What is claimed is:

1. A polysaccharide preparation having the following characteristics:

(a) a weight average chain molecular weight between 3,500 and 7,000 Da;

(b) anti-Xa activity of 5-20 IU/mg and anti-IIa activity of less than 25 IU/mg; and

(c) greater than 5% and less than 50% glycol split uronic acid residues.

2. The preparation of claim 1, wherein the preparation has less than 30% glycol split uronic acid residues.

3. The preparation of claim 1, wherein the preparation has between 10% and 30% glycol split uronic acid residues.

4. A polysaccharide preparation having the following characteristics:

(a) a weight average chain molecular weight between 3,500 and 7,000 Da;

(b) anti-Xa activity of 5-20 IU/mg and anti-IIa activity of less than 25 IU/mg;

(c) a polysaccharide chain having a glycol split uronic acid residue (U_G); and

(d) polysaccharide chains each having no more than 3 glycol split uronic acid residues (U_G).

5. The preparation of claim 4, wherein each polysaccharide chain has no more than 2 glycol split uronic acid residues (U_G).

6. A polysaccharide preparation having the following characteristics:

(a) a weight average chain molecular weight between 3,500 and 7,000 Da;

(b) anti-Xa activity of 5-20 IU/mg and anti-IIa activity of less than 25 IU/mg; and

(c) polysaccharide chains having on average between 0.2 and 3 glycol split uronic acid residues (U_G) per polysaccharide chain.

7. The preparation of claim 6, having on average no more than 1 glycol split uronic acid residue (U_G) per polysaccharide chain.

8. A composition comprising a polysaccharide preparation having the following characteristics:

(a) a weight average chain molecular weight between 3,500 and 7,000 Da;

(b) anti-Xa activity of 5-20 IU/mg and anti-IIa activity of less than 25 IU/mg; and

(c) polysaccharide chains having greater than 40% $U_{2S}H_{NS,6S}$ disaccharide residues.

9. The composition of claim 8, having greater than 70% $U_{2S}H_{NS,6S}$ disaccharide residues.

10. The composition of claim 8, having a degree of desulfation less than 40%.

11. The composition of claim 8, having a degree of desulfation less than 30%.

12. The composition of claim 8, having a degree of desulfation less than 10%.

13. A composition comprising a polysaccharide preparation lacking substantial anticoagulant activity, wherein the preparation consists essentially of polysaccharides that include Formula I:

$$[U_w\text{-}H_{x,y,z}]_m\sim[U_G\text{-}H_{x,y,z}]_n$$

wherein U indicates a uronic acid residue and H indicates a hexosamine residue;

wherein m and n are integers such that

m = 4-16, and

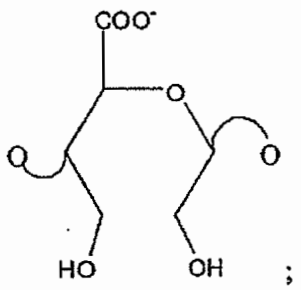
n = 1-4;

w = –2OS or –2OH;

x = –NS or –NAc;

y = –3OS or –3OH;

z = –6OS or –6OH;

and U_G =  ;

wherein the symbol ~ indicates that the units marked m and n are distributed along the polysaccharide chain and are not necessarily in sequence, wherein w, x, y, and z are each the same or different on each unit marked m, and wherein x, y, and z are each the same or different on each unit marked n, and

wherein the polysaccharide preparation has anti-Xa activity of 5-20 IU/mg and anti-IIa activity of less than 25 IU/mg.

14. A composition comprising a polysaccharide preparation with weight average chain molecular weight between 3,500 and 7,000 Da and reduced anticoagulant activity, wherein the preparation comprises polysaccharides comprising Formula I:

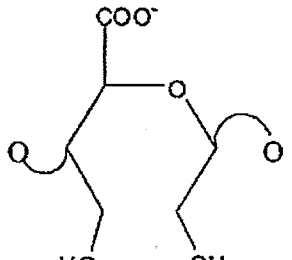
$[U_w\text{-}H_{x,y,z}]_m\sim[U_G\text{-}H_{x,y,z}]_n$

wherein U indicates a uronic acid residue and H indicates a hexosamine residue;

wherein m and n are integers such that
m = 4-16, and
n = 1-4;

w = –2OS or –2OH;
x = –NS or –NAc;
y = –3OS or –3OH;

z = –6OS or –6OH;

and U_G =  ;

wherein the symbol ~ indicates that the units marked m and n are distributed along the polysaccharide chain and are not necessarily in sequence, wherein w, x, y, and z are each the same or different on each unit marked m, and wherein x, y, and z are each the same or different on each unit marked n, and

wherein the polysaccharide preparation has anti-Xa activity of 5-20 IU/mg and anti-IIa activity of less than 25 IU/mg.

15. A preparation of polysaccharides and their pharmaceutically acceptable salts, which composition lacks substantial anticoagulant activity, has antimetastatic activity and consists essentially of polysaccharides that include Formula II:

$$[U_w\text{-}H_{x,y,z}]_m\text{-}[U_G\text{-}H_{x,y,z}]_n\text{-}[U_w\text{-}H_{x,y,z}]_o\text{-}[U_G\text{-}H_{x,y,z}]_p\text{-}[U_w\text{-}H_{x,y,z}]_q$$

wherein U indicates a uronic acid residue and H indicates a hexosamine residue;

wherein m-r are integers such that:

m = 0-10;

n = 0-3;

o = 0-10;

p = 0-3;

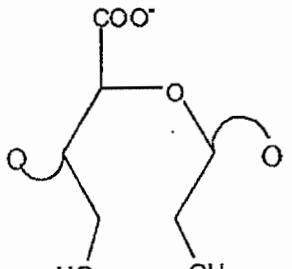
q = 0-10;

w = –2OS or –2OH;

x = –NS or –NAc;

y = –3OS or –3OH;

z = –6OS or –6OH;

and U_G =  ;

wherein w, x, y, and z are each the same or different on each unit marked m, n, o, p, or q.

16. The preparation of claim 15, wherein the sum of n + p is less than or equal to 3.

17. The preparation of claim 15, wherein the preparation has a weight average chain molecular weight between 3,500 and 7,000 Da.

18. The preparation of claim 1, wherein the non-reducing end uronic acid of a polysaccharide chain in the preparation has a 4,5-unsaturation.

19. The preparation of claim 18, wherein about 30% of the non-reducing uronic acids in the preparation have a 4,5-unsaturation.

20. The preparation of claim 18, wherein the 4,5-unsaturation is a result of heparinase digestion or benzyl esterification followed by beta-elimination.

21. The preparation of claim 1, wherein the reducing end further comprises a 2,5-anhydromannitol residue.

22. The preparation of claim 21, wherein about 50% of the reducing ends comprise a 2,5-anhydromannitol residue.

23. The preparation of claim 1, wherein the preparation is a pharmaceutical preparation.

24. The preparation of claim 1, wherein 10-50% of the oligosaccharides of the preparation have a molecular weight < 3000 Da; 40-65% of the oligosaccharides have a molecular weight between 3000-8000 Da, and 5-30% of the oligosaccharides have a molecular weight > 8000 Da.

25. The preparation of claim 1 wherein the polysaccharide is produced by a process comprising:

depolymerizing UFH to produce a depolymerized heparin; and

following depolymerization, performing a glycol split reaction on the depolymerized heparin.

26. The preparation of claim 25, wherein the step of glycol splitting comprises:

oxidizing the depolymerized heparin with periodate; and

reducing the oxidized depolymerized heparin with sodium borohydride.

27. A use of a preparation of claim 1 for the preparation of a medicament for treating metastatic disease, VEGF-, FGF-, SDF-1α- and/or selectin-mediated disease; inflammatory disease, an infectious disease, an autoimmune disease, fibrosis, or a disease involving angiogenesis in a subject.

28. The use of claim 27, wherein the preparation is administered chronically.

29. The use of claim 27, wherein the disease is a cancer.

30. The use of claim 29, wherein the cancer is breast cancer, colon cancer, or prostate cancer.

31. The use of claim 29, wherein the preparation is administered in combination with surgery, radiotherapy, a chemotherapy agent, an antibody or a tyrosine kinase inhibitor.

32. The use of claim 29, wherein the preparation is administered to the subject at dose of 5-50 mg/kg.

33. A method of manufacturing a preparation, the method comprising:

(1) depolymerizing an unfractionated heparin (UFH) with nitrous acid (HONO) to yield a polysaccharide preparation;

(2) oxidizing the polysaccharide preparation with periodate;

(3) reducing the oxidized polysaccharide preparation with sodium borohydride; and

(4) isolating the polysaccharide preparation, to thereby make a LMWH composition.

34. The method of claim 33, wherein the step of depolymerizing comprises treating the UFH with about 0.02 to 0.04 M nitrous acid at a pH of about 2 to 4 for about 1 to 5 hours at a temperature of about 10 to 30 °C .

35. The method of claim 33, wherein the step of oxidizing comprises treating the polysaccharide preparation with about 0.05 M to 0.2 M periodate for about 10 to 20 hours at a temperature of about 0 to 10 °C.

36. The method of claim 33, wherein the step of reducing comprises treating the oxidized polysaccharide preparation with about 0.5 to 2.0% (w/v) sodium borohydride for about 0.5 to 1.5 hours at a pH of about 6.0 to 7.0 and a temperature of about 0 to 10 °C.

37. A preparation according to claim 1, for use in treating metastatic disease, VEGF-, FGF-, SDF-1α- and/or selectin-mediated disease; inflammatory disease, an infectious disease, an autoimmune disease, fibrosis, or a disease involving angiogenesis in a subject.

CLAIMS

1. A pharmaceutical composition comprising a polysaccharide preparation having the following characteristics:

(a) anti-Xa activity of less than 20 IU/mg and anti-IIa activity less than 20 IU/mg;

(b) greater than 5% and less than 25% glycol split uronic acid residues; and

(c) the polysaccharide preparation has a molecular weight distribution such that 10-40% of the oligosaccharides of the preparation have a molecular weight < 3000 Da; 45-65% of the oligosaccharides have a molecular weight between 3000-8000 Da, and 15-30% of the oligosaccharides have a molecular weight > 8000 Da.

2. The pharmaceutical composition of claim 1, wherein the preparation has greater than 5% and less than 20% glycol split uronic acid residues.

3. The pharmaceutical composition of claim 1, wherein the preparation has between 10% and 20% glycol split uronic acid residues.

4. The pharmaceutical composition of claim 1, wherein the polysaccharide preparation has one or more chains having a glycol split uronic acid residue and polysaccharide chains of the preparation each having no more than 3 glycol split uronic acid residues (U_G).

5. The pharmaceutical composition of claim 4, wherein each polysaccharide chain of the preparation has no more than 2 glycol split uronic acid residues (U_G).

6. The pharmaceutical composition of claim 1, wherein each polysaccharide chain of the preparation has on average between 0.2 and 3 glycol split uronic acid residues (U_G) .

7. The pharmaceutical composition of claim 6, wherein each polysaccharide chain of the preparation has no more than 1 glycol split uronic acid residue (U_G) .

8. The pharmaceutical composition of claim 1,wherein the preparation has polysaccharide chains having greater than 40% $U_{2S}H_{NS,6S}$ disaccharide residues.

9. The pharmaceutical composition of claim 8, wherein the polysaccharide chains have greater than 70% $U_{2S}H_{NS,6S}$ disaccharide residues.

10. The pharmaceutical composition of claim 1, wherein the preparation has a degree of desulfation less than 40%.

11. The pharmaceutical composition of claim 1, wherein the preparation has a degree of desulfation less than 30%.

12. The pharmaceutical composition of claim 1, wherein the preparation has a degree of desulfation less than 10%.

13. The pharmaceutical composition of claim 1, wherein the preparation comprises polysaccharides that include Formula I:

$$[U_w\text{-}H_{x,y,z}]_m\sim[U_G\text{-}H_{x,y,z}]_n$$

wherein each occurrence of U indicates a uronic acid residue and each occurrence of H indicates a hexosamine residue;

wherein m and n are integers such that

m = 4-16, and

n = 1-4;

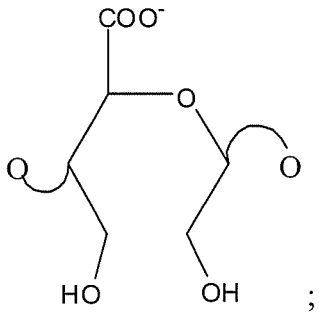
each of w, x, y and z can, independently, be the same or different for each occurrence of $[U_w\text{-}H_{x,y,z}]$ and each of x, y and z, independently, can be the same or different for each occurrence of $[U_G\text{-}H_{x,y,z}]$, wherein

w = –2OS or –2OH;

x = –NS or –NAc;

y = –3OS or –3OH;

z = –6OS or –6OH;

and U_G = 

;

wherein the symbol ~ indicates that the units marked m and n are distributed along the polysaccharide chain and are not necessarily in sequence.

14. The pharmaceutical composition of claim 1, wherein the preparation consists essentially of polysaccharides that include Formula II:

$$[U_w\text{-}H_{x,y,z}]_m\text{-}[U_G\text{-}H_{x,y,z}]_n\text{-}[U_w\text{-}H_{x,y,z}]_o\text{-}[U_G\text{-}H_{x,y,z}]_p\text{-}[U_w\text{-}H_{x,y,z}]_q$$

wherein each occurrence of U indicates a uronic acid residue and each occurrence of H indicates a hexosamine residue;

wherein m-q are integers such that:

m = 0-10;

n= 0-3;

o = 0-10;

p = 0-3;

q = 0-10;

wherein the sum of n + p is less than or equal to 3, 2, 1 or 0 and the sum of m + n + o + p + q is greater than 2; and

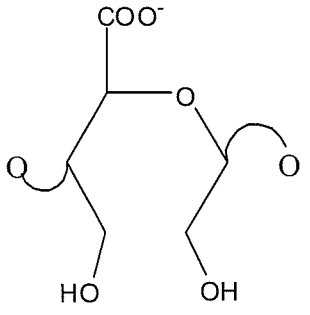
each of w, x, y and z can, independently, be the same or different for each occurrence of $[U_w\text{-}H_{x,y,z}]$ and each of x, y and z, independently, can be the same or different for each occurrence of $[U_G\text{-}H_{x,y,z},]$ wherein

w = –2OS or –2OH;

x = –NS or –NAc;

y = –3OS or –3OH;

z = –6OS or –6OH;

and U_G = 

.

15. The pharmaceutical composition of claim 1, wherein the preparation has a weight average chain molecular weight between 3,500 and 7,000 Da.

16. The pharmaceutical composition of claim 1, wherein the polysaccharides of the preparation have a uronic acid at the non-reducing end.

17. The pharmaceutical composition of claim 1, wherein the reducing end of the polysaccharide in the preparation further comprises a 2,5-anhydromannitol residue.

18. The pharmaceutical composition of claim 17, wherein 50% of the reducing ends comprise a 2,5-anhydromannitol residue.

19. The pharmaceutical composition of claim 1, wherein the polysaccharide preparation is produced by a process comprising:

depolymerizing unfractionated heparin (UFH) to produce a depolymerized heparin; and

following depolymerization, performing a glycol split reaction on the depolymerized heparin.

20. The pharmaceutical composition of claim 19, wherein the step of glycol splitting comprises:

oxidizing the depolymerized heparin with periodate; and

reducing the oxidized depolymerized heparin with sodium borohydride.

21. The pharmaceutical composition of claim 1, wherein the preparation has a polydispersity of 1.2 to 1.7.

22. The pharmaceutical composition of claim 1, wherein the composition has one or more of a sodium content less than 30%; less than 20 ppm iodine; less than 30% sulfur; and less than 50 ppm boron.

23. The pharmaceutical composition of claim 1, wherein the preparation comprises polysaccharides having a glycol split uronic acid at the non-reducing end.

24. The pharmaceutical composition of claim 1, wherein the polysaccharide preparation has an anti-Xa activity of less than 15 IU/mg.

25. The pharmaceutical composition of claim 1, wherein the polysaccharide preparation has an anti-Xa activity of less than 10 IU/mg.

26. The pharmaceutical composition of claim 1, wherein the polysaccharide preparation has an anti-IIa activity of 3 IU/mg or less.

27. The pharmaceutical composition of claim 13, wherein the reducing end of the polysaccharides comprise a 2,5-anhydromannitol residue.

28. The pharmaceutical composition of claim 13, wherein 50% of the reducing end of the polysaccharides comprise a 2,5-anhydromannitol residue.

29. The pharmaceutical composition of claim 13, wherein the preparation has a polydispersity of 1.2 to 1.7.

30. The pharmaceutical composition of claim 13, wherein the composition has one or more of a sodium content less than 30%; less than 20 ppm iodine; less than 30% sulfur; and less than 50 ppm boron.

31. The pharmaceutical composition of claim 13, wherein the polysaccharides of the preparation have a uronic acid at the non-reducing end.

32. The pharmaceutical composition of claim 13, wherein the polysaccharides of the preparation have a glycol split uronic acid at the non-reducing end.

33. The pharmaceutical composition of claim 13, wherein the polysaccharide preparation has an anti-Xa activity of less than 15 IU/mg.

34. The pharmaceutical composition of claim 13, wherein the polysaccharide preparation has an anti-Xa activity of less than 10 IU/mg.

35. The pharmaceutical composition of claim 13, wherein the polysaccharide preparation has an anti-IIa activity of 3 IU/mg or less.

36. A pharmaceutical composition comprising a polysaccharide preparation having the following characteristics:

(a) anti-Xa activity of less than 20 IU/mg and anti-IIa activity of 3 IU/mg or less;

(b) greater than 5% and less than 30% glycol split uronic acid residues; and

(c) the polysaccharide preparation has a molecular weight distribution such that 10-40% of the oligosaccharides of the preparation have a molecular weight < 3000 Da;

45-65% of the oligosaccharides have a molecular weight between 3000-8000 Da, and 15-30% of the oligosaccharides have a molecular weight > 8000 Da.

37. The pharmaceutical composition of claim 36, wherein the preparation has a weight average chain molecular weight between 3,500 and 7,000 Da.

38. A pharmaceutical composition comprising a polysaccharide preparation having the following characteristics:

(a) anti-Xa activity of less than 20 IU/mg and anti-IIa activity of 3 IU/mg or less;

(b) greater than 5% and less than 50% glycol split uronic acid residues;

(c) the polysaccharide preparation has a molecular weight distribution such that 10-40% of the oligosaccharides of the preparation have a molecular weight < 3000 Da; 45-65% of the oligosaccharides have a molecular weight between 3000-8000 Da, and 15-30% of the oligosaccharides have a molecular weight > 8000 Da; and

(d) the polysaccharides of the preparation have a uronic acid at the non-reducing end.

39. A pharmaceutical composition comprising a polysaccharide preparation having the following characteristics:

(a) a molecular weight distribution such that 10-40% of the oligosaccharides of the preparation have a molecular weight < 3000 Da; 45-65% of the oligosaccharides have a molecular weight between 3000-8000 Da, and 15-30% of the oligosaccharides have a molecular weight > 8000 Da;

(b) greater than 5% and less than 50% glycol split uronic acid residues; and

(c) anti-Xa activity of less than 20 IU/mg and anti-IIa activity of 3 IU/mg or less,

wherein the preparation consists essentially of polysaccharides that comprise Formula I:

$[U_w\text{-}H_{x,y,z}]_m\sim[U_G\text{-}H_{x,y,z}]_n$

wherein each occurrence of U indicates a uronic acid residue and each occurrence of H indicates a hexosamine residue;

wherein m and n are integers such that

m = 4-16, and

n = 1-3;

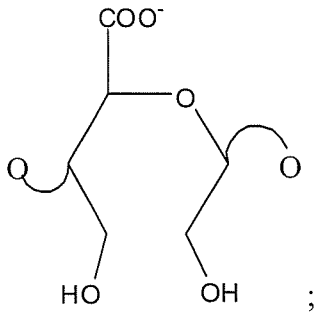
each of w, x, y and z can independently be the same or different for each occurrence of $[U_w\text{-}H_{x,y,z}]$ and each of x, y and z can independently be the same or different for each occurrence of $[U_G\text{-}H_{x,y,z}]$, wherein

w = –2OS or –2OH;

x = –NS or –NAc;

y = –3OS or –3OH;

z = –6OS or –6OH;

and U_G = 

;

wherein the symbol ~ indicates that the units marked m and n are distributed along the polysaccharide chain and are not necessarily in sequence; and

wherein a plurality of the polysaccharides in the preparation have a 2,5-anhydromannitol residue at the reducing end and non native uronic acid at the non-reducing end.

40. The pharmaceutical composition of claim 39, wherein the preparation has a weight average chain molecular weight between 3,500 and 7,000 Da.

41. The pharmaceutical composition of any one of claims 1-40, for use in the treatment of a metastatic disease, VEGF-, FGF-, SDF-1α- and/or selectin-mediated disease; inflammatory disease, an infectious disease, an autoimmune disease, fibrosis, or a disease involving angiogenesis in a subject.

42. The composition for use of claim 41, wherein the composition is administered chronically.

43. The composition for use of claim 41, wherein the disease is a cancer.

44. The composition for use of claim 43, wherein the cancer is breast cancer, colon cancer, pancreatic cancer, or prostate cancer.

45. The composition for use of claim 43, wherein the composition is administered in combination with surgery, radiotherapy, a chemotherapy agent, an antibody or a tyrosine kinase inhibitor.

46. The composition for use of claim 43, wherein the preparation is administered to the subject at dose of 5-50 mg/kg.

47. A method of manufacturing a polysaccharide preparation, as defined by any one of claims 1-40, the method comprising:

(1) depolymerizing an unfractionated heparin (UFH) with nitrous acid (HONO) to yield a polysaccharide preparation;

(2) oxidizing the polysaccharide preparation with periodate;

(3) reducing the oxidized polysaccharide preparation with sodium borohydride; and

(4) isolating the polysaccharide preparation, to thereby make a low molecular weight heparin (LMWH) composition.

48. The method of claim 47, wherein the step of depolymerizing comprises treating the UFH with 0.02 to 0.04 M nitrous acid at a pH of 2 to 4 for 1 to 5 hours at a temperature of 10 to 30 °C .

49. The method of claim 47, wherein the step of oxidizing comprises treating the polysaccharide preparation with 0.05 M to 0.2 M periodate for 10 to 20 hours at a temperature of 0 to 10 °C.

50. The method of claim 47, wherein the step of reducing comprises treating the oxidized polysaccharide preparation with 0.5 to 2.0% (w/v) sodium borohydride for 0.5 to 1.5 hours at a pH of 6.0 to 7.0 and a temperature of 0 to 10 °C.

51. The composition for use of claim 43, wherein the cancer is pancreatic cancer.

52. The composition for use of claim 43, wherein the cancer is colorectal cancer.

53. The composition for use of claim 41, wherein the preparation lacks substantial anticoagulation activity.

54. The composition for use of claim 43, wherein the cancer is a metastatic cancer.

55. The composition for use of claim 54, wherein the metastatic cancer is metastatic pancreatic cancer.

56. The composition for use of claim 41, wherein the composition is administered intravenously.

57. The composition for use of claim 41, wherein the composition is administered subcutaneously.

58. The composition for use of claim 41, wherein the composition is administered daily.

59. The composition for use of claim 41, wherein the composition is administered in combination with a second therapy.

60. The composition for use of claim 59, wherein the second therapy comprises administration of one or more therapeutic agents.

61. The composition for use of claim 60, wherein the therapeutic agent is a cytotoxic or cytostatic agent or a combination thereof.

62. The composition for use of claim 60, wherein the one or more therapeutic agent comprises docetaxel, leucovorin, or fluorouracil.

63. The composition for use of claim 60, wherein the one or more therapeutic agent comprises gemcitabine.

64. The composition for use of claim 63, further comprising administering a taxane in combination with gemcitabine.

65. The composition for use of any one of claims 41-46 and 51-64, wherein the pharmaceutical composition comprises a polysaccharide preparation of any of claims 1-40.

66. A kit comprising the pharmaceutical composition of any of claims 1-40.

67. The kit of claim 66, further comprising one or more of: instructions for use; other reagents such as a therapeutic agent; devices or other materials for preparing the pharmaceutical composition for administration; pharmaceutically acceptable carriers; and devices or other materials for administration to a subject.

68. The kit of claim 67, wherein the instructions include a suggested dose and/or a mode of administration, for example, in a patient having a disorder.

69. The kit of claim 67, further comprising at least one additional reagent, such as a diagnostic or therapeutic agent.

70. The kit of claim 66, further comprising instructions for use in combination with an additional therapeutic agent.

71. The kit of claim 70, wherein the additional therapeutic agent is a chemotherapeutic agent.

72. The kit of claim 71, further comprising at least one additional reagent, such as a diagnostic or therapeutic agent.

73. The kit of claim 71, wherein the chemotherapeutic agent is gemcitabine.

74. The kit of claim 71, wherein the chemotherapeutic agent is gemcitabine in combination with a taxane.