CLAIMS

1. An anti-human SIRPa antibody or antigen-binding fragment thereof, which comprises:

a) a heavy chain variable domain comprising HCDR1, HCDR2 and HCDR3, and

b) a light chain variable domain comprising LCDR1, LCDR2 and LCDR3,

wherein:

- HCDR1 comprises or consists of the amino acid sequence set forth in SEQ ID NO: 14,

- HCDR2 comprises or consists of the amino acid sequence set forth in SEQ ID NO: 15 or SEQ ID NO: 16,

- HCDR3 comprises or consists of the amino acid sequence set forth in SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20,

- LCDR1 comprises or consists of the amino acid sequence set forth in SEQ ID NO: 21,

- LCDR2 comprises or consists of the amino acid sequence set forth in SEQ ID NO: 22, and

- LCDR3 comprises or consists of the amino acid sequence set forth in SEQ ID NO: 23.

2. The anti-human SIRPa antibody or antigen-binding fragment thereof according to claim 1 which does not specifically bind to human SIRPg.

3. The anti-human SIRPa antibody or antigen-binding fragment thereof according to claim 1 or 2, wherein:

- the heavy chain variable domain comprises or consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29 and SEQ ID NO: 30, and

- the light chain variable domain comprises or consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 31, SEQ ID NO: 32 and SEQ ID NO: 33,

in particular, wherein:

- the light chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 33, and

- the heavy chain variable domain comprises or consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29 and SEQ ID NO: 30, in particular SEQ ID NO: 29, SEQ ID NO: 30, and more particularly SEQ ID NO: 30.

4. The anti-human SIRPa antibody or antigen-binding fragment thereof according to any one of claims 1 to 3, wherein:

- the heavy chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 24, and

- the light chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 31,

or

- the heavy chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 25, and

- the light chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 32,

or

- the heavy chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 25, and

- the light chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 33,

or

- the heavy chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 26, and

- the light chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 32,

or

- the heavy chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 26, and

- the light chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 33,

or

- the heavy chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 27, and

- the light chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 32,

or

- the heavy chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 27, and

- the light chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 33,

or

- the heavy chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 28, and

- the light chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 32,

or

- the heavy chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 28, and

- the light chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 33,

or

- the heavy chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 29, and

- the light chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 32,

or

- the heavy chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 29, and

- the light chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 33,

or

- the heavy chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 30, and

- the light chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 32,

or

- the heavy chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 30, and

- the light chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 33.

5. The anti-human SIRPa antibody or antigen-binding fragment thereof according to any one of claims 1 to 4, wherein:

- the heavy chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 30; and

- the light chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 33.

6. The anti-human SIRPa antibody or antigen-binding fragment thereof according to any one of claims 1 to 4, wherein:

- the heavy chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 30; and
- the light chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 32.

7. The anti-human SIRPa antibody or antigen-binding fragment thereof according to any one of claims 1 to 4, wherein:

- the heavy chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 29; and
- the light chain variable domain comprises or consists of the amino acid sequence set forth in SEQ ID NO: 32.

8. The anti-human SIRPa antibody or antigen-binding fragment thereof according to any one of claims 1 to 4, which comprises:

- a heavy chain comprising or consisting of the amino acid sequence SEQ ID NO: 56, and
- a light chain comprising or consisting of the amino acid sequence SEQ ID NO: 57,

or

- a heavy chain comprising or consisting of the amino acid sequence SEQ ID NO: 36, and
- a light chain comprising or consisting of the amino acid sequence SEQ ID NO: 43,

or

- a heavy chain comprising or consisting of the amino acid sequence SEQ ID NO: 37, and
- a light chain comprising or consisting of the amino acid sequence SEQ ID NO: 44,

or

- a heavy chain comprising or consisting of the amino acid sequence SEQ ID NO: 37, and
- a light chain comprising or consisting of the amino acid sequence SEQ ID NO: 45,

or

- a heavy chain comprising or consisting of the amino acid sequence SEQ ID NO: 38, and
- a light chain comprising or consisting of the amino acid sequence SEQ ID NO: 44,

or

- a heavy chain comprising or consisting of the amino acid sequence SEQ ID NO: 38, and

- a light chain comprising or consisting of the amino acid sequence SEQ ID NO: 45,

or

- a heavy chain comprising or consisting of the amino acid sequence SEQ ID NO: 39, and
- a light chain comprising or consisting of the amino acid sequence SEQ ID NO: 44,

or

- a heavy chain comprising or consisting of the amino acid sequence SEQ ID NO: 39, and
- a light chain comprising or consisting of the amino acid sequence SEQ ID NO: 45,

or

- a heavy chain comprising or consisting of the amino acid sequence SEQ ID NO: 40, and
- a light chain comprising or consisting of the amino acid sequence SEQ ID NO: 44,

or

- a heavy chain comprising or consisting of the amino acid sequence SEQ ID NO: 40, and
- a light chain comprising or consisting of the amino acid sequence SEQ ID NO: 45,

or

- a heavy chain comprising or consisting of the amino acid sequence SEQ ID NO: 41, and
- a light chain comprising or consisting of the amino acid sequence SEQ ID NO: 44,

or

- a heavy chain comprising or consisting of the amino acid sequence SEQ ID NO: 41, and
- a light chain comprising or consisting of the amino acid sequence SEQ ID NO: 45,

or

- a heavy chain comprising or consisting of the amino acid sequence SEQ ID NO: 42, and
- a light chain comprising or consisting of the amino acid sequence SEQ ID NO: 44,

or

- a heavy chain comprising or consisting of the amino acid sequence SEQ ID NO: 42, and
- a light chain comprising or consisting of the amino acid sequence SEQ ID NO: 45.

9. The anti-human SIRPa antibody or antigen-binding fragment thereof according to any one of claims 1 to 4, which comprises:

- a heavy chain comprising or consisting of the amino acid sequence SEQ ID NO: 42, and
- a light chain comprising or consisting of the amino acid sequence SEQ ID NO: 45.

10. The anti-human SIRPa antibody or antigen-binding fragment thereof according to any one of claims 1 to 4, which comprises:

- a heavy chain comprising or consisting of the amino acid sequence SEQ ID NO: 42, and
- a light chain comprising or consisting of the amino acid sequence SEQ ID NO: 44.

11. The anti-human SIRPa antibody or antigen-binding fragment thereof according to any one of claims 1 to 3 or 6, which comprises:

- a heavy chain comprising or consisting of the amino acid sequence SEQ ID NO: 41, and
- a light chain comprising or consisting of the amino acid sequence SEQ ID NO: 44.

12. The anti-human SIRPa antibody or antigen-binding fragment thereof according to any one of claims 1 to 11, which is a humanized monoclonal antibody or antigen-binding fragment thereof, in particular wherein the antibody light chain constant domain is derived from human kappa light chain constant domain, and wherein the antibody heavy chain constant domain is derived from a human IgG1, IgG2, IgG3, or IgG4 heavy chain constant domain, in particular from a human IgG4 heavy chain constant domain.

13. The anti-human SIRPa antibody or antigen-binding fragment thereof according to claim 12, wherein the antibody light chain constant domain consists of the sequence of SEQ ID NO: 35.

14. The anti-human SIRPa antibody or antigen-binding fragment thereof according to claim 12, wherein the antibody heavy chain constant domain is derived from a human IgG4 heavy chain constant domain.

15. The anti-human SIRPa antibody or antigen-binding fragment thereof according to claim 12, wherein the antibody heavy chain constant domain consists of the sequence of SEQ ID NO: 34.

16. The anti-human SIRPa antibody or antigen-binding fragment thereof according to any one of claims 1 to 15, wherein the antibody or antigen-binding fragment thereof is an antagonist of SIRPa and inhibits the binding of human SIRPa to human CD47.

17. The anti-human SIRPa antibody or antigen-binding fragment thereof according to any one of claims 1 to 16, which does not specifically bind to human T-cells, in particular CD3+ T-cells.

18. The anti-human SIRPa antibody or antigen-binding fragment thereof according to any one of claims 1 to 17, which does not inhibit the proliferation of human T-cells.

19. The anti-human SIRPa antibody or antigen-binding fragment thereof according to any one of claims 1 to 18, which does not inhibit the binding of human CD47 to human SIRPg.

20. The anti-human SIRPa antibody or antigen-binding fragment thereof according to any one of claims 1 to 19, for use as a medicament.

21. Use of the anti-human SIRPa antibody or antigen-binding fragment thereof according to any one of claims 1 to 19,

in the manufacture of medicament for the prevention or treatment of a disease selected from the group consisting of a cancer (in particular inflammatory cancer and cancer with infiltrated myeloid cells, particularly with infiltrated MDSCs and/or TAM cells), an infectious disease, a chronic inflammatory disease, an auto-immune disease, a neurologic disease, a brain injury, a nerve injury, a polycythemia, a hemochromatosis, a trauma, a septic shock, a chronic infectious disease (in particular Pseudomonas and CMV), fibrosis, atherosclerosis, obesity, type II diabetes and a transplant dysfunction.

22. Use of the anti-human SIRPa antibody or antigen-binding fragment thereof according to any one of claims 1 to 19,

in the manufacture of a medicament for the prevention or treatment of a cancer, the cancer being selected among the group of carcinomas, adenocarcinomas, prostate cancers, germ cell cancers, lung cancers, mesothelioma cancers, ovary cancers, liver cancers, bladder cancers, brain cancers, breast cancers, colon cancers, sarcomas, pancreas cancers, head and neck cancers, kidney cancers, thymomas, gliomas, blastomas, melanomas and hematologic cancers such as lymphomas (Hodgkin's lymphoma and non-Hodgkin's lymphoma), leukemias such as T and B Acute or Chronic Lymphoblastic Leukemia (ALL or CLL) or Acute or Chronic myeloid leukemia (AML or CML) and Myelomas.

23. The anti-human SIRPa antibody or antigen-binding fragment thereof as defined in any one of claims 1 to 19 for its use according to claim 20, or the use according to claim 21 or 22, wherein said anti-human SIRPa antibody or antigen-binding fragment thereof is to be administered to a patient presenting a SIRPa-positive tumor.

24. A pharmaceutical composition comprising at least one anti-human SIRPa antibody or antigen-binding fragment thereof as defined in any one of claims 1 to 19, and a pharmaceutically acceptable carrier.

25. A combination product comprising:

- at least one anti-human SIRPa antibody or antigen-binding fragment thereof as defined in any one of claims 1 to 19, and

- at least one second therapeutic agent selected from the group consisting of chemotherapeutic agents, radiotherapy agents, immunotherapeutic agents, cell therapy agents, antibiotics and probiotics; in particular immunotherapeutic agents selected from the group consisting of checkpoint blocker or activator of adaptive immune cells, particularly selected from the group consisting of anti-PDL1, anti-PD1, anti-CTLA4, anti-CD137, anti-CD2, anti-CD28, anti-CD40, anti-HVEM, anti-BTLA, anti-CD160, anti-TIGIT, anti-TIM-1/3, anti-LAG-3, anti-2B4, and anti-OX40, anti-CD40 agonist, CD40-L, TLR agonists, anti-ICOS, ICOS-L and B-cell receptor agonists,

for simultaneous, separate or sequential use as a medicament.

26. The combination product according to claim 25, wherein the at least one second therapeutic agent is an anti-PD1 compound and/or an anti-PDL1 compound.

27. The combination product according to claim 25, wherein the at least one second therapeutic agent is an anti-CD137 compound.

28. An isolated nucleic acid molecule encoding an antibody or antigen-binding fragment thereof according to any one of claims 1 to 19.

29. A vector comprising a nucleic acid molecule according to claim 28.

30. An isolated host cell comprising a nucleic acid molecule according to claim 28 and/or a vector according to claim 29.

31. A method of manufacturing an antibody as defined in any one of claims 1 to 19 comprising immunizing a non-human animal, in particular a non-human mammal, against at least one antigen, said antigen comprising or consisting of the epitope sequence of human SIRPa consisting of SEQ ID NO: 3, and at least one epitope sequence of human SIRPa selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 5 or SEQ ID NO: 6, more particularly an antigen comprising or consisting of the epitope sequences of human SIRPa consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6,
or comprising or consisting of a conformational epitope comprising at least two peptides selected from the group consisting of SEQ ID No: 70, SEQ ID NO: 71, SEQ ID NO: 72, or SEQ ID NO: 73 and an SIR amino acid sequence, said antigen consisting of a sequence of up to 300 amino acids, and

collecting the resulting serum from said immunised non-human animal to obtain antibodies directed against said antigen, and isolate the antibodies according to any one of claims 1 to 19 from said resulting serum.

32. An *in vitro* or *ex vivo* method to determine SIRPa positive cells in a subject from a biological sample previously obtained from said subject, comprising:

i) determining *in vitro* the expression and/or the level of expression of SIRPa, in a biological sample previously obtained from said subject using the anti-human SIRPa antibody or antigen-binding fragment thereof as defined in any one of claims 1 to 19.

33. An *in vitro* or *ex vivo* method of diagnosis, in particular a method of diagnostic suitable for use in personalized medicine, more particularly in a companion diagnosis, wherein an anti-SIRPa antibody or an antigen-binding fragment thereof according to any one of claims 1 to 19 is used for the detection of SIRPa+ cells in a sample previously obtained from a subject and optionally for the quantification of the expression of SIRPa.

34. Use of an anti-SIRPa antibody or an antigen-binding fragment thereof according to any one of claims 1 to 19, in an *in vitro* or *ex vivo* diagnostic test, in particular in personalized medicine diagnostic test or in a companion diagnostic test.

35. *In vitro* or *ex vivo* use of at least one anti-human SIRPa antibody or antigen-binding fragment thereof as defined in any one of claims 1 to 19 in a method wherein SIRPa is used as a biomarker that is predictive for the response to a treatment in a subject, in particular in a cancer subject.

36. An *in vitro* or *ex vivo* method of predicting the response of a cancer subject to a treatment with anti-human SIRPa antibody or antigen-binding fragment as defined in any one of claims 1 to 19, comprising:

- determining the expression level of SIRPa in a tumor sample previously obtained from a subject, with anti-human SIRPa antibody or antigen-binding fragment thereof as defined in any one of claims 1 to 19, and
- comparing the expression level of SIRPa to a value representative of an expression level of SIRPa in a non-responding subject population,

wherein a higher expression level of SIRPa in the tumor sample of the subject is indicative for a patient who will respond to the treatment.

37. The anti-human SIRPa antibody or antigen-binding fragment thereof according to any one of claims 1 to 19, for use as a vaccine.