3. SUMMARY

[0007] In a first aspect, the present invention refers to the use of a Platelet Factor-4 (PF-4) interacting heparinoid in the manufacture of a medicament for treating cancer in a subject, wherein the medicament is adjunctively administered with a myelosuppressive treatment regimen and wherein the PF-4 interacting heparinoid is substantially non-anticoagulating. In a second aspect, the present invention refers to the use of a Platelet Factor-4 (PF-4) interacting heparinoid in the preparation of a medicament for use in preventing or treating radiation-induced thrombocytopenia in a subject, wherein the subject is exposed to ionizing radiation and wherein the PF4-interating heparinoid is substantially non-anticoagulating. In a third aspect, the present invention refers to the use of a Platelet Factor-4 (PF-4) interacting heparinoid in the preparation of a medicament for treating thrombocytopenia in a subject, wherein the PF4-interacting heparinoid is substantially non-anticoagulating. In a fourth aspect, the present invention refers to the use of a Platelet Factor-4 (PF-4) interacting heparinoid in the preparation of a medicament for treating neutropenia in a subject, wherein the PF-4 interacting heparinoid is substantially non-anticoagulating. In ~~a first aspect~~one example, methods are ~~provided~~described for attenuating a myelosuppressive side effect of a patient treatment regimen. The methods comprise adjunctively administering to the patient a therapeutically effective amount of a platelet factor 4-interacting heparinoid (hereinafter "PF4-interacting heparinoid"). As ~~provided~~disclosed herein, a myelosuppressive side effect is the occurrence of thrombocytopenia and/or neutropenia, and a patient treatment regimen having a myelosuppressive side effect is a treatment regimen that induces, as a side effect, one or both of thrombocytopenia and neutropenia. In various ~~embodiments~~examples, this ~~aspect~~ provides uses of a PF4-interacting heparinoid, e.g., ODSH, in the attenuation of a myelosuppressive side effect of a patient treatment regimen.

[0008] Numerous patient treatment regimens have myelosuppressive side effects, including antineoplastic treatment regimens, such as chemotherapy and radiation therapy, antibody therapy, including treatment regimens used to treat cancer and/or auto-immune diseases, and transplant procedures, such as bone marrow or stem cell transplant. In certain ~~embodiments~~examples, the patient treatment regimen comprises chemotherapy and/or radiation therapy and/or antibody therapy. In ~~an exemplary embodiment~~one

example, the patient treatment regimen is a chemotherapeutic regimen comprising gemcitabine and nab-paclitaxel. In ~~an exemplary embodiment~~another example, the patient treatment regimen is a chemotherapeutic regimen comprising ifosfamide, carboplatin, and etoposide, optionally including rituximab. In certain ~~embodiments~~examples, the patient treatment regimen comprises one or more regimens suitable for the treatment of subjects diagnosed with acute myelogenous or myeloid leukemia ("AML"). In ~~an exemplary embodiment~~one example, a regimen suitable for the treatment of subjects diagnosed with AML comprises a chemotherapy regimen suitable for inducing remission of AML (known in the art as induction chemotherapy), a chemotherapy regimen for preventing remission of AML (known in the art as consolidation chemotherapy), or both induction and consolidation chemotherapy. Optionally, a regimen suitable for the treatment of subjects diagnosed with AML can also comprise one or more non-chemotherapy-based regimens for preventing remission of AML, which can be used instead of or in combination with consolidation chemotherapy. These non-chemotherapy-based regimens include stem cell transplant, such as allogeneic

stem cell transplant, and immunotherapy. Further patient treatment regimens are described in Section 5.1.1.

[0009] In various ~~embodiments~~examples, the methods are useful for treating subjects diagnosed with cancer, for example pancreatic cancer, solid tumors including osteosarcoma, neuroblastoma, or AML. The subject being treated can be an adult or a pediatric patient. In some ~~embodiments~~examples, the subject is diagnosed with a cancer in which PF4 levels are elevated either in platelets or in blood (referred to hereinafter as "PF4-positive cancer"). Examples of PF4-positive cancers include pancreatic cancer and colorectal cancer. Further suitable subjects are described in Section 5.1.2.

[0010] In some ~~embodiments~~examples, the methods may further comprise adjunctive administration of one or more additional agent or therapy that is pro-thrombopoietic, anti-thrombocytopenic, anti-neutropenic, pro-granulopoietic, and/or anticoagulant. Suitable agents and therapies for further adjunctive administration are described herein at Section 5.1.3. In some ~~embodiments~~examples, two or more agents and/or therapies are administered. The two or more agents can have the same activity (*e.g.*, anti-thrombocytopenic), different activity (*e.g.*, a first agent is pro-thrombopoietic and a second agent is anti-neutropenic), or overlapping activity (*e.g.*, a first agent is pro-granulopoietic and anticoagulant and a second agent is anti-coagulant).

[0011] The PF4-interacting heparinoid, and any adjunctively administered additional agent(s) or therapy, can be administered concurrently, sequentially, or separately from administration of the patient treatment regimen. Suitable routes and modes of administration are provided below in Section 5.8.

[0012] In ~~a second aspect~~another example, methods are provided for promoting thrombopoiesis in a subject. The methods comprise administering an effective amount of a PF4-interacting heparinoid to the subject. The subject can be thrombocytopenic or non-thrombocytopenic, as described below in Section 5.2. In various ~~embodiments~~examples, the methods comprise treating myelosuppression caused by a disease or condition that reduces platelet count in a subject. In ~~an exemplary embodiment~~one example, the subject is diagnosed with systemic inflammatory response syndrome (SIRS), sepsis, or septicemia. Optionally, the subject has elevated serum or plasma level of PF4. In some

~~embodiments~~examples, the methods further comprise adjunctive administration of one or more additional agent or

therapy that is pro-thrombopoietic, anti-thrombocytopenic, anti-neutropenic, pro-granulopoietic, and/or anticoagulant. Suitable agents and therapies for further adjunctive administration are described herein at Section 5.2.1.

[0013] In ~~a third aspect~~one example, methods are ~~provided~~described for promoting neutrophil production in a subject. The methods comprise administering an effective amount of a PF4-interacting heparinoid to the subject. The subject can be neutropenic or non-neutropenic, as described below in Section 5.3. In various ~~embodiments~~examples, the methods comprise treating myelosuppression caused by a disease or condition that reduces neutrophil count in a subject. Optionally, the subject has elevated serum or plasma level of PF4. In some ~~embodiments~~examples, the methods further comprise adjunctive administration of one or more additional agent or therapy that is pro-thrombopoietic, anti-thrombocytopenic, anti-neutropenic, pro-granulopoietic, and/or anticoagulant. Suitable agents and therapies for further adjunctive administration are described herein at Section 5.3.1.

[0014] In ~~a fourth aspect~~another example, methods are ~~provided~~described for increasing the efficacy of a patient treatment regimen having a myelosuppressive side effect. The methods comprise administering a therapeutically effective amount of a PF4-interacting heparinoid to the subject patient as an adjunct to the patient treatment regimen having a myelosuppressive side effect, without reducing the dose and/or dosage frequency of the patient treatment regimen following a reference treatment administration or treatment cycle.

[0015] In some ~~embodiments~~examples, the method further comprises administering a dose higher than is typically used for such administration or cycle in the absence of adjunctive administration of a PF4-interacting heparinoid.

[0016] In certain embodiments, the methods further comprise determining an initial platelet count in a blood sample from a patient and administering an amount of a PF4-interacting heparinoid effective to raise the patient's platelet count above a threshold level below which therapy with patient treatment regimen having a myelosuppressive side effect is contraindicated. In various ~~embodiments~~examples, an amount of a PF4-interacting heparinoid is administered sufficient to maintain platelet levels above levels that indicate grade 3 (severe) or grade 4 (life-threatening) thrombocytopenia. Optionally,

the methods can further comprise administering adjunctively to the PF4-interacting heparinoid one or more agents or therapies that is anti-thrombocytopenic, anti-neutropenic, anticoagulant, or

has some other therapeutic activity. In some ~~embodiments~~examples, the methods comprise a further step of administering a patient treatment regimen having a myelosuppressive side effect to the patient whose platelet count is above a threshold level that contraindicates such therapy. Optionally, the dose amount and/or frequency of the patient treatment regimen can be increased.

[0017] In certain ~~embodiments~~examples, the methods comprise determining an initial neutrophil count in a blood sample from a patient and administering an amount of a PF4-interacting heparinoid effective to raise the patient's neutrophil count above a threshold level below which therapy with patient treatment regimen having a myelosuppressive side effect is contraindicated. In various ~~embodiments~~examples, an amount of a PF4-interacting heparinoid is administered sufficient to maintain neutrophil levels above levels that indicate grade 3 or grade 4 neutropenia, *i.e.*, above about 1000 neutrophils/μl of blood and above about 500 neutrophils/μl of blood, respectively. Optionally, the methods can further comprise administering adjunctively to the PF4-interacting heparinoid one or more agents or therapies that is anti-neutropenic, anti-thrombocytopenic, anticoagulant, or has some other therapeutic activity. In some ~~embodiments~~examples, the methods comprise a further step of administering a patient treatment regimen having a myelosuppressive side effect to the patient whose neutrophil count is above a level that contraindicates such therapy. Optionally, the dose amount and/or frequency of the patient treatment regimen can be increased.

[0018] The PF4-interacting heparinoids of the present disclosure are heparinoids that are capable of interacting with PF4 and counteracting PF4's ability to suppress production of platelets and neutrophils. PF4-interacting heparinoids bind to PF4 and/or compete with PF4 for binding to progenitor cells in the myeloid cell lineage, *e.g.*, megakaryocytes. Preferably, PF4-interacting heparinoids have an average molecular weight above about 8 kDa, such as an average molecular weight between about 8 kDa and about 15 kDa, more preferably between about 11 kDa and 13 kDa. The PF4-interacting heparinoid is preferably partially desulfated. In some ~~embodiments~~examples, the PF4-interacting heparinoid is substantially sulfated at the 6-O and/or the N position. An exemplary PF4-interacting heparinoid, which is suitable for use in the methods described herein, is substantially 2-O, 3-O desulfated, referred to herein as ODSH. *See also* Section 5.6.

[0019] The present disclosure further provides pharmaceutical compositions and unit dosage forms comprising PF4-interacting heparinoids, suitable for use in the methods described herein, either alone or adjunctive to a patient treatment regimen and/or one or more additional agent or therapy. The pharmaceutical compositions may be prepared for parenteral administration, such as intravenous or subcutaneous administration. For intravenous administration, pharmaceutical compositions can be formulated for administration as a bolus or as a continuous infusion.

[0020] Pharmaceutical compositions for use in the methods disclosed herein comprise an amount of a PF4-interacting heparinoid, as described below in Section 5.9, sufficient to allow effective doses to be administered.

[0021] In some ~~embodiments~~examples, pharmaceutical compositions of PF4-interacting heparinoid are suitable for intravenous administration at doses ranging from about 0.1 mg/kg/hr to about 2.5 mg/kg/hr for infusions and from about 1 mg/kg to about 25 mg/kg for bolus doses. In some ~~embodiments~~examples, pharmaceutical compositions of PF4-interacting heparinoid are suitable for subcutaneous administration and are formulated for administration at doses ranging from about 25 mg to about 400 mg, in volumes of 2.0 ml or less per injection site.

4. BRIEF DESCRIPTION OF THE FIGURES

[0022] **FIG. 1** provides a graph illustrating the effect of 8 different treatment regimens on tumor weight in an *in vivo* murine xenograft model of human pancreatic cancer, as described further in Example 1 and at Table 1: vehicle control (Group 1, ●); ODSH alone (Group 2, ○); oxaliplatin/gemcitabine/nab-paclitaxel (Group 3, ■); gemcitabine alone (Group 4, □); oxaliplatin/gemcitabine/nab-paclitaxel with ODSH (Group 5, ▲); gemcitabine with ODSH (Group 6, △); oxaliplatin/gemcitabine (Group 7, ×); and oxaliplatin/gemcitabine with ODSH (Group 8, ☆).

[0023] **FIG. 2** provides a graph illustrating the effect on tumor weight of a subset of the treatment regimens used in Example 1 and shown in **FIG. 1**: vehicle control (Group 1, ●); ODSH alone (Group 2, ○); gemcitabine alone (Group 4, □); and gemcitabine with ODSH (Group 6, △).

WHAT IS CLAIMED IS:

1. A method of attenuating a myelosuppressive side effect of a patient treatment regimen comprising:

adjunctively administering a therapeutically effective amount of a PF4-interacting heparinoid to the patient.

2. The method of claim 1, wherein the myelosuppressive side effect is thrombocytopenia.

3. The method of claim 2, wherein the patient is diagnosed with grade 1, 2, 3, or 4 thrombocytopenia.

4. The method of claim 1, wherein the myelosuppresive side effect is neutropenia.

5. The method of claim 4, wherein the patient is diagnosed with grade 1, 2, 3, or 4 neutropenia.

6. The method of claim 1, wherein the myelosuppresive side effect is thrombocytopenia and neutropenia.

7. The method of claim 6, wherein the patient is diagnosed with grade 1, 2, 3, or 4 thrombocytopenia and grade 1, 2, 3, or 4 neutropenia.

8. The method of claim 1, wherein the patient treatment regimen comprises an antineoplastic treatment regimen.

9. The method of claim 8, wherein the antineoplastic treatment regimen comprises one or more chemotherapeutic agents.

10. The method of claim 9, in which the one or more chemotherapeutic agents is selected from a folate antagonist, methotrexate and pemetrexed; a purine antagonist, cladribine, clofarabine, fludarabine, 6-mercaptopurine, nelarabine, pentostatin; a pyrimidine antagonist, capecitabine, cytarabine, 5-fluorouracil, gemcitabine, hydroxyurea; a biologic response modifier, interferon-alfa; bleomycin; a DNA alkylating agent, nitrosureas, carmustine, lomustine; a DNA cross-linking drug, a DNA alkylating agent, bendamustine, chlorambucil,

cyclophosphamide, ifosfamide, mechlorethamine, melphalan, dacarbazine, temozolomide, procarbazine; asparaginase; an antibiotic, mitomycin; a platinum complex, carboplatin, cisplatin, oxaliplatin; a proteosome inhibitor, bortezomib; a spindle poison, a taxane, docetaxel, paclitaxel, nab-paclitaxel, a vinca, vinblastine, vincristine, vinorelbine; a topoisomerase inhibitor, an anthracycline, daunorubicin, daunomycin, doxorubicin, epirubicin, a camptothecine, irinotecan, topotecan, a podophyllotoxin, etoposide, teniposide, mitoxantrone; a tyrosine kinase inhibitor, erlotinib, gefitinib, imatinib, lapatinib, sorafenib, sunitinib; and ifosfamide.

11. The method of claim 10, in which one of the one or more chemotherapeutic agents is gemcitabine.

12. The method of claim 10 or 11, in which one of the one or more chemotherapeutic agents is a taxane.

13. The method of claim 12, in which the taxane is taxol.

14. The method of claim 12, in which the taxane is paclitaxel.

15. The method of claim 13 or 14, in which the paclitaxel is nab-paclitaxel.

16. The method of any one of claims 12-15, in which one or more additional chemotherapeutic agents are administered to the patient.

17. The method of any one of claims 12-15, in which one or more therapeutic antibodies are administered to the patient.

18. The method of any one of claims 12-17, in which the subject has breast cancer, optionally metastatic breast cancer.

19. The method of any one of claims 12-17, in which the subject has recurrent breast cancer.

20. The method of any one of claims 12-17, in which the subject has pancreatic cancer, optionally metastatic pancreatic cancer.

21. The method of claim 19, wherein an antineoplastic treatment regimen comprising one or more chemotherapeutic agents was administered to the patient within 6 months of breast cancer recurrence.

22. The method of claim 21, wherein the antineoplastic treatment regimen administered to the patient within 6 months of breast cancer recurrence comprised an anthracycline.

23. The method of claim 9 or claim 10, in which two or more chemotherapeutic agents are administered to the patient, wherein the two or more agents are selected from cisplatin and etoposide; carboplatin and etoposide; cisplatin and irinotecan; carboplatin and irinotecan; cyclophosphamide, doxorubicin (Adriamycin), and vincristine; cyclophosphamide/ doxorubicin/vincristine; gemcitabine with vinorelbine or paclitaxel or nab-paclitaxel (Abraxane®), gemcitabine or capecitabine with oxaliplatin; cisplatin or carboplatin plus another chemotherapeutic agent; 5-fluorouracil with one or more of leuvocorin, oxaliplatin, irinotecan.

24. The method of claim 9 or claim 10, in which the two or more chemotherapeutic agents are administered according to a specific regimen is selected from 5FU Mayo, 5FU Roswell Park, LVFU2, FOLFOX4, FOLFOX6, bFOL, FUFOX, IFL, XELOX, XELIRI, CAPIRI, and ICE.

25. The method of claim 8, wherein the antineoplastic treatment regimen comprises radiation therapy.

26. The method of claim 25, wherein the radiation therapy is selected from x-ray radiation, gamma ray radiation, neutron radiation, proton radiation, external beam radiation therapy, and brachytherapy.

27. The method of claim 25 or 26, wherein the antineoplastic treatment regimen further comprises one or more chemotherapeutic agents.

28. The method of claim 27, wherein the radiation therapy is selected from x-ray radiation, gamma ray radiation, neutron radiation, proton radiation, external beam radiation therapy, and brachytherapy and the one or more chemotherapeutic agents is selected from a folate antagonist, methotrexate and pemetrexed; a purine antagonist, cladribine, clofarabine, fludarabine, 6-mercaptopurine, nelarabine, pentostatin; a pyrimidine antagonist, capecitabine, cytarabine, 5-fluorouracil, gemcitabine, hydroxyurea; a biologic response modifier, interferon-alfa;

bleomycin; a DNA alkylating agent, nitrosureas, carmustine, lomustine; a DNA cross-linking drug, a DNA alkylating agent, bendamustine, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, dacarbazine, temozolomide, procarbazine; asparaginase; an antibiotic, mitomycin; a platinum complex, carboplatin, cisplatin, oxaliplatin; a proteosome inhibitor, bortezomib; a spindle poison, a taxane, docetaxel, paclitaxel, nab-paclitaxel, a vinca, vinblastine, vincristine, vinorelbine; a topoisomerase inhibitor, an anthracycline, daunorubicin, daunomycin, doxorubicin, epirubicin, a camptothecine, irinotecan, topotecan, a podophyllotoxin, etoposide, teniposide, mitoxantrone; a tyrosine kinase inhibitor, erlotinib, gefitinib, imatinib, lapatinib, sorafenib, and sunitinib.

29. The method of claim 25 or 26, wherein the patient treatment regimen further comprises a bone marrow transplant.

30. The method of claim 29, wherein the bone marrow transplant is autologous or allogeneic.

31. The method of claim 25 or 26, wherein the patient treatment regimen further comprises a stem cell transplant.

32. The method of claim 31, wherein the stem cell transplant is autologous or allogeneic.

33. The method of claim 1, wherein the patient treatment regimen comprises antibody therapy.

34. The method of claim 33, in which one or more antibodies selected from abciximab and rituximab is administered to the patient.

35. The method of claim 33 or 34, wherein the patient treatment regimen further comprises chemotherapy.

36. The method of claim 35, in which one or more chemotherapeutic agent administered to the patient is selected from a folate antagonist, methotrexate and pemetrexed; a purine antagonist, cladribine, clofarabine, fludarabine, 6-mercaptopurine, nelarabine, pentostatin; a pyrimidine antagonist, capecitabine, cytarabine, 5-fluorouracil, gemcitabine, hydroxyurea; a biologic response

modifier, interferon-alfa; bleomycin; a DNA alkylating agent, nitrosureas, carmustine, lomustine; a DNA cross-linking drug, a DNA alkylating agent, bendamustine, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, dacarbazine, temozolomide, procarbazine; asparaginase; an antibiotic, mitomycin; a platinum complex, carboplatin, cisplatin, oxaliplatin; a proteosome inhibitor, bortezomib; a spindle poison, a taxane, docetaxel, paclitaxel, nab-paclitaxel, a vinca, vinblastine, vincristine, vinorelbine; a topoisomerase inhibitor, an anthracycline, daunorubicin, daunomycin, doxorubicin, epirubicin, a camptothecine, irinotecan, topotecan, a podophyllotoxin, etoposide, teniposide, mitoxantrone; a tyrosine kinase inhibitor, erlotinib, gefitinib, imatinib, lapatinib, sorafenib, and sunitinib.

37. The method of claim 33 or 34, wherein the patient treatment regimen further comprises radiation therapy.

38. The method of claim 37, in which the radiation therapy is x-ray radiation, gamma ray radiation, neutron radiation, proton radiation, external beam radiation therapy, or brachytherapy.

39. The method of claim 1, wherein the patient treatment regimen comprises a transplant.

40. The method of claim 39, wherein the transplant is a liver transplant, a bone marrow transplant, or a stem cell transplant.

41. The method of claim 40, wherein the transplant is an autologous or allogeneic bone marrow transplant.

42. The method of claim 40, wherein the transplant is an autologous or allogeneic stem cell transplant.

43. The method of claim 1, wherein the patient treatment regimen comprises one or more agent(s) selected from valproic acid, proton pump inhibitors, interferon, interferon-alpha, isotretinoin, panobinostat, thiazide diurectics, montelukast sodium (Singulair), quinidine, quinine, gold, sulfonamides, cephalothin, phenylbutazone, diphenylhydantoin, digitoxin and phenothiazine tranquilizers, heparin, and combinations thereof.

44. The method of claim 1, wherein the patient treatment regiment comprises one or more agent(s) selected from cyclophosphamide, psychotropic drugs, anticonvulsants, clozapine, olanzapine, thionamides, ticlopidine, carbimazole, dapsone, dipyrone, methimazole, penicillin G, procainamide, propylthiouracil, trimethoprim, chloramphenicol, penicillins, cephalosporins, aminoglycosides, tetracyclines, nitroimidazoles, nitrofurantoin, flucytosine, rifampin, isoniazid, ethambutol, dapsone, sulfonamide antibiotics, clomiprimine, thiacetazone, dipyrone, sulfasalazine, mesalazine, ciprofloxacin, chloroquin, mebendazole, terbendafine, pyrimethamine, levamisole, ristocetin, griseofulvin, phenothiazines, benzodiazepines, amoxapine, meprobamate, barbiturates, risperidone, imipramine, desipramine, thiothixene, haloperidol, valproic acid, hydantoins, succinimides, trimethadione, carbamazepine, procainamide, quinidine, propafenone, captopril, propranolol, hydralazine, methyldopa, ibuprofen, indomethacin, sulindac, tolmetin, aspirin, aminopyine, phenylbutazone, diflunisal, benoxaprofen, allopurinol, colchicine, propylthiouracil, thiouracil, methimazole, carbimazole, thiocyanate, potassium perchlorate, cimetidine, ranatadine, tripelennamine, methaphenilene, thenalidine, mianserin, bromopheneramine, quinine, hydroxychloroquin, quinacrine, diazoxide, dihydropyridines, vesnarinone, aprindine, imipenem/cilastatin, zidovudine, fludarabine, acyclovir, turbinafine, aminoglutethimide, famotidine, bezafibrate, flutamide, tamoxafen, penicillamine, retinoic acid, metoclopramide, phenindone, dinitrophenol, ethacrynic acid, rauwolfia, ethanol, chlorpropamide, tolbutamide, thiazides, spironolactone, methazolamide, acetazolamide, levodopa and combinations thereof.

45. The method according to any one of the preceding claims, further comprising adjunctively administering one or more additional agent or therapy.

46. The method of claim 45, wherein at least one of the one or more additional agent or therapy is anti-thrombocytopenic, anti-neutropenic, pro-thrombopoietic, pro-neutropenic, or anti-coagulant.

47. The method of claim 46, wherein one or more additional agent or therapy is anti-thrombocytopenic, pro-thrombopoietic, or both.

48. The method of claim 47, wherein one or more additional agent or therapy is selected from the group consisting of: platelet transfusion, splenectomy, corticosteroids, prednisone, dexamethasone, platelet clearance inhibitors, danazol, thrombopoeitin, thrombopoietin mimetics, eltrombopag, thrombopoietin receptor agonists, romiplostim, interleukins, recombinant human interleukin-1, recombinant human interleukin-3, recombinant human interleukin-6, recombinant human interleukin-11, lithium carbonate, and folate.

49. The method of claim 46, wherein one or more additional agent or therapy is anti-neutropenic, pro-granulopoietic, or both.

50. The method of claim 49, wherein one or more additional agent or therapy is selected from the group consisting of: recombinant human granulocyte colony stimulating factor, filgrastim, pegfilgrastim, recombinant human granulocyte-macrophage colony stimulating factor, and sargramostim.

51. The method of claim 46, where one or more additional agent is an anti-coagulation agent.

52. The method of claim 51, wherein the anti-coagulation agent is an unfractionated heparin or a low molecular weight heparin.

53. The method of claim 52, wherein the low molecular weight heparin is selected from the group consisting of: dalteparin, enoxaparin, fondaparinux, reviparin, and tinzaperin.

54. The method of any one of the preceding claims wherein the PF4-interacting heparinoid is administered parenterally.

55. The method of claim 54, wherein the PF4-interacting heparinoid is administered intravenously.

56. The method of claim 55, wherein the PF4-interacting heparinoid is administered as one or more bolus injections.

57. The method according to claim 56, wherein the one or more bolus injections are administered at a dose of about 1 mg/kg to about 25 mg/kg, about 1 mg/kg to

about 10 mg/kg, about 1 mg/kg to about 5 mg/kg, about 2 mg/kg to about 4 mg/kg.

58. The method of claim 55, wherein the PF4-interacting heparinoid is administered as a continuous infusion.

59. The method of claim 58, wherein the continuous infusion is administered at a dose of about 0.1 mg/kg/hr to about 2.5 mg/kg/hr, about 0.2 mg/kg/hr to about 2 mg/kg/hr, about 0.3 mg/kg/hr to about 1.5 mg/kg/hr, or about 0.3 mg/kg/hr to about 0.5 mg/kg/hr.

60. The method of claim 55, wherein the PF4-interacting heparinoid is administered as a bolus followed or preceeded by a continuous infusion.

61. The method of claim 60, wherein the bolus injection is administered at a dose of about 1 mg/kg to about 25 mg/kg, about 1 mg/kg to about 10 mg/kg, about 1 mg/kg to about 5 mg/kg, about 2 mg/kg to about 4 mg/kg and the continuous infusion is administered at a dose of about 0.1 mg/kg/hr to about 2.5 mg/kg/hr, about 0.2 mg/kg/hr to about 2 mg/kg/hr, about 0.3 mg/kg/hr to about 1.5 mg/kg/hr, or about 0.3 mg/kg/hr to about 0.5 mg/kg/hr.

62. The method of claim 58 or 60, wherein the continuous infusion is carried out for a period of about 0.5 hours, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 16 hours, about 20 hours, about 24 hours, about 36 hours, about 48 hours, about 1 day, about 2, days, or about 3 days.

63. The method of claim 54, wherein the PF4-interacting heparinoid is administered subcutaneously.

64. The method according to any one of the preceding claims, wherein the PF4-interacting heparinoid is administered concurrently with the patient treatment regimen.

65. The method according to any one of claims 1 to 63, wherein the PF4-interacting heparinoid is administered sequentially or separately with the patient treatment regimen.

66. The method according to claim 65, wherein the PF4-interacting heparinoid is administered sequentially before, after, or both before and after the patient treatment regimen.

67. The method according to claim 65, wherein the PF4-interacting heparinoid is administered separately before, after, or both before and after the patient treatment regimen.

68. The method according to any one of claims 65 to 67, further comprising administering the PF4-interacting heparinoid concurrently with the patient treatment regimen.

69. A method of promoting thrombopoiesis in a human subject comprising:

administering an effective amount of a PF4-interacting heparinoid to the subject.

70. The method of claim 69, wherein the subject is thrombocytopenic.

71. The method of claim 70, wherein the subject is diagnosed with thrombocytopenia selected from immune-mediate thrombocytopenia, drug-induced thrombocytopenia, or radiation-induced thrombocytopenia.

72. The method of claim 71, wherein the subject is diagnosed with immune thrombocytopenic purpura.

73. The method of claim 71, wherein the subject is diagnosed with radiation-induced thrombocytopenia.

74. The method of claim 73, wherein the radiation-induced thrombocytopenia is caused by exposure to ionizing radiation, optionally non-therapeutic exposure to ionizing radiation.

75. The method of claim 69, wherein the subject is non-thrombocytopenic.

76. A method of promoting neutrophil production in a human subject comprising:

administering an effective amount of a PF4-interacting heparinoid to the subject.

77. The method of claim 76, wherein the subject is neutropenic.

78. The method of claim 77, wherein the subject is diagnosed with neutropenia selected from immune-mediate neutropenia, drug-induced neutropenia, or radiation-induced neutropenia.

79. The method of claim 78, wherein the subject is diagnosed with radiation-induced neutropenia.

80. The method of claim 79, wherein the radiation-induced neutropenia is caused by exposure to ionizing radiation, optionally non-therapeutic exposure to ionizing radiation.

81. The method of claim 76, wherein the subject is non-neutropenic.

82. A method of increasing efficacy of a patient treatment regimen having a myelosuppressive effect comprising:

administering a therapeutically effective amount of a PF4-interacting heparinoid to a patient as an adjunct to the patient treatment regimen having a myelosuppressive side effect, without reducing the dose and/or dosage frequency of the patient treatment regimen as compared to a reference treatment.

83. The method of claim 82, which further comprises administering a dose of the patient treatment regimen higher than the dose administered when the patient treatment regimen is administered in the absence of adjunctive administration of a PF4-interacting heparinoid.

84. The method of claim 82 or 83, which further comprises administering an amount of a PF4-interacting heparinoid sufficient to maintain platelet levels above levels that indicate grade 3 or grade 4 thrombocytopenia.

85. The method of claim 82 or 83, which further comprises:

determining an initial platelet count in a blood sample from a human patient and administering an amount of a PF4-interacting heparinoid effective to raise the patient's platelet count above a threshold level below which therapy with patient treatment regimen having a myelosuppressive side effect is contraindicated.

86. The method of claim 82 or 83, which further comprises:

administering an amount of a PF4-interacting heparinoid sufficient to maintain neutrophil levels above levels that indicate grade 3 or grade 4 neutropenia.

87. The method of claim 82 or 83, which further comprises:

determining an initial neutrophil count in a blood sample from a human patient and administering an amount of a PF4-interacting heparinoid effective to raise the patient's neutrophil count above a threshold level below which therapy with patient treatment regimen having a myelosuppressive side effect is contraindicated.

88. The method according to any one of claims 82 to 87, which further comprises administering adjunctive to the PF4-interacting heparinoid one or more agents or therapies, wherein the agents or therapies are anti-neutropenic, anti-thrombocytopenic, or anticoagulant.

89. The method according to any one of the preceding claims, wherein the PF4-interacting heparinoid is capable of binding PF4.

90. The method according to any one of the preceding claims, wherein the PF4-interacting heparinoid has an average molecular weight of about 8 kDa to about 15 kDa, of about 11 kDa to about 14 kDa, or of about 11 kDa to about 13 kDa.

91. The method according to any one of the preceding claims, wherein the PF4-interacting heparinoid is substantially non-anti-coagulant.

92. The method according to any one of the preceding claims, wherein the PF4-interacting heparinoid is substantially desulfated at the 2-O position or the 3-O position.

93. The method according to any one of the preceding claims, wherein the PF4-interacting heparinoid is substantially 2-O, 3-O desulfated.

94. The method of any one of the preceding claims, wherein the patient is a mammal.

95. The method of claim 94, wherein the mammal is a human.

96. The method of claim 95, wherein the human is an adult or a child.

97. The method of any one of claims 94 to 96, wherein the patient is diagnosed with cancer.

98. The method of claim 97, wherein the cancer is pancreatic cancer, ovarian cancer, breast cancer, colorectal cancer, esophageal cancer, lymphoma, liver cancer, osteosarcoma or leukemia.

99. The method of claim 97, wherein the patient has an elevated level of platelet factor 4 (PF4).

100. The method of claim 99, wherein the PF4 level in serum is elevated.

101. The method of claim 99, wherein the PF4 level in platelets is elevated.

102. The method of claim 99, wherein the cancer is pancreatic cancer, colorectal cancer, osteosarcoma or leukemia.

103. The method of any one of claims 94 to 96, wherein the patient is diagnosed with an autoimmune disease.

104. The method of claim 103, wherein the autoimmune disease is selected from rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis.

105. The method of any one of claims 94 to 96, wherein the patient has a condition or disease causing impaired liver function.

106. The method of claim 105, wherein the patient is diagnosed with liver cancer, viral hepatitis, or liver cirrhosis.

107. The method of any one of claims 94 to 96, wherein the patient has an elevated level of PF4.

108. The method of claim 107, wherein the PF4 level in serum is elevated.

109. The method of claim 107, wherein the PF4 level in platelets is elevated.

110. The method of any one of claims 94 to 96, wherein the patient has antibodies against a heparin-PF4 complex.

111. A method of treating a patient with cancer, comprising:

administering ODSH adjunctive to a myelosuppressive chemotherapeutic treatment regimen to said patient.

112. The method of claim 111, wherein the myelosuppressive chemotherapeutic treatment regimen comprises a taxane.

113. The method of claim 112, wherein the taxane is taxol.

114. The method of claim 113, wherein the taxol is paclitaxel.

115. The method of claim 114, wherein the paclitaxel is nab-paclitaxel.

116. The method of any one of claims 111 to 115, wherein the patient has pancreatic cancer, ovarian cancer, uterine cancer, breast cancer, metastatic breast cancer, recurrent breast cancer, head and neck cancer, bladder cancer, urothelial cancer, lung cancer, colorectal cancer, gastric cancer, esophageal cancer, lymphoma, liver cancer, melanoma, prostate cancer, osteosarcoma, leukemia, acute myelogenous leukemia or pediatric acute lymphoblastic leukemia.

117. In a method of treating cancer by administering one or more chemotherapeutic agents having a myelosuppressive side effect, the improvement comprising:

adjunctively administering an effective amount of a PF4-interacting heparinoid to a patient in need thereof.

118. The method of claim 117, wherein the one or more chemotherapeutic agents comprises a taxane.

119. The method of claim 118, wherein the taxane is taxol.

120. The method of claim 119, wherein the taxol is paclitaxel.

121. The method of claim 120, wherein the paclitaxel is nab-paclitaxel.

122. The method of any one of claims 117 to 121, wherein the patient has pancreatic cancer, ovarian cancer, uterine cancer, breast cancer, metastatic breast cancer, recurrent breast cancer, head and neck cancer, bladder cancer, urothelial cancer, lung cancer, colorectal cancer, gastric cancer, esophageal cancer, lymphoma, liver cancer, melanoma, prostate cancer, osteosarcoma, leukemia, acute myelogenous leukemia or pediatric acute lymphoblastic leukemia.

123. The method of any one of claims 117 to 122, wherein the PF4-interacting heparinoid is ODSH.

124. The method of claim 111, wherein the myelosuppressive treatment regimen is a regimen suitable for treating acute myelogenous leukemia (AML).

125. The method of claim 124, wherein the regimen suitable for treating AML comprises induction chemotherapy.

126. The method of claim 124 or 125, wherein the regimen suitable for treating AML comprises consolidation chemotherapy.

127. The method of any one of claims 124, 125, and 126, wherein the myelosuppressive treatment regimen comprises cytarabine and, optionally, an anthracycline.

128. The method of any one of claims 111 and 124 to 127, wherein the patient has AML.

129. The method of claim 117, wherein the one or more chemotherapeutic agents having a myelosuppressive effect is part of a regimen for treating AML.

130. The method of claim 129, wherein the regimen for treating AML comprises induction chemotherapy.

131. The method of claim 129 or 130, wherein the regimen for treating AML comprises consolidation chemotherapy.

132. The method of any one of claims 129-131, wherein the regimen for treating AML comprises cytarabine.

133. The method of claim 129 or 130, wherein the regimen for treating AML comprises an anthracycline.

134. The method of any one of claims 128 to 133, wherein the PF4-interacting heparinoid is ODSH.

What is claimed is:

1. Use of a Platelet Factor-4 (PF-4) interacting heparinoid in the manufacture of a medicament for treating cancer in a subject, wherein the medicament is adjunctively administered with a myelosuppressive treatment regimen and wherein the PF-4 interacting heparinoid is substantially non-anticoagulating.

2. The use according to claim 1, wherein the myelosuppressive treatment regimen induces thrombocytopenia and/or neutropenia.

3. The use according to claim 1 or 2, wherein the myelosuppressive treatment regimen comprises an antineoplastic treatment regimen.

4. The use according to claim 3, wherein the antineoplastic treatment regimen comprises one or more chemotherapeutic agents.

5. The use according to claim 4, wherein the one or more chemotherapeutic agents comprises gemcitabine and/or nab-paclitaxel.

6. The use according to claim 3, wherein the antineoplastic treatment regimen comprises radiation therapy.

7. The use according to any of claims 1 to 6, wherein the cancer is pancreatic cancer, ovarian cancer, uterine cancer, breast cancer, metastatic breast cancer, recurrent breast cancer, head and neck cancer, bladder cancer, urothelial cancer, lung cancer, colorectal cancer, gastric cancer, esophageal cancer, lymphoma, liver cancer, melanoma, prostate cancer, osteosarcoma, leukemia, acute myelogenous leukemia or pediatric acute lymphoblastic leukemia.

8. The use according to claim 7, wherein the cancer is acute myelogenous leukemia (AML) and the myelosuppressive treatment regimen is a regimen suitable for treating the acute myelogenous leukemia (AML).

9. The use according to claim 8, wherein the myelosuppressive treatment regimen comprises cytarabine and/or anthracycline.

10. The use of any of claims 1 to 9, wherein the subject is a human.

11. The use according to any of claims 1 to 10, wherein the PF4-interacting heparinoid is substantially desulfated at the 2-O position and/or the 3-O position.

12. The use according to claim 11, wherein the PF4-interacting heparinoid is at least 85%, 90%, or 95% desulfated at the 2-O position.

13. The use according to claim 11, wherein the PF4-interacting heparinoid is at least 85%, 90%, or 95% desulfated at the 3-O position.

14. The use according to any of claims 1 to 10, wherein the PF4-interacting heparinoid is substantially desulfated at each of the 2-O-and 3-O positions.

15. The use according to claim 14, wherein the PF4 interacting heparinoid is at least 85%, 90%, or 95% desulfated at each of the 2-O and 3-O positions.

16. The use according to any of claims 1 to 15, wherein the PF4-interacting heparinoid has an average molecular weight of about 8 kDa to about 15 kDa, about 11 kDa to about 14 kDa, or about 11 kDa to about 13 kDa.

17. The use according to any of claims 1 to 16, wherein the PF4-interacting heparinoid is ODSH.

18. The use according to any of claims 1 to17, wherein the medicament is for administration parenterally or subcutaneously.

19. The use according to claim 18, wherein the medicament is for administration intravenously.

20. The use according to claim 18 or 19, wherein the medicament is for administration as one or more bolus injections.

21. The use according to claim 20, wherein the one or more bolus injections are administered at a dose of about 1 mg/kg to about 25 mg/kg, about 1 mg/kg to about 10 mg/kg, about 1 mg/kg to about 5 mg/kg, or about 2 mg/kg to about 4 mg/kg.

22. The use according to any of claims 1 to 21, wherein the medicament is for administration concurrently, sequentially, and/or separately with the myelosuppressive treatment regimen.

23. The use according to claim 22, wherein the medicament is for administration sequentially before, and/or after the myelosuppressive treatment regimen, or for administration separately before and/or after the myelosuppressive treatment regimen.

24. Use of a Platelet Factor-4 (PF-4) interacting heparinoid in the preparation of a medicament for use in preventing or treating radiation-induced thrombocytopenia in a subject, wherein the subject is exposed to ionizing radiation and wherein the PF4-interating heparinoid is substantially non-anticoagulating.

25. The use according to claim 24, wherein the ionizing radiation is part of a patient treatment regimen or is not part of a patient treatment regimen.

26. Use of a Platelet Factor-4 (PF-4) interacting heparinoid in the preparation of a medicament for treating thrombocytopenia in a subject, wherein the PF4-interacting heparinoid is substantially non-anticoagulating.

27. Use of a Platelet Factor-4 (PF-4) interacting heparinoid in the preparation of a medicament for treating neutropenia in a subject, wherein the PF-4 interacting heparinoid is substantially non-anticoagulating.