginal and rectal.

61. A pharmaceutical composition according to Claim 59 suitable for administration via an implant.

62. A pharmaceutical composition according to any one of Claims 60 to 61 wherein the pharmaceutical composition is associated with a device or material to be used in medicine.

63. A pharmaceutical composition according to Claim 62 wherein the device used in by-pass surgery, extracorporeal circulation, wound care and/or dialysis.

64. A pharmaceutical composition according to Claim 62 or 63 wherein the pharmaceutical composition is coated, painted, sprayed or otherwise applied to a suture, prosthesis, implant, wound dressing, catheter, lens, skin graft, skin substitute, fibrin glue or bandage.

65. A pharmaceutical composition according to any one of Claims 62 to 64 wherein the device or material comprise or consists of a polymer, metal, metal oxide and/or ceramic.

66. A polypeptide according to any one of Claims 34 to 52 for use in medicine.

67. A polypeptide according to Claim 66 for use in the treatment or prevention of inflammation and/or excessive coagulation.

68. A polypeptide according to Claim 66 or 67 for use in the treatment and/prevention of acute and/or chronic inflammation.

69. A polypeptide according to Claim 66 for use in the treatment and/prevention of microbial infection (*e.g.* bacterial infection).

70. A polypeptide according to Claim 66 for use in the modulation of blood coagulation.

71. A polypeptide according to Claim 66 for use in the treatment of wounds.

72. A polypeptide according to any one of Claims 66 or 71 for use in the treatment or prevention of a disease, condition or indication selected from the following:

i) Acute systemic inflammatory disease, with or without an infective component, such as systemic inflammatory response syndrome (SIRS), ARDS, sepsis, severe sepsis, and septic shock. Other generalized or localized invasive infective and inflammatory disease, including erysipelas, meningitis, arthritis, toxic shock syndrome, diverticulitis, appendicitis, pancreatitis, cholecystitis, colitis, cellulitis, burn wound infections, pneumonia, urinary tract infections, postoperative infections, and peritonitis.

ii) Chronic inflammatory and or infective diseases, including cystic fibrosis, COPD and other pulmonary diseases, gastrointestinal disease including chronic skin and stomach ulcerations, other epithelial inflammatory and or infective disease such as atopic dermatitis, oral ulcerations (aphtous ulcers), genital ulcerations and inflammatory changes, parodontitis, eye inflammations including conjunctivitis and keratitis, external otitis, mediaotitis, genitourinary inflammations.

iii) Postoperative inflammation. Inflammatory and coagulative disorders including thrombosis, DIC, postoperative coagulation disorders, and coagulative disorders related to contact with foreign material, including extracorporeal circulation, and use of biomaterials. Furthermore,

vasculitis related inflammatory disease, as well as allergy, including allergic rhinitis and asthma..

iv) Excessive contact activation and/or coagulation in relation to, but not limited to, stroke.

v) Excessive inflammation in combination with antimicrobial treatment. The antimicrobial agents used may be administred by various routes; intravenous (iv), intraarterial, intravitreal, subcutaneous (sc), intramuscular (im), intraperitoneal (ip), intravesical, intratechal, epidural, enteral (including oral, rectal, gastric, and other enteral routes), or topically, (including dermal, nasal application, application in the eye or ear, eg by drops, and pulmonary inhalation). Examples of agents are penicillins, cephalosporins, carbacephems, cephamycins, carbapenems, monobactams, aminoglycosides, glycopeptides, quinolones, tetracyclines, macrolides, and fluoroquinolones. Antiseptic agents include iodine, silver, copper, clorhexidine, polyhexanide and other biguanides, chitosan, acetic acid, and hydrogen peroxide.

73. Use of a polypeptide according to any one of Claims 34 to 52 in the preparation of a medicament for the treatment or prevention of inflammation and/or excessive coagulation.

74. A use according to Claim 73 wherein the medicament is for use in the treatment or prevention of acute inflammation, sepsis, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), cystic fibrosis, asthma, allergic and other types of rhinitis, cutaneous and systemic vasculitis, thrombosis and disseminated intravascular coagulation (DIC).

75. A use according to Claim 74 wherein the medicament is for use in the treatment or prevention of sepsis.

76. A use according to Claim 74 wherein the medicament is for use in the treatment or prevention of chronic obstructive pulmonary disease (COPD).

77. A use according to any one of Claims 73 to 76 wherein the medicament is for use in combination with one or more additional therapeutic agent.

78. A use according to Claim 77 wherein the additional therapeutic agent is selected from the group consisting of antibiotic agents, anti-fungal agents, anti-inflammatory agents, immunosuppressive agents, vasoactive agents and antiseptic agents.

79. A use according to Claim 78 wherein the antibiotic agents are selected from the groups consisting of anti-bacterial agents, anti-fungicides, anti-viral agents and anti-parasitic agents.

80. A use according to Claim 78 wherein the additional therapeutic agent is a steroid.

81. A method for treating or preventing inflammation in a patient, the method comprising administering to the patient a therapeutically-effective amount of a polypeptide according to any one of Claims 1 to 52 or a pharmaceutical composition according to any one of Claims 59 to 65

82. A method according to Claim 81 wherein the patient is human.

83. A method according to Claim 95 or 96 for the treatment or prevention of acute inflammation, sepsis, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), cystic fibrosis, asthma, allergic and other types of rhinitis, cutaneous and systemic vasculitis, thrombosis and disseminated intravascular coagulation (DIC).

84. A method according to Claim 83 for the treatment or prevention of sepsis.

85. A method according to Claim 83 for the treatment or prevention of chronic obstructive pulmonary disease (COPD).

86. A method according to any one of Claims 81 to 85 wherein the method further administering to the patient one or more additional therapeutic agent.

87. A method according to Claim 86 wherein the additional therapeutic agent is selected from the group consisting of antibiotic agents, anti-inflammatory agents, immunosuppressive agents, vasoactive agents, receptor blockers, receptor agonists and antiseptic agents.

88. A method according to Claim 87 wherein the antibiotic agents are selected from the groups consisting of anti-bacterial agents, anti-fungicides, anti-viral agents and anti-parasitic agents.

89. A method according to Claim 87 wherein the additional therapeutic agent is a steroid.

90. A polypeptide substantially as described herein with reference to the description and figures.

91. A pharmaceutical composition substantially as described herein with reference to the description and figures.

92. A medical implant or device, or biomaterial for use in the same, substantially as described herein with reference to the description and figures.

93. Use of a polypeptide substantially as described herein with reference to the description and figures.

94. A method for treating or preventing inflammation substantially as described herein with reference to the description and figures.

STATEMENT UNDER ARTICLE 19 (1)

The claims as amended herein under Article 19 PCT introduce two new limitations into the claims as originally filed.

Firstly, the claims are amended to exclude fusion polypeptides.

Secondly, the claims are amended to specify a size limitation on the polypeptides of the invention, such that the polypeptides must be from 15 to 100 amino acids in length (basis for this amendment can be found in the application as filed at page 15, lines 14 to 18).

As a consequence of these amendments:

(a) Sequence 166 of D1 falls outside the scope of the claims, since it is only eleven amino acids in length;

(b) The chimeric (*i.e.* fusion) molecules of D2 fall outside the scope of the claims;

(c) The chimeric (*i.e.* fusion) molecules of D3 fall outside the scope of the claims;

(d) The mutant heparin cofactor II protein of D4 falls outside the scope of the claims, since it is 499 amino acids in length (see SEQ ID NO: 2 of D4);

(e) The heparin cofactor II protein described in D5 falls outside the scope of the claims, since this wildtype protein is more than 100 amino acids in length (for example, see D4 and D6);

(f) The heparin cofactor II deletion mutants of D6 fall outside the scope of the claims, since they are more than 100 amino acids in length (see Figure 1 of D6); and

(g) The chimeric (*i.e.* fusion) proteins of D7 fall outside the scope of the claims.

Accordingly, we submit that the claims as amended herein are novel over the prior art documents cited in the International Search Report.