THERAPEUTIC USE OF A TLR AGONIST AND COMBINATION THERAPY

CROSS-REFERENCE TO RELATED APPLICATION

[01] This application claims priority to, and the benefit of, U.S. provisional application No. 61/388,953, filed October 1, 2010, U.S. provisional application No. 61/388,967, filed October 1, 2010, and U.S. provisional application No. 61/390,447, filed October 6, 2010, the contents of which are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

[02] The present invention is directed to formulations of a TLR agonist, preferably a TLR8 agonist, and a combination therapy comprising administration of a TLR8 agonist and an anti-cancer agent for use in the treatment of cancer.

BACKGROUND OF THE INVENTION

[03] Stimulation of the immune system, which includes stimulation of either or both innate immunity and adaptive immunity, is a complex phenomenon that can result in either protective or adverse physiologic outcomes for the host. In recent years there has been increased interest in the mechanisms underlying innate immunity, which is believed to initiate and support adaptive immunity. This interest has been fueled in part by the recent discovery of a family of highly conserved pattern recognition receptor proteins known as Toll-like receptors (TLRs) believed to be involved in innate immunity as receptors for pathogen associated molecular patterns (PAMPs). Compositions and methods useful for modulating innate immunity are therefore of great interest, as they may affect therapeutic approaches to conditions involving cancer, infectious disease, autoimmunity, inflammation, allergy, asthma, graft rejection, graft versus host disease (GvHD), and immunodeficiency.

[04] Toll-like receptors (TLRs) are a family of type I transmembrane proteins whose in vivo activation initiates an innate immune response involving specific cytokines, chemokines and growth factors. While all TLRs can activate certain intracellular signaling molecules such as nuclear factor kappa beta (NF-kB) and mitogen activated protein kinases (MAP kinases), the specific set of cytokines and chemokines released appears to be unique for each TLR. TLR7, 8,

or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

[0119] All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same.

[0120] The invention is further defined by reference to the following examples, which are not meant to limit the scope of the present invention. It will be apparent to those skilled in the art that many modifications, both to the materials and methods, may be practiced without departing from the purpose and interest of the invention.

1.5 Examples

[0121] Example 1: TLR8 Agonist and Doxil chemotherapy potently activate human antitumor immune response in a human immune system mouse model

[0122] Because of differences between mouse and human immune systems, many of the effects of immunomodulatory drugs cannot be fully studied in syngeneic mouse models. A novel tumor-bearing mouse model with human immune system (HIS) was generated to study interactions between chemotherapy and immune modulatory therapy. The individual effects and the interactions between doxorubicin, a drug which induces immunogenic tumor cell death and activates antigen-presenting cells, and VTX-2337, a TLR8 agonist, which induces potent activation and type 1 polarization of human myeloid DCs were tested and showed reduced activity on murine leukocytes. Nod/SCID/ILRγc knock out (NSG) mice were inoculated with human CD34+ cord blood cells from HLA-A2+ human donors; transplanted s.c. with human HLA-A2+ OVCAR5 ovarian cancer tumors; and treated with pegylated liposomal doxorubicin (Doxil or PLD); VTX-2337; or the two agents in combination. NSG-HIS mice exhibited a full human hematopoietic system, including human monocytes, macrophages and plasmacytoid and myeloid DCs as well as T cell subsets. In NSG-HIS mice, VTX-2337 induced dose-dependent activation of human CD14+ and CD11c+ cells in vivo within 6 hrs. Transient, dose-dependent upregulation of human Th1 cytokines but also IL-10 was observed in the plasma of mice treated

[0171] In sum, it was observed that weekly subcutaneous administration of the novel TLR8 agonist VTX-2337 was generally safe and well tolerated; plasma levels of VTX-2337 and PD responses to VTX-2337 increased in a dose dependent manner; and that subcutaneous administration of VTX-2337 stimulated the production of multiple inflammatory mediators including cytokines and chemokines consistent with activation of an innate immune response.

INCORPORATION BY REFERENCE

[0172] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[0173] The invention can be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

What is claimed is

1. A pharmaceutical composition for use in a combinational therapy of treating cancer comprising a formulation including a benzo[b]azepine TLR8 agonist and a pharmaceutically acceptable carrier, wherein the combinational therapy further comprises one or more additional treatment modalities.

2. The pharmaceutical composition of claim 1, wherein the TLR8 agonist is 2-amino-N,N-dipropyl-8-(4-(pyrrolidine-1-carbonyl)phenyl)-3H-benzo[b]azepine-4-carboxamide or a pharmaceutically acceptable salt thereof.

3. The pharmaceutical composition of claim 1 or 2, wherein the cancer is a solid cancer selected from the group consisting of ovarian cancer, breast cancer, head and neck cancer, renal cancer, bladder cancer, hepatocellular cancer, colorectal cancer, lymphoma, and any combination thereof.

4. The pharmaceutical composition of any of claims 1-3, wherein the one or more additional treatment modalities comprise administering an effective amount of an anti-cancer agent.

5. The pharmaceutical composition of any of claims 1-4, wherein the anti-cancer agent is doxorubicin, gemcitabine, cyclophosphamide, or a pharmaceutically acceptable salt thereof.

6. The pharmaceutical composition of any of claims 1-5, wherein the TLR8 agonist and the anti-cancer agent are administered concurrently or sequentially.

7. The pharmaceutical composition of any of claims 1-5, wherein the TLR8 agonist and the anti-cancer agent are administered separately by 5 days.

8. The pharmaceutical composition of claim 1 or 2, wherein the cancer is ovarian cancer, and the anti-cancer agent is a pegylated liposomal form of doxorubicin.

9. The pharmaceutical composition of claim 8, wherein the doxorubicin is administered intravenously.

10. The pharmaceutical composition of claim 1 or 2, wherein the cancer is breast cancer, and the anti-cancer agent is gemcitabine or cyclophosphamide.

11. The pharmaceutical composition of any of claims 1-10, wherein the subject is a mammal.

12. The pharmaceutical composition of any of claims 1-11, wherein the formulation is injected by a subcutaneous route, an intravenous route, an intramuscular route, or transdermal route.

13. The pharmaceutical composition of any of claims 1-11, wherein the formulation is administered subcutaneously.

14. The pharmaceutical composition of any of claims 1-13, wherein the one or more additional treatment modalities are selected from a chemotherapeutic agent, a cytokine, an antibody, a hormonal therapy, and a radiation therapy.

15. The pharmaceutical composition of any of claims 1-14, wherein the TLR8 agonist is dosed at a concentration from about 0.02 to about 10 mg/kg or from about 0.04 to about 5 mg/kg body weight of the subject.

16. The pharmaceutical composition of any of claims 1-14, wherein the TLR8 agonist is dosed at a concentration of about 0.02 mg/kg, about 0.05 mg/kg, about 0.075 mg/kg, about 0.1 mg/ kg, about 0.5 mg/kg, about 1 mg/kg, about 2 mg/kg, or about 5 mg/kg body weight of the subject.

17. The pharmaceutical composition of any of claims 1-14, wherein the TLR8 agonist is dosed at a concentration of from about 2.5 to 3.5 mg/m^2 of body surface area of the subject.

18. The pharmaceutical composition of any of claims 1-14, wherein the TLR8 agonist is dosed at a concentration of between 0.002 mg/kg and 0.006 mg/kg body weight of the subject.

19. The pharmaceutical composition of any of claims 1-18, wherein the TLR8 agonist is administered to the subject on a weekly or biweekly basis.

20. The pharmaceutical composition of any of claims 4-9 and 11-19, wherein doxorubicin is administered at a dose of from about 0.02 to 10 mg/kg of body weight or from about 0.04 to 5 mg/kg of body weight of the subject.

21. The pharmaceutical composition of any of claims 1-20, wherein the formulation further comprises about from 1% to about 30%, from about 5% to 15%, or from about 5% to about10% weight/volume of a cyclodextrin.

22. The pharmaceutical composition of any of claims 1-20, wherein the formulation further comprises about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, or about 30% weight/volume of a cyclodextrin.

23. The pharmaceutical composition of any of claims 1-20, wherein the formulation further comprises about 15% w/v of a cyclodextrin.

24. The pharmaceutical composition of any of claims 21-23, wherein the cyclodextrin is a beta-cyclodextrin.

25. The pharmaceutical composition of claim 1, wherein the cancer is lymphoma, and the one or more treatment modalities comprises a radiation therapy.

26. The pharmaceutical composition of claim 25, wherein the lymphoma is Non-Hodgkin's lymphoma.

27. A pharmaceutical composition for treating cancer comprising a benzo[b]azepine TLR8 agonist at a dose between 0.002 mg/kg/week and 0.006 mg/kg/week.

28. The pharmaceutical composition of claim 27, wherein the benzo[b]azepine TLR8 agonist is 2-amino-N,N-dipropyl-8-(4-(pyrrolidine-1-carbonyl)phenyl)-3H-benzo[b]azepine-4-carboxamide.

29. The pharmaceutical composition of claim 27, wherein the TLR8 agonist is 2-amino-N,N-dipropyl-8-(4-(pyrrolidine-1-carbonyl)phenyl)-3H-benzo[b]azepine-4-carboxamide or a pharmaceutically acceptable salt thereof.

30. A pharmaceutical composition comprising an anti-cancer agent and a formulation of a benzo[b]azepine TLR8 agonist.

31. The pharmaceutical composition of claim 30, wherein the TLR8 agonist is 2-amino-N,N-dipropyl-8-(4-(pyrrolidine-1-carbonyl)phenyl)-3H-benzo[b]azepine-4-carboxamide or a pharmaceutically acceptable salt thereof.

32. The pharmaceutical composition of claim 30, wherein the anti-cancer agent is doxorubicin, gemcitabine, cyclophosphamide, or a pharmaceutically acceptable salt thereof.

33. The pharmaceutical composition of claim 32, wherein doxorubicin is in a pegylated liposomal form.

34. The pharmaceutical composition of claim 30, wherein the formulation has a concentration from about 0.01 to 50 mg/ml of the TLR8 agonist.

35. The pharmaceutical composition of claim 30, wherein the formulation has a concentration from about 0.5 mg/ml to about 50 mg/ml, from about 1 mg/ml to about 40 mg/ml, or from about 2 mg/ml to about 15 mg/ml of the TLR8 agonist.

36. The pharmaceutical composition of claim 30, wherein the formulation has a concentration from about 0.5 mg/ml to about 10 mg/ml, from about 0.5 mg/ml to about 8 mg/ml, from about 0.5 mg/ml to about 15 mg/ml, from about 0.5 mg/ml to about 4 mg/ml, or from about 0.5 mg/ml to about 2 mg/ml of the TLR8 agonist.

37. The pharmaceutical composition of claim 30, wherein the formulation has a concentration of about 0.01 mg/ml, about 0.5 mg/ml, about 1 mg/ml, about 2 mg/ml, about 4 mg/ml, about 15 mg/ml, about 8 mg/ml, about 10 mg/ml, about 15 mg/ml, about 20 mg/ml, about 25 mg/ml, about 30 mg/ml, about 40 mg/ml, or about 50 mg/ml of the TLR8 agonist.

38. The pharmaceutical composition of claim 30, wherein the formulation further comprises about from 1% to about 30%, from about 5% to 15%, or from about 5% to about10% weight/volume of a cyclodextrin.

39. The pharmaceutical composition of claim 30, wherein the formulation further comprises about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, or about 30% weight/volume of a cyclodextrin.

40. The pharmaceutical composition of claim 30, wherein the formulation further comprises about 15% w/v of a cyclodextrin.

41. The pharmaceutical composition of any of claims 38-40, wherein the cyclodextrin is a beta-cyclodextrin.

42. The pharmaceutical composition of claim 41, wherein the beta-cyclodextrin is sulfobutyl ether beta-cyclodextrin.

43. A pharmaceutical pack or kit comprising one or more containers filled with a liquid or lyophilized form a pharmaceutical composition of any of claims 30-42.

44. The pack or kit of claim 43, wherein the pharmaceutical composition is in aqueous formulation.

45. A pharmaceutical pack or kit comprising one or more first containers filled with a liquid or lyophilized form a formulation of a benzo[b]azepine TLR8 agonist and one or more second containers filled with an anti-cancer agent.

46. The pack or kit of claim 45, wherein the TLR8 agonist is 2-amino-N,N-dipropyl-8-(4-(pyrrolidine-1-carbonyl)phenyl)-3H-benzo[b]azepine-4-carboxamide or a pharmaceutically acceptable salt thereof.

47. The pack or kit of claim 45, wherein the anti-cancer agent is doxorubicin, gemcitabine, cyclophosphamide, or a pharmaceutically acceptable salt thereof.

Claims

1. A pharmaceutical composition for use in a combinational therapy of treating cancer in a subject, comprising a formulation including a benzo[b]azepine TLR8 agonist and a pharmaceutically acceptable carrier, wherein the combinational therapy further comprises an effective amount of doxorubicin, and the TLR8 agonist is 2-amino-N,N-dipropyl-8-(4-(pyrrolidine-1-carbonyl)phenyl)-3H-benzo[b]azepine-4-carboxamide or a pharmaceutically acceptable salt thereof.

2. The pharmaceutical composition for use of claim 1, wherein the cancer is a solid cancer selected from the group consisting of ovarian cancer, breast cancer, head and neck cancer, renal cancer, bladder cancer, hepatocellular cancer, colorectal cancer, lymphoma, and any combination thereof.

3. The pharmaceutical composition for use of any of claims 1-2, wherein the cancer is ovarian cancer.

4. The pharmaceutical composition for use of any of claims 1-3, wherein the TLR8 agonist formulation and the doxorubicin are administered concurrently or sequentially.

5. The pharmaceutical composition for use of any of claims 1-3, wherein the TLR8 agonist formulation and the doxorubicin are administered sequentially and the administrations of the TLR8 agonist formulation and the doxorubicin are separated by 5 days.

6. The pharmaceutical composition for use of claim 1, wherein the cancer is ovarian cancer, and the doxorubicin is a pegylated liposomal form of doxorubicin.

7. The pharmaceutical composition for use of claim 6, wherein the doxorubicin is administered intravenously.

8. The pharmaceutical composition for use of any of claims 1-7, wherein the subject is a mammal.

9. The pharmaceutical composition for use of any of claims 1-8, wherein the TLR8 agonist formulation is injected by a subcutaneous route, an intravenous route, an intramuscular route, or transdermal route.

10. The pharmaceutical composition for use of any of claims 1-8, wherein the TLR8 agonist formulation is administered subcutaneously.

11. The pharmaceutical composition for use of any of claims 1-10, wherein the TLR8 agonist formulation is dosed to provide a concentration of the TLR8 agonist of from 0.02 to 10 mg/kg or from 0.04 to 5 mg/kg body weight of the subject.

12. The pharmaceutical composition for use of any of claims 1-10, wherein the TLR8 agonist formulation is dosed to provide a concentration of the TLR8 agonist of 0.02 mg/kg, 0.05 mg/kg, 0.075 mg/kg, 0.1 mg/ kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, or 5 mg/kg body weight of the subject.

13. The pharmaceutical composition for use of any of claims 1-10, wherein the TLR8 agonist formulation is dosed to provide a concentration of the TLR8 agonist of from 2.5 to 3.5 mg/m^2 of body surface area of the subject.

14. The pharmaceutical composition for use of any of claims 1-10, wherein the TLR8 agonist formulation is dosed to provide a concentration of the TLR8 agonist of between 0.002 mg/kg and 0.006 mg/kg body weight of the subject.

15. The pharmaceutical composition for use of any of claims 1-14, wherein the TLR8 agonist formulation is administered to the subject on a weekly or biweekly basis.

16. The pharmaceutical composition for use of any of claims 3-15, wherein the doxorubicin is administered at a dose of from 0.02 to 10 mg/kg of body weight or from 0.04 to 5 mg/kg of body weight of the subject.

17. The pharmaceutical composition for use of any of claims 1-16, wherein the TLR8 agonist formulation further comprises from 1% to 30%, from 5% to 15%, or from 5% to % weight/volume of a cyclodextrin.

18. The pharmaceutical composition for use of any of claims 1-16, wherein the TLR8 agonist formulation further comprises about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, or about 30% weight/volume of a cyclodextrin.

19. The pharmaceutical composition for use of any of claims 1-16, wherein the TLR8 agonist formulation further comprises about 15% w/v of a cyclodextrin.

20. The pharmaceutical composition for use of any of claims 17-19, wherein the cyclodextrin is a beta-cyclodextrin.

21. The pharmaceutical composition for use of claim 20, wherein the cyclodextrin is a sulfobutyl ether β-cyclodextrin.

22. The pharmaceutical composition for use of any of claims 1-21, wherein the doxorubicin is in a pegylated liposomal form.

23. The pharmaceutical composition for use of any of claims 1-22, wherein the TLR8 agonist formulation contains from 0.01 to 50 mg/ml of the TLR8 agonist.

24. The pharmaceutical composition for use of any of claims 1-22, wherein the TLR8 agonist formulation contains from 0.5 mg/ml to 50 mg/ml, from 1 mg/ml to 40 mg/ml, or from 2 mg/ml to 15 mg/ml of the TLR8 agonist.

25. The pharmaceutical composition for use of any of claims 1-22, wherein the TLR8 agonist formulation contains from 0.5 mg/ml to 10 mg/ml, from 0.5 mg/ml to 8 mg/ml, from 0.5 mg/ml to 15 mg/ml, from 0.5 mg/ml to 4 mg/ml, or from 0.5 mg/ml to 2 mg/ml of the TLR8 agonist.

26. The pharmaceutical composition for use of any of claims 1-22, wherein the TLR8 agonist formulation contains about 0.01 mg/ml, about 0.5 mg/ml, about 1 mg/ml, about 2 mg/ml, about 4 mg/ml, about 15 mg/ml, about 8 mg/ml, about 10 mg/ml, about 15 mg/ml, about 20 mg/ml, about 25 mg/ml, about 30 mg/ml, about 40 mg/ml, or about 50 mg/ml of the TLR8 agonist.

27. A pharmaceutical pack or kit comprising one or more first containers filled with a liquid or lyophilized form of a formulation of a benzo[b]azepine TLR8 agonist and one or more second containers filled with doxorubicin, wherein the TLR8 agonist is 2-amino-N,N-dipropyl-8-(4-

(pyrrolidine-1-carbonyl)phenyl)-3H-benzo[b]azepine-4-carboxamide or a pharmaceutically acceptable salt thereof.

28. The pharmaceutical pack or kit of claim 27, wherein the TLR8 agonist formulation is an aqueous formulation.

29. The pharmaceutical pack or kit of claim 27 or 28, wherein the TLR8 agonist formulation contains from 0.01 to 50 mg/ml of the TLR8 agonist.

30. The pharmaceutical pack or kit of any of claims 27-29, wherein the doxorubicin is in a pharmaceutically acceptable salt form.

31. The pharmaceutical pack or kit of any of claims 27-30, wherein the doxorubicin is in a pegylated liposomal form.