— PROPOSED AMENDMENTS —

CLAIMS

We claim:

1. An isolated protein, comprising angiostatin, ~~wherein angiostatin is~~ a protein having ~~an endothelial cell proliferation inhibiting activity and having~~ a molecular weight of between approximately 38 kilodaltons and 45 kilodaltons as determined by reducing polyacrylamide gel electrophoresis, and having ~~wherein the angiostatin further has~~ an amino acid sequence substantially similar to that of a plasminogen fragment beginning at ~~approximately~~ amino acid ~~number~~ 98 of a ~~murine~~ plasminogen molecule.

2. An isolated protein, comprising a protein having an amino acid sequence of ~~The~~ angiostatin ~~Claim 1, wherein the angiostatin contains~~ approximately 9 kringle ~~regions~~ 1 through 4 region of a plasminogen molecule, and having anti-angiogenic activity.

3. ~~The~~ A protein of angiostatin Claim 1 or 2, wherein the ~~amino acid sequence~~ protein is a plasminogen fragment of ~~derived from~~ human plasminogen, murine plasminogen, bovine plasminogen, Rhesus plasminogen or porcine plasminogen.

4. ~~The~~ A protein angiostatin of Claim 1 or 2, having a beginning ~~wherein the~~ amino acid sequence is selected from the group consisting of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6.

5. ~~The~~ A protein angiostatin of Claim 1 or 2, wherein the ~~angiostatin is capable of inhibiting angiogenesis~~ plasminogen fragment has in endothelial cell proliferation inhibiting activity in a bovine endothelial cell assay.

6. ~~The~~ A protein angiostatin of Claim 1 or 2 wherein the ~~angiostatin~~ protein is capable of inhibiting ~~angiogenesis related diseases~~ the growth of a cancer.

7. ~~The~~ A protein angiostatin of Claim 6, wherein the ~~angiogenesis related disease is~~ cancer is selected from the group consisting of prostate cancer, breast cancer, colon cancer and lung cancer.

A composition comprising, an 8. ~~I~~isolated nucleotide molecule having a sequence that codes for ~~angiostatin, wherein the~~ angiostatin protein having anti-angiogenic ~~an endothelial cell proliferation inhibiting~~ activity, ~~and~~ having a molecular weight of between approximately 38 ~~kilodaltons~~ and 45 kilodaltons as determined by reducing polyacrylamide gel electrophoresis, and an amino acid sequence ~~wherein the angiostatin contains~~ substantially similar to ... Plasminogen fragment beginning at approximately amino acid 98 ~~kringle regions 1 through 4~~ of a plasminogen molecule, ~~the protein being capable of binding lysine, and the protein being capable of inhibiting angiogenesis~~.

~~9. A method of treating a human or animal~~ with an angiogenic mediated disease comprising administering to the human or animal with the angiogenic mediated disease an effective amount of angiostatin, wherein angiostatin is a protein having an endothelial cell proliferation inhibiting activity and having a molecular weight of between approximately 38 kilodaltons and 45 kilodaltons as determined by reducing polyacrylamide gel electrophoresis, and wherein the angiostatin further has an amino acid sequence substantially similar to that of a plasminogen fragment beginning at amino ~~acid number 98 of a murine plasminogen molecule~~.

~~10. The method Claim 9~~, wherein the protein angiostatin contains approximately kringle regions 1 through 4 of a plasminogen molecule.

9. A composition comprising, an isolated nucleotide molecule having a sequence that codes for angiostatin protein having anti-angiogenic activity

~~11. The method of Claim 10, wherein the~~ amino acid sequence is a plasminogen ~~fragment~~ derived from human plasminogen, murine plasminogen, bovine ~~plasminogen, Rhesus plasminogen or porcine plasminogen~~.

composition 8 or 9 nucleotide sequence codes for a protein
10~~12~~. The ~~method~~ of Claim ~~10~~, wherein the amino acid sequence ~~is~~ selected from the group consisting of having a beginning SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6.

→ Insert claim 11 : The composition .... angiostatin protein has in vitro endothelial cell proliferation inhibiting activity in a bovine endothelial cell assay.

~~13. The method of Claim 9, wherein the~~ angiogenic disease is selected from ~~the~~ group consisting of cancer, arthritis, ~~macular~~ degeneration and diabetic ~~retinopathy~~.

→ Insert claim 12 : The composition . . . inhibiting the growth of a cancer

~~14. A method of diagnosing a disease or~~ determining the prognosis of a disease mediated by angiogenesis comprising the step of determining the concentration of angiostatin, wherein angiostatin is a protein having an endothelial cell proliferation inhibiting activity and having a molecular weight of between approximately 38 kilodaltons and 45 kilodaltons as determined by reducing polyacrylamide gel electrophoresis, and wherein the angiostatin further has an amino acid sequence substantially similar to that of a plasminogen fragment beginning at amino ~~acid number 98 of a murine plasminogen molecule.~~

→ Insert claim 13 : The composition . . . . a colon cancer & a lung cancer.

~~15. The method Claim 14, wherein the~~ angiostatin contains approximately kringle regions ~~1~~ through 4 of a plasminogen molecule.

~~16.~~ The method of Claim 14, wherein the ~~disease is cancer~~.

Insert claim 14 : The composition . . . . the vector is capable of expressing angiostatin protein when present in a cell.

An method of expressing an protein comprising, ... sequence that codes for

15. ~~17.~~ ^~~Isolated~~ angiostatin, ^~~wherein~~ angiostatin ~~is a~~ protein having ^anti-angiogenic ~~an endothelial cell proliferation inhibiting~~ activity, ~~and~~ having a molecular weight of between approximately 38 ~~kilodaltons~~ and 45 kilodaltons as determined by reducing polyacrylamide gel electrophoresis, and ~~wherein the angiostatin further has~~ an amino acid sequence substantially similar to that of a plasminogen fragment beginning at approximately amino acid ~~number~~ 98 of a ~~murine~~ plasminogen molecule, ~~for use in a medicament~~ ^wherein the vector is capable of expressing the angiostatin protein when present in the cell.

A method of expressing . . . . a cell a vector

16 ~~18.~~ ^~~The angiostatin Claim 17~~, wherein the ^vector contains a nucleotide molecule . . . encodes for an protein having an anti-angiogenic activity and containing angiostatin ^~~contains~~ approximately kringle regions 1 through 4 of a plasminogen molecule, ^, wherein the cell is capable . . . . angiostatin protein.

→ Insert new claim 17 : The method of claim 15 or 16, wherein the expression is in vitro.

18 ~~19.~~ The ^method of Claim 15 or 16 ~~angiostatin for use as a medicament of Claim 18~~, wherein the ^nucleotide sequence encodes for a beginning amino acid sequence ~~is~~ selected from the group consisting of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6.

→ Insert claims 19 & 20

An antibody capable selectively binding to

21 ~~20.~~ ^~~Use~~ of ^~~angiostatin wherein~~ angiostatin ~~is a~~ protein having ~~an endothelial cell proliferation inhibiting~~ activity and having a molecular weight of between approximately 38 ~~kilodaltons~~ and 45 kilodaltons as determined by reducing polyacrylamide gel electrophoresis, and ~~wherein the angiostatin further has~~ an amino acid sequence substantially similar to that of a plasminogen fragment beginning at approximately amino acid ~~number~~ 98 of a ~~murine~~ plasminogen molecule, ~~for the manufacture of a medicament for treating a human or animal with an angiogenic mediated disease~~

An antibody capable of selectively binding to angiostatin protein having anti-angiogenic activity, and

~~22.~~ ~~21.~~ ~~The use of angiostatin of Claim 20,~~ wherein the angiostatin protein contains approximately kringle regions 1 through 4 of a plasminogen molecule.

~~22. The use of Claim 21, wherein the amino~~ acid sequence is a plasminogen ~~fragment derived~~ from human plasminogen, ~~murine~~ plasminogen, bovine plasminogen, ~~Rhesus plasminogen or porcine plasminogen.~~

23. The ~~use~~ antibody of Claim 21 or 22, wherein the amino acid sequence ~~is~~ selected from the group consisting of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6.

angiostatin protein has a beginning

→ Insert claim 24 : The antibody of Claim 21 or 22, wherein the angiostatin protein has in vitro endothelial cell proliferation inhibiting activity in a bovine endothelial cell assay.

~~24. The use of Claim 20, wherein the~~ angiogenic disease is selected from ~~the~~ group consisting of cancer, arthritis, ~~macular~~ degeneration and diabetic ~~retinopathy~~.

→ Insert claim 25 : The antibody of Claim 21 or 22, wherein the angiostatin protein is capable of inhibiting the growth of a cancer.

~~25. A composition comprising, an isolated~~ DNA sequence that codes for angiostatin, wherein angiostatin is a protein having an endothelial cell proliferation inhibiting activity and having a molecular ~~weight~~ of between approximately 38 kilodaltons and ~~45~~ kilodaltons as determined by reducing polyacrylamide gel electrophoresis, and wherein the angiostatin ~~further~~ has an amino acid sequence substantially similar to that of a plasminogen fragment beginning at approximately amino acid number 98 of a murine plasminogen ~~molecule.~~

~~26. The composition Claim 25, wherein the~~ angiostatin contains ~~approximately~~ kringle regions 1 through 4 ~~of a plasminogen molecule~~.

→ Insert claim 26 : The antibody . . . . a colon cancer, and a lung cancer.

~~27. The composition of Claim 26, wherein the~~ DNA sequence codes for an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6.

28. The composition of Claim 25, further comprising a vector containing the DNA sequence encoding angiostatin, wherein the vector is capable of expressing angiostatin when present in a cell.

29. The composition of Claim 28, in a ~~unicellular organism capable of expressing angiostatin~~.

of detecting angiostatin protein in a sample, the

~~27~~ ~~30~~. A method ~~comprising, implanting into a human or non-human animal a cell containing a vector, wherein the vector contains a DNA sequence encoding angiostatin, wherein~~ angiostatin ~~is a~~ protein having ~~an endothelial cell proliferation inhibiting~~ anti-angiogenic activity, ~~and~~ having a molecular weight of between approximately 38 kilodaltons and 45 kilodaltons as determined by reducing polyacrylamide gel electrophoresis, and ~~wherein the angiostatin further has~~ an amino acid sequence substantially similar to that of a plasminogen fragment beginning at approximately amino acid ~~number~~ 98 of a ~~murine~~ plasminogen molecule, ~~wherein the vector is capable of expressing angiostatin when present in the cell~~ comprising: a. combining a sample . . . . antibody; and b. detecting the presence . . . . in the sample.

A of detecting angiostatin protein in a sample,

~~28~~ ~~31~~. ~~The~~ method ~~Claim 30,~~ wherein the angiostatin protein contains approximately kringle regions 1 through 4 of a plasminogen molecule, and has anti-angiogenic activity, comprising:

a. combining a sample suspected of containing angiostatin protein with an angiostatin protein-specific binding antibody; and

b. detecting the presence of binding between angiostatin protein and the antibody, thereby detecting angiostatic protein in the sample.

29 ~~32~~. The method of Claim ~~31~~ 27 or 28, wherein the ~~DNA~~ angiostatin protein has a beginning ~~sequence codes for an~~ amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6.

30 ~~33~~. The method of Claim 27 or 28, ~~A composition comprising a pharmaceutically acceptable excipient and angiostatin~~, wherein the angiostatin ~~is a~~ protein having ~~an~~ endothelial cell proliferation inhibiting activity in a bovine endothelial cell assay. ~~and having a molecular weight of between approximately 38 kilodaltons and 45 kilodaltons as determined by reducing polyacrylamide gel electrophoresis, and wherein the angiostatin further has an amino acid sequence substantially similar to that of a plasminogen fragment beginning at approximately amino acid number 98 of a murine plasminogen molecule.~~

→ Insert new claims 31 to 33.

Use of an effective amount of . . . in a mammal

34. ~~The composition Claim 33~~, wherein the angiostatin protein contains approximately kringle regions 1 through 4 of a plasminogen molecule, and has anti-angiogenic activity.

~~35. The composition of Claim 34, further comprising a sustained release matrix.~~

Use of an effective amount of angiostatin protein . . . in a mammal

35 ~~36~~. ~~A composition comprising an antibody that specifically binds to angiostatin~~, wherein the angiostatin ~~is a~~ protein ~~having an endothelial cell proliferation inhibiting~~ has anti-angiogenic activity, ~~and having~~ has a molecular weight of between approximately 38 kilodaltons and 45 kilodaltons as determined by reducing polyacrylamide gel electrophoresis, and ~~wherein the angiostatin further~~ has an amino-terminal amino acid sequence substantially similar to that of a plasminogen fragment beginning at approximately amino acid ~~number~~ 98 of a ~~murine~~ plasminogen molecule.

→ Insert claim 36 : The use according to claim 34 or 35, ... SEQ ID NO:5 and SEQ ID NO:6.

~~37. The composition of Claim 36, wherein the angiostatin contains approximately kringle regions 1 through 4 of a plasminogen molecule.~~

→ Insert new claim 37 : The use according to Claim 34 or 35, wherein the angiostatin protein has endothelial cell proliferation inhibiting activity in a bovine endothelial cell assay.

→ Insert new Claim 38 : The use according to Claim 34 or 35, wherein the mammal has a disease or condition mediated by angiogenesis.

→ Insert new claim 39 : The use according to Claim 38, wherein the mammal has a cancer.