

CLAIMS

1. An anti-human SIRPa antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic that specifically binds to at least one peptide of amino acid sequence selected from
5 the group 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 within human SIRPa,

in particular, that specifically binds to the peptide of amino acid sequence set forth in SEQ ID NO: 3 within human SIRPa and to at least another peptide of amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6 within
10 human SIRPa; and/or

that specifically binds to a conformational epitope comprising at least one peptide selected from the group consisting of SEQ ID NO: 70, SEQ ID NO: 71 and SEQ ID NO: 72 within human SIRPa.

2. The anti-human SIRPa antibody or antigen-binding fragment thereof or antigen-binding
15 antibody mimetic according to claim 1, that specifically binds to the peptides of amino acid sequence set forth in 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 within human SIRPa; and/or

that specifically binds to a conformational epitope consisting of the peptide of amino acid sequence set forth in SEQ ID NO: 73 and the peptide of SIR amino acid sequence within human SIRPa.
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3. The anti-human SIRPa antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic according to claims 1 or 2, which comprises:

- a) a heavy chain variable domain comprising HCDR1, HCDR2 and HCDR3, and/or
- b) a light chain variable domain comprising LCDR1, LCDR2 and LCDR3,

25 wherein:

- HCDR1 comprising or consisting of the amino acid sequence set forth in SEQ ID NO: 14,
- HCDR2 comprising or consisting of the amino acid sequence set forth in SEQ ID NO: 15 or
SEQ ID NO: 16,
- HCDR3 comprising or consisting of the amino acid sequence set forth in SEQ ID NO: 17 SEQ
30 ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20,
- LCDR1 comprising or consisting of the amino acid sequence set forth in SEQ ID NO: 21,
- LCDR2 comprising or consisting of the amino acid sequence set forth in SEQ ID NO: 22 and
- LCDR3 comprising or consisting of the amino acid sequence set forth in SEQ ID NO: 23.

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

- a) a heavy chain variable domain comprising HCDR1, HCDR2 and HCDR3, and/or
- b) a light chain variable domain comprising LCDR1, LCDR2 and LCDR3,

5 wherein:

- HCDR1 comprising or consisting of the amino acid sequence set forth in SEQ ID NO: 14,
- HCDR2 comprising or consisting of the amino acid sequence set forth in SEQ ID NO: 15 or

SEQ ID NO: 16,

- HCDR3 comprising or consisting of the amino acid sequence set forth in SEQ ID NO: 17 SEQ

10 ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20,

- LCDR1 comprising or consisting of the amino acid sequence set forth in SEQ ID NO: 21,
- LCDR2 comprising or consisting of the amino acid sequence set forth in SEQ ID NO: 22 and
- LCDR3 comprising or consisting of the amino acid sequence set forth in SEQ ID NO: 23.

15 5. The anti-human SIRPa antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic according to any one of claims 1 to 4, which is an anti-SIRPa antagonist antibody, which inhibits the binding of human CD47 to human SIRPa.

20 6. The anti-human SIRPa antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic according to any one of claims 1 to 5, which does not specifically bind to human SIRPg.

25 7. The anti-human SIRPa antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic according to any one of claims 1 to 6, which does not specifically bind to human T-cells, in particular CD3+ T-cells.

30 8. The anti-human SIRPa antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic according to any one of claims 1 to 7, which does not inhibit the proliferation of human T-cells.

9. The anti-human SIRPa antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic according to any one of claims 1 to 8, which does not inhibit the binding of human CD47 to human SIRPg.

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

- a heavy chain variable domain comprising or consisting 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/or
- a light chain variable domain comprising or consisting 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, which comprises:
 - a light chain variable domain comprising or consisting of the amino acid sequence set forth in SEQ ID NO: 33, and
 - a heavy chain variable domain comprising or consisting 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.

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

- a heavy chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 24, and
- 20 - a light chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 31,
- or
- a heavy chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 25, and
- 25 - a light chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 32,
- or
- a heavy chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 25, and
- 30 - a light chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 33,
- or
- a heavy chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 26, and

- a light chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 32,
 - or
 - a heavy chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 26, and
- a light chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 33,
 - or
 - a heavy chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 27, and
- a light chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 32,
 - or
 - a heavy chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 27, and
- a light chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 33,
 - or
 - a heavy chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 28, and
- a light chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 32,
 - or
 - a heavy chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 28, and
- a light chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 33,
 - or
 - a heavy chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 29, and
- a light chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 32,
 - or
 - a heavy chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 29, and

- a light chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 33,

or

- a heavy chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 30, and

- a light chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 32,

or

- a heavy chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 30, and

- a light chain variable domain comprising or consisting of amino acid sequence set forth in SEQ ID NO: 33.

12. The anti-human SIRPa antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic according to any one of claims 1 to 11, wherein said antibody is a humanized monoclonal antibody, in particular wherein the antibody light chain constant domain is derived from a human kappa light chain constant domain, more particularly wherein the light chain constant domain consists of the sequence of SEQ ID NO: 35, 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, more particularly wherein the antibody heavy chain constant domain consists of the sequence with SEQ ID NO: 34.

13. The anti-human SIRPa antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic according to any one of claims 1 to 12, or
an anti-human SIRPa antagonist antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic, which inhibits the binding of human CD47 to human SIRPa, and which does not bind specifically to human SIRPg, and/or which does not bind specifically to human T-cells, and/or which does not inhibit the proliferation of human T-cells, and/or which does not inhibit the binding of human CD47 to human SIRPg,
for use as a medicament.

14. The anti-human SIRPa antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic according to any one of claims 1 to 12, or
an anti-human SIRPa antagonist antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic, which inhibits the binding of human CD47 to human SIRPa, and which

does not bind specifically to human SIRP α , and/or which does not bind specifically to human T-cells, and/or which does not inhibit the proliferation of human T-cells, and/or which does not inhibit the binding of human CD47 to human SIRP α ,

for use in the prevention or treatment of a disease selected from the group consisting of a
5 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, or for use
10 in vaccination.

15. The anti-human SIRP α antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic as defined in any one of claims 1 to 14, for its use according to claim 14, wherein said anti-human SIRP α antibody or antigen-binding fragment thereof or antigen-binding antibody
15 mimetic is administered to a patient presenting a SIRP α -positive tumor.

16. A pharmaceutical composition comprising at least one anti-human SIRP α antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic as defined in any one of claims 1 to 14, and a pharmaceutically acceptable carrier.

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17. A combination product comprising:

- at least one anti-human SIRP α antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic as defined in any one of claims 1 to 14, and
 - at least one second therapeutic agent selected from the group consisting of
25 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-
30 CD40 agonist, CD40-L, TLR agonists, anti-ICOS, ICOS-L and B-cell receptor agonists,
- for simultaneous, separate or sequential use as a medicament.

18. An isolated nucleic acid molecule encoding an antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic according to any one of claims 1 to 12.

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19. A vector comprising a nucleic acid molecule according to claim 18.

20. An isolated host cell comprising a nucleic acid molecule according to claim 18 and/or a vector according to claim 19.

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21. A polypeptide, particularly an antigen, comprising or consisting of the epitope sequence of human SIRPa consisting of SEQ ID NO: 3,

in particular an 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
10 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,
said polypeptide consisting of a sequence of up to 300 amino acids.

15 22. A method of manufacturing an antibody as defined in any one of claims 1 to 12 comprising immunizing a non-human animal, in particular a non-human mammal, against at least one antigen as defined in claim 21 and/or against at least one antigen comprising or consisting of at least one peptide selected from the group consisting of SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73 and the peptide of SIR amino acid sequence, said antigen consisting of a sequence of up to
20 300 amino acids, and in particular collecting the resulting serum from said immunised non-human animal to obtain antibodies directed against said antigen.

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

25 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 or antigen-binding antibody mimetic as defined in any one of claims 1 to 14.

30 24. 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 or an antigen-binding mimetic according to any one of claims 1 to 14 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.

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25. Use of an anti-SIRPa antibody or an antigen-binding fragment thereof or an antigen-binding mimetic according to any one of claims 1 to 14, in the manufacture of a medicament suitable for use in a diagnostic test, in particular for use in personalized medicine, or in a companion diagnostic test.

5 26. *In vitro* or *ex vivo* use of at least one anti-human SIRPa antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic as defined in any one of claims 1 to 14 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.

10 27. An *in vitro* or *ex vivo* method of predicting the response of a cancer subject to a treatment, in particular with anti-human SIRPa antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic as defined in any one of claims 1 to 14, comprising:

- determining the expression level of SIRPa in a tumor sample previously obtained from a subject, in particular with anti-human SIRPa antibody or antigen-binding fragment thereof or antigen-binding
15 antibody mimetic as defined in any one of claims 1 to 14, 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.