There is a need to provide therapeutic agents and methods for treating AML that overcome, or at least ameliorate, one or more of the disadvantages described above.

There is a need to provide a formulation of the therapeutic agents for treating AML that can be produced easily, and that is in a form that is suitable for administration to a human patient while retaining efficacy of the agent.

## Summary

~~According to a first aspect~~In one embodiment, there is provided a method of treating cancer comprising administering an agonist of CD137 ligand (CD137L) to a subject in need thereof.

Advantageously, the agonist is capable of crosslinking CD137L to initiate reverse CD137L signaling in malignant cells, resulting in a two- fold therapeutic effect: (a) increased differentiation of malignant cells which reduces or prevents their proliferative potential thereby slowing tumour progression, and (b) inducing differentiation of the malignant cells to cells with DC-like properties which results in tumour cells with enhanced T cell-activating abilities.

Advantageously, the agonist is capable of inducing differentiation of malignant cells from all AML subtypes, including subtypes Ml, M2, M5a and M5b, compared to conventional therapy for AML which only induces differentiation of AML subtype M3 cells.

~~According to a second aspect~~In another embodiment, there is provided an agonist of CD137 ligand (CD137L) for use in treating cancer.

~~According to a third~~ In one aspect, there is provided the use of an agonist of CD137 ligand (CD137L) in the manufacture of a medicament for treating cancer.

~~According to a fourth aspect~~In another embodiment, there is provided a method for inducing differentiation in cancer cells, comprising administering an agonist of CD137 ligand (CD137L) as defined herein to the cancer cells.

In another aspect, there is provided an *in vitro* or *ex vivo* method for inducing differentiation in cancer cells, comprising administering an agonist of CD137 ligand (CD137L) as defined herein to said cancer cells.

~~According to a fifth~~In another aspect, there is provided a method for delivering a therapeutic or diagnostic agent to a cell in need thereof, comprising coupling an agonist of CD137 ligand (CD137L) as defined herein to an agent selected from the group consisting of cytotoxic drugs, radiotherapeutics , chemotherapeutics, enzyme, and a carrier molecule.

In another aspect, there is provided use of an agonist of CD137 ligand (CD137L) as defined herein in the manufacture of a medicament for inducing differentiation in cancer cells.

**Definitions**

The following words and terms used herein shall have the meaning indicated:

The terms "treat" and "treatment" refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. Where the treatment relates to cancer, the term "treatment" also includes: (i) the prevention or inhibition of cancer or cancer recurrence, (ii) the reduction or elimination of symptoms or cancer cells, and (iii) the substantial or complete elimination of the

## Claims

1. The use of an agonist of CD137 ligand (CD137L) in the manufacture of a medicament for treating cancer.

2. The use according to claim 1, wherein the cancer is selected from the group consisting of a myeloid malignancy, a lymphoid malignancy and multiple myeloma.

3. The use according to claim 2, wherein the myeloid malignancy is selected from the group consisting of acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute promyelocytic leukemia (APL), chronic myelomonocytic leukemia (CMML), myelodysplastic syndrome, and juvenile myelomonocytic leukemia.

4. The use according to claim 2, wherein the lymphoid malignancy is selected from the group consisting of chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), B cell lymphoma, and mantle cell lymphoma (MCL).

5. The use according to claim 3, wherein the AML comprises a FAB subtype selected from the group consisting of M0, M1, M2, M3, M4, M5, M5a, M5b, M6 and M7.

6. The use according to any one of claims 1 to 5, wherein the agonist of CD137L is selected from the group consisting of a fragment of CD137 protein, a recombinant CD137 protein, a CD137 fusion protein, an anti-CD137L antibody or a fragment thereof, a peptide, a small molecule, an aptamer, and an antibody mimetic.

7. The use according to claim 6, wherein the recombinant CD137 protein comprises the extracellular domain of CD137 fused to the Fc region of human IgG (CD137-Fc).

8. The use according to claim 6, wherein the anti-CD137L antibody or fragment thereof comprises an agonistic anti-CD137L antibody or a fragment thereof.

9. The use according to any one of claims 1 to 8, wherein the agonist of CD137L is immobilized on a particle.

10. The use according to any one of claims 1 to 9, wherein the agonist of CD137L is coupled to an agent selected from the group consisting of cytotoxic drugs, radiotherapeutics, chemotherapeutics, enzyme, and a carrier molecule.

11. The use according to any one of claims 1 to 10, wherein the cancer is not APL or AML subtype M3.

12. An *in vitro* or *ex vivo* method for inducing differentiation in cancer cells, comprising administering an agonist of CD137 ligand (CD137L) as defined in any one of claims 6-10 to said cancer cells.

13. A method for delivering a therapeutic or diagnostic agent to a cell in need thereof, comprising coupling an agonist of CD137 ligand (CD137L) as defined in any one of claims 6-10 to an agent selected from the group consisting of cytotoxic drugs, radiotherapeutics, chemotherapeutics, enzyme, and a carrier molecule.

14. Use of an agonist of CD137 ligand (CD137L) as defined in any one of claims 6-10 in the manufacture of a medicament for inducing differentiation in cancer cells.

## Claims

1. A method of treating cancer comprising administering an agonist of CD137 ligand (CD137L) to a subject in need thereof.

2. The method according to claim 1, wherein the cancer is selected from the group consisting of a myeloid malignancy, a lymphoid malignancy, and multiple myeloma.

3. The method according to claim 2, wherein the myeloid malignancy is selected from the group consisting of acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute promyelocytic leukemia (APL), chronic myelomonocytic leukemia (CMML), myelodysplastic syndrome, and juvenile myelomonocytic leukemia.

4. The method according to claim 2, wherein the lymphoid malignancy is selected from the group consisting of chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), B cell lymphoma, and mantle cell lymphoma (MCL).

5. The method according to claim 3, wherein the AML comprises a FAB subtype selected from the group consisting of M0, M1, M2, M3, M4, M5, M5a, M5b, M6 and M7.

6. The method according to any one of claims 1 to 5, wherein the agonist of CD137L is selected from the group consisting of a fragment of CD137 protein, a recombinant CD137 protein, a CD137 fusion protein, an anti-CD137L antibody or a fragment thereof, a peptide, a small molecule, an aptamer, and an antibody mimetic.

7. The method according to claim 6, wherein the recombinant CD137 protein comprises the extracellular domain of CD137 fused to the Fc region of human IgG (CD137-Fc).

8. The method according to claim 6, wherein the anti-CD137L antibody or fragment thereof comprises an agonistic anti-CD137L antibody or a fragment thereof.

9. The method according to any one of claims 1 to 8, wherein the agonist of CD137L is immobilized on a particle.

10. The method according to any one of claims 1 to 9, wherein the agonist of CD137L is coupled to an agent selected from the group consisting of cytotoxic drugs, radiotherapeutics, chemotherapeutics, enzyme, and a carrier molecule.

11. The method according to any one of claims 1 to 10, wherein the cancer is not APL or AML subtype M3.

12. An agonist of CD137 ligand (CD137L) for use in treating cancer.

13. The agonist according to claim 12, wherein the cancer is selected from the group consisting of a myeloid malignancy, a lymphoid malignancy and multiple myeloma.

14. The agonist according to claim 13, wherein the myeloid malignancy is selected from the group consisting of acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute promyelocytic leukemia (APL), chronic myelomonocytic leukemia (CMML), myelodysplastic syndrome, and juvenile myelomonocytic leukemia.

15. The agonist according to claim 13, wherein the lymphoid malignancy is selected from the group consisting of chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), B cell lymphoma, and mantle cell lymphoma (MCL).

16. The agonist according to claim 14, wherein the AML comprises a FAB subtype selected from the group consisting of M0, M1, M2, M3, M4, M5, M5a, M5b, M6 and M7.

17. The agonist according to any one of claims 12 to 16, wherein the agonist of CD137L is selected from the group consisting of a fragment of CD137 protein, a recombinant CD137 protein, a CD137 fusion protein, an anti-CD137L antibody or a fragment thereof, a peptide, a small molecule, an aptamer, and an antibody mimetic.

18. The agonist according to claim 17, wherein the recombinant CD137 protein comprises the extracellular domain of CD137 fused to the Fc region of human IgG (CD137-Fc).

19. The agonist according to claim 17, wherein the anti-CD137L antibody or fragment thereof comprises an agonistic anti-CD137L antibody or a fragment thereof.

20. The agonist according to any one of claims 12 to 19, wherein the agonist of CD137L is immobilized on a particle.

21. The agonist according to any one of claims 12 to 20, wherein the agonist of CD137L is coupled to an agent selected from the group consisting of cytotoxic

drugs, radiotherapeutics, chemotherapeutics, enzyme, and a carrier molecule.

22. The agonist according to any one of claims 12 to 21, wherein the cancer is not APL or AML subtype M3.

23. The use of an agonist of CD137 ligand (CD137L) in the manufacture of a medicament for treating cancer.

24. The use according to claim 23, wherein the cancer is selected from the group consisting of a myeloid malignancy, a lymphoid malignancy and multiple myeloma.

25. The use according to claim 24, wherein the myeloid malignancy is selected from the group consisting of acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute promyelocytic leukemia (APL), chronic myelomonocytic leukemia (CMML), myelodysplastic syndrome, and juvenile myelomonocytic leukemia.

26. The use according to claim 24, wherein the lymphoid malignancy is selected from the group consisting of chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), B cell lymphoma, and mantle cell lymphoma (MCL).

27. The use according to claim 25, wherein the AML comprises a FAB subtype selected from the group consisting of M0, M1, M2, M3, M4, M5, M5a, M5b, M6 and M7.

28. The use according to any one of claims 23 to 27, wherein the agonist of CD137L is selected from the group consisting of a fragment of CD137 protein, a recombinant CD137 protein, a CD137 fusion protein, an anti-CD137L antibody or a fragment thereof, a

peptide, a small molecule, an aptamer, and an antibody mimetic.

29. The use according to claim 28, wherein the recombinant CD137 protein comprises the extracellular domain of CD137 fused to the Fc region of human IgG (CD137-Fc).

30. The use according to claim 28, wherein the anti-CD137L antibody or fragment thereof comprises an agonistic anti-CD137L antibody or a fragment thereof.

31. The use according to any one of claims 23 to 30, wherein the agonist of CD137L is immobilized on a particle.

32. The use according to any one of claims 23 to 31, wherein the agonist of CD137L is coupled to an agent selected from the group consisting of cytotoxic drugs, radiotherapeutics, chemotherapeutics, enzyme, and a carrier molecule.

33. The use according to any one of claims 23 to 32, wherein the cancer is not APL or AML subtype M3.

34. A method for inducing differentiation in cancer cells, comprising administering an agonist of CD137 ligand (CD137L) as defined in any one of claims 6-10, 17-21 and 28-32 to said cancer cells.

35. A method for delivering a therapeutic or diagnostic agent to a cell in need thereof, comprising coupling an agonist of CD137 ligand (CD137L) as defined in any one of claims 6-10, 17-21 and 28-32 to an agent selected from the group consisting of cytotoxic drugs, radiotherapeutics, chemotherapeutics, enzyme, and a carrier molecule.