~~In one aspect, there is provided~~Also disclosed is the use of an effective dose of an antibody able to bind to CSF-1R in the manufacture of a medicament for the generation of dendritic cells, wherein said medicament is to be exposed to suitable precursor cells.

In ~~another~~ one aspect, there is provided a method for the generation ex vivo of dendritic cells by exposing suitable precursor cells to an effective dose of an antibody able to bind to CSF-1R, wherein said antibody able to bind to CSF-1R is an antibody that binds to at least one epitope located between position amino acids 20 to 41 of SEQ ID NO: 23.

Disclosure of Invention

The invention is broadly directed to methods for immunomodulation by modulating monocyte differentiation.

The invention is more specifically directed to methods for the generation *in vivo* or *ex vivo* of dendritic cells by

CLAIMS

1. Use of an effective dose of an antibody able to bind to CSF-1R in the manufacture of a medicament for the generation of dendritic cells, wherein said medicament is to be exposed to suitable precursor cells.

2. The use of claim 1 wherein said medicament is for increasing the dendritic cells pool in a patient suffering from conditions associated with undesirable macrophage differentiation and M2 polarization.

3. The use of claim 2, wherein patient is further suffering from conditions associated with CSF-1R activity.

4. The use of any of the preceding claims, wherein said medicament decreases the macrophage M2 pool.

5. The use of any of the preceding claims, wherein said medicament further increases M1-type macrophage pool.

6. The use of any of the preceding claims, wherein said medicament inhibits macrophage MCP-1, IL10 and IL-6 production.

7. The use of any of the preceding claims, wherein said medicament down regulates surface FcγRI (CD64) and FcγRIII (CD16) expression on macrophages.

8. The use of any of the preceding claims, wherein said medicament up-regulates IL-12/IL10 ratio in patient samples, e.g blood samples.

9. The use of any of the preceding claims, wherein said medicament reduces at least one of the followings:

(i) TAM recruitment into tumor;
(ii) at least one macrophage pro-tumoral functions;
(iii) tumor angiogenesis;
(iv) tumor invasion and metastasis;
(v) tumor growth;
(vi) tumor cell proliferation

10. The use of any of the preceding claims, wherein said conditions associated with undesirable M2 polarization is selected in the group consisting of cancer, asthma, allergy and progressive fibrosis diseases.

11. The use of any of the preceding claims, wherein said antibody able to bind to CSF-1R is an antibody that binds to at least one epitope located between position amino acids 20 to 41 of SEQ ID N0:23.

12. The use of any of the preceding claims, wherein said antibody able to bind to CSF-1R is an antibody that binds to one epitope located between position amino acids 20 to 39 of SEQ ID N0:23, to amino acids Asn72, Ser94-Ala95-Ala96, Lys102, Asp131-Pro132-Val133 and Trp159 of SEQ ID N0:23.

13. The use of any of the preceding claims, wherein said antibody able to bind to human CSF-1R is an antibody that does not compete with IL-34 ligand for binding to the CSF-1R receptor.

14. The use of any of the preceding claims, wherein said antibody able to bind to human CSF-1R is an antibody that competes partially with CSF-1 ligand for binding to the CSF-1R receptor.

15. The use of any of the preceding claims, wherein said antibody able to bind to human CSF-1R is an antibody that binds specifically to human CSF-1R, comprising:

(a) a first variable region being defined by the following formula

FR1 - CDR1 – FR2 – CDR2 – FR3 – CDR3 – FR4

wherein:

FR1, FR2, FR3 and FR4 are each framework regions;

CDR1, CDR2 and CDR3 are each complementarity determining regions;

wherein:

CDR1 has at least five consecutive amino acids and is defined in the sequence starting in position 45 and finishing in position 54 of SEQ ID NO:1;

CDR2 has at least five consecutive amino acids and is defined in the sequence starting in position 66 and finishing in position 87 of SEQ ID NO:1; and

CDR3 has at least five consecutive amino acids and is defined in the sequence starting in position 117 and finishing in position 126 of SEQ ID NO:1;

and

(b a second variable region being defined by the following formula

FR1 - CDR1 – FR2 – CDR2 – FR3 – CDR3 – FR4

wherein:

FR1, FR2, FR3 and FR4 are each framework regions;

CDR1, CDR2 and CDR3 are each complementarity determining regions;

wherein:

CDR1 has at least five consecutive amino acids and is defined in the sequence starting in position 44 and finishing in position 56 of SEQ ID NO:2;

CDR2 has at least five consecutive amino acids and is defined in the sequence starting in position 66 and finishing in position 76 of SEQ ID NO:2; and

CDR3 has at least five consecutive amino acids and is defined in the sequence starting in position 109 and finishing in position 117 of SEQ ID NO:2.

16. The use of any of the preceding claims, wherein said antibody able to bind to CSF-1R is comprising (a) an heavy chain consisting in SEQ ID N0:24, and (b) a light chain consisting in SEQ ID N0:28.

17. A method for the generation ex vivo of dendritic cells by exposing suitable precursor cells to an effective dose of an antibody able to bind to CSF-1R.

18. The method of claim 17, wherein said method decreases the macrophage M2 pool.

19. The method of claim 17 or 18, wherein said method further increases M1-type macrophage pool.

20. The method of any one of the claims 17 to 19, wherein said method inhibits macrophage MCP-1, IL10 and IL-6 production.

21. The method of any one of the claims 17 to 20, wherein said method down regulates surface FcγRI (CD64) and FcγRIII (CD16) expression on macrophages.

22. The method of any one of the claims 17 to 21, wherein said method up-regulates IL-12/IL10 ratio in patient samples, e.g blood samples.

23. The method of any one of the claims 17 to 22, wherein said method reduces at least one of the followings:

(i) TAM recruitment into tumor;

(ii) at least one macrophage pro-tumoral functions;
(iii) tumor angiogenesis;
(iv) tumor invasion and metastasis;
(v) tumor growth;
(vi) tumor cell proliferation

24. The method of any one of the claims 17 to 23, wherein said conditions associated with undesirable M2 polarization is selected in the group consisting of cancer, asthma, allergy and progressive fibrosis diseases.

25. The method of any one of the claims 17 to 24, wherein said antibody able to bind to CSF-1R is an antibody that binds to at least one epitope located between position amino acids 20 to 41 of SEQ ID N0:23.

26. The method of any one of the claims 17 to 25, wherein said antibody able to bind to CSF-1R is an antibody that binds to one epitope located between position amino acids 20 to 39 of SEQ ID N0:23, to amino acids Asn72, Ser94-Ala95-Ala96, Lys102, Asp131-Pro132-Val133 and Trp159 of SEQ ID N0:23.

27. The method of any one of the claims 17 to 26, wherein said antibody able to bind to human CSF-1R is an antibody that does not compete with IL-34 ligand for binding to the CSF-1R receptor.

28. The method of any one of the claims 17 to 27, wherein said antibody able to bind to human CSF-1R is an antibody that competes partially with CSF-1 ligand for binding to the CSF-1R receptor.

29. The method of any one of the claims 17 to 28, wherein said antibody able to bind to human CSF-1R is an antibody that binds specifically to human CSF-1R, comprising:
(a) a first variable region being defined by the following formula

FR1 - CDR1 – FR2 – CDR2 – FR3 – CDR3 – FR4

wherein:
FR1, FR2, FR3 and FR4 are each framework regions;
CDR1, CDR2 and CDR3 are each complementarity determining regions;
wherein:
CDR1 has at least five consecutive amino acids and is defined in the sequence starting in position 45 and finishing in position 54 of SEQ ID NO:1;

CDR2 has at least five consecutive amino acids and is defined in the sequence starting in position 66 and finishing in position 87 of SEQ ID NO:1; and
CDR3 has at least five consecutive amino acids and is defined in the sequence starting in position 117 and finishing in position 126 of SEQ ID NO:1;
and
(b a second variable region being defined by the following formula

FR1 - CDR1 – FR2 – CDR2 – FR3 – CDR3 – FR4

wherein:
FR1, FR2, FR3 and FR4 are each framework regions;
CDR1, CDR2 and CDR3 are each complementarity determining regions;
wherein:
CDR1 has at least five consecutive amino acids and is defined in the sequence starting in position 44 and finishing in position 56 of SEQ ID NO:2;
CDR2 has at least five consecutive amino acids and is defined in the sequence starting in position 66 and finishing in position 76 of SEQ ID NO:2; and
CDR3 has at least five consecutive amino acids and is defined in the sequence starting in position 109 and finishing in position 117 of SEQ ID NO:2.

30. The method of any one of the claims 17 to 29, wherein said antibody able to bind to CSF-1R is comprising (a) an heavy chain consisting in SEQ ID N0:24, and (b) a light chain consisting in SEQ ID N0:28.

CLAIMS

1. A method for the generation ex vivo of dendritic cells by exposing suitable precursor cells to an effective dose of an antibody able to bind to CSF-1R, wherein said antibody able to bind to CSF-1R is an antibody that binds to at least one epitope located between position amino acids 20 to 41 of SEQ ID N0:23.

2. The method of claim 1, wherein said method decreases the macrophage M2 pool.

3. The method of claim 1 or 2, wherein said method further increases M1-type macrophage pool.

4. The method of any one of the claims 1 to 3, wherein said method inhibits macrophage MCP-1, IL10 and IL-6 production.

5. The method of any one of the claims 1 to 4, wherein said method down regulates surface FcγRI (CD64) and FcγRIII (CD16) expression on macrophages.

6. The method of any one of the claims 1 to 5, wherein said method up-regulates IL-12/IL10 ratio in patient samples, e.g blood samples.

7. The method of any one of the claims 1 to 6, wherein the dendritic cells generated ex vivo are suitable for reducing at least one of the followings:

(i) TAM recruitment into tumor;
(ii) at least one macrophage pro-tumoral functions;
(iii) tumor angiogenesis;
(iv) tumor invasion and metastasis;
(v) tumor growth;
(vi) tumor cell proliferation

8. The method of any one of the claims 1 to 7, wherein the dendritic cells generated ex vivo are suitable to be used for treatment of a patient suffering from conditions associated with undesirable M2 polarization is selected in the group consisting of cancer, asthma, allergy and progressive fibrosis diseases.

9. The method of any one of the claims 1 to 8, wherein said antibody able to bind to CSF-1R is an antibody that binds to one epitope located between position amino acids 20 to 39 of SEQ ID N0:23, to amino acids Asn72, Ser94-Ala95-Ala96, Lys102, Asp131-Pro132-Val133 and Trp159 of SEQ ID N0:23.

10. The method of any one of the claims 1 to 9, wherein said antibody able to bind to human CSF-1R is an antibody that does not compete with IL-34 ligand for binding to the CSF-1R receptor.

11. The method of any one of the claims 1 to 10, wherein said antibody able to bind to human CSF-1R is an antibody that competes partially with CSF-1 ligand for binding to the CSF-1R receptor.

12. The method of any one of the claims 1 to 11, wherein said antibody able to bind to human CSF-1R is an antibody that binds specifically to human CSF-1R, comprising:

(a) a first variable region being defined by the following formula

FR1 - CDR1 – FR2 – CDR2 – FR3 – CDR3 – FR4

wherein:

FR1, FR2, FR3 and FR4 are each framework regions;

CDR1, CDR2 and CDR3 are each complementarity determining regions;

wherein:

CDR1 has at least five consecutive amino acids and is defined in the sequence starting in position 45 and finishing in position 54 of SEQ ID NO:1;

CDR2 has at least five consecutive amino acids and is defined in the sequence starting in position 66 and finishing in position 87 of SEQ ID NO:1; and

CDR3 has at least five consecutive amino acids and is defined in the sequence starting in position 117 and finishing in position 126 of SEQ ID NO:1;

and

(b a second variable region being defined by the following formula

FR1 - CDR1 – FR2 – CDR2 – FR3 – CDR3 – FR4

wherein:

FR1, FR2, FR3 and FR4 are each framework regions;

CDR1, CDR2 and CDR3 are each complementarity determining regions;

wherein:

CDR1 has at least five consecutive amino acids and is defined in the sequence starting in position 44 and finishing in position 56 of SEQ ID NO:2;

CDR2 has at least five consecutive amino acids and is defined in the sequence starting in

position 66 and finishing in position 76 of SEQ ID NO:2; and
CDR3 has at least five consecutive amino acids and is defined in the sequence starting in position 109 and finishing in position 117 of SEQ ID NO:2.

13. The method of any one of the claims 1 to 12, wherein said antibody able to bind to CSF-1R is comprising (a) an heavy chain consisting in SEQ ID N0:24, and (b) a light chain consisting in SEQ ID N0:28.