

Claims

1. An antibody or an antigen-binding fragment thereof or antigen-binding antibody mimetic which specifically binds to the epitope sequences from domain D1 and from the 2b site of human CD127 comprising or consisting of the sequence of SEQ ID No: 86 or SEQ ID No:116 and the sequence of SEQ ID No:110 or SEQ ID No:115 and the sequence of SEQ ID No:111 or SEQ ID No:117,
 - i. wherein the epitope sequence of human CD127 comprising SEQ ID No:110 does not extend to comprise the amino acids adjacent to said sequence in the sequence of human CD127 by more than 1 N-terminal amino acid or by more than 7 C-terminal amino acids; and/or
 - ii. wherein the epitope sequence of human CD127 comprising SEQ ID No:111 does not extend to comprise the amino acids adjacent to said sequence in the sequence of human CD127 by more than 30 N-terminal amino acid or by more than 30 C-terminal amino acids;

wherein said antibody, antigen-binding fragment or mimetic is an antagonist of IL-7R signaling induced by IL-7.
2. An antibody, antigen-binding fragment or mimetic according to claim 1, which specifically binds to the epitope sequences from domain D1 and from the 2b site of human CD127 wherein the epitope sequences comprise or consist of the sequence of SEQ ID No:116 and the sequence of SEQ ID No:115 and the sequence of SEQ ID No:117.
3. An antibody or antigen-binding fragment or mimetic according to claim 1 or 2 which does not increase the maturation of dendritic cells induced by TSLP.
4. An antibody or antigen-binding fragment or mimetic according to any one of claims 1 to 3 which comprises a VH chain comprising at least one of the following amino acid sequences:
 - VHCDR1 SEQ ID No:10;
 - VHCDR2 SEQ ID No:12;
 - VHCDR3 SEQ ID No:14 or SEQ ID No:48;

and/or a VL chain comprising at least one of the following amino acid sequences:

 - VLCDR1 SEQ ID No:16 or SEQ ID No:50;
 - VLCDR2 SEQ ID No:18 or SEQ ID No:52;
 - VLCDR3 SEQ ID No:20;

in particular comprising at least two, three, four or five CDR sequences selected from the

group consisting in VHCDR1 SEQ ID No:10, VHCDR2 SEQ ID No:12, VHCDR3 SEQ ID No:14 or SEQ ID No:48 , VLCDR1 SEQ ID No:16 or SEQ ID No:50, VLCDR2 SEQ ID No:18 or SEQ ID No:52 and VLCDR3 SEQ ID No:20.

5. An antibody or antigen-binding fragment thereof according to claim 4, which comprises
 - a heavy chain with the sequence of SEQ ID No:2 or of SEQ ID No:6 or of SEQ ID No:54 or which comprises the sequence of SEQ ID No:22 or of SEQ ID No:36 or of SEQ ID No:38 or of SEQ ID No:40; and
 - a light chain with the sequence of SEQ ID No:4 or of SEQ ID No:56 or which comprises the sequence of SEQ ID No:24 or of SEQ ID No:42 or of SEQ ID No:44 or of SEQ ID No:46.
6. An antibody or antigen-binding fragment thereof according to any one of claims 1 to 5 which is a chimeric antibody or a humanized antibody or a deimmunized antibody.
7. A macromolecule which is a chimeric molecule comprising an antibody or an antigen-binding fragment or mimetic according to any one of claims 1 to 6, wherein said antibody is associated with a functionally different molecule, said chimeric molecule being either a fusion chimeric protein or a conjugate resulting from covalent attachment of a chemical group or molecule, such as a PEG polymer or a labelled antibody.
8. A nucleic acid molecule encoding an antibody or antigen-binding fragment or mimetic according to any one of claims 1 to 6, or macromolecule according to claim 7.
9. A nucleic acid molecule according to claim 8, wherein the nucleic acid molecule encodes an amino acid chosen from the group consisting of SEQ ID No:2; SEQ ID No:4; SEQ ID No:6; SEQ ID No:8; SEQ ID No:10; SEQ ID No:12; SEQ ID No:14; SEQ ID No:16; SEQ ID No:18; SEQ ID No:20; SEQ ID No:22; SEQ ID No:24; SEQ ID No:36; SEQ ID No:38; SEQ ID No:40; SEQ ID No:42; SEQ ID No:44; SEQ ID No:46; SEQ ID No:48; SEQ ID No:50; SEQ ID No:52; SEQ ID No:54 and SEQ ID No:56, or wherein the nucleic acid molecule comprises or consists of a nucleotide sequence chosen from the group consisting of SEQ ID No:1; SEQ ID No:3; SEQ ID No:5; SEQ ID No:7; SEQ ID No:9; SEQ ID No:11; SEQ ID No:13; SEQ ID No:15; SEQ ID No:17; SEQ ID No:19; SEQ ID No:21; SEQ ID No:23; ; SEQ ID No:35; SEQ ID No:37; SEQ ID No:39; SEQ ID No:41; SEQ ID No:43; SEQ ID No:45; SEQ ID No:47; SEQ ID No:49; SEQ ID No:51; SEQ ID No:53 and SEQ ID No:55.
10. A pharmaceutical composition comprising an antibody or antigen-binding fragment or mimetic according to any one of claims 1 to 6, a macromolecule according to claim 7, or a nucleic acid molecule according to claim 8 or 9, with a pharmaceutical vehicle.
11. A pharmaceutical composition according to claim 10, wherein said pharmaceutical

composition further comprises an additional compound having a therapeutic immunomodulator effect in particular on cells involved in an autoimmune disease or an allergic disease, leukemia such as acute lymphoblastic leukemia, lymphoma, a cancer, a chronic viral infection, an inflammatory disease, transplantation, a respiratory disease or autoimmunity.

12. A macromolecule which is an antibody or antigen-binding fragment or mimetic according to any one of claims 1 to 6, a macromolecule according to claim 7, a nucleic acid molecule according to claim 8 or 9 or a pharmaceutical composition according to claim 10 or 11 for use as a therapeutically active ingredient in a combination or in an add-on therapeutic regimen in a patient in need thereof.
13. A macromolecule which is an antibody or antigen-binding fragment or mimetic according to any one of claims 1 to 6, a macromolecule according to claim 7, a nucleic acid according to claim 8 or 9, or a pharmaceutical composition according to claim 10 or 11 for use in the treatment of a patient in need of transplantation, about to be transplanted, or having received a transplant, or a patient with or at risk of a disease.
14. A macromolecule, a nucleic acid or a pharmaceutical composition according to claim 13, wherein the disease is an autoimmune disease such as rheumatoid arthritis, multiple sclerosis, type I diabetes, autoimmune thyroiditis or lupus, an inflammatory disease such as inflammatory bowel disease (IBD) or encephalomyelitis, an allergic disease, a cancer, a respiratory disease, or a disease related to transplantation.
15. Use of an antibody or antigen-binding fragment or mimetic according to any one of claims 1 to 6, a macromolecule according to claim 7, or a nucleic acid molecule according to claim 8 or 9 or a pharmaceutical composition according to claim 10 or 11 in the manufacture of a medicament for administration to a patient in need of transplantation, about to be transplanted, or having received a transplant.
16. Use of an antibody or antigen-binding fragment or mimetic according to any one of claims 1 to 6, a macromolecule according to claim 7, or a nucleic acid molecule according to claim 8 or 9 or a pharmaceutical composition according to claim 10 or 11 in the manufacture of a medicament for administration to a patient having, or at risk of developing a disease selected from an autoimmune disease an inflammatory disease an allergic disease, a cancer, a respiratory disease or a disease related to transplantation.
17. An antigen consisting of a fragment of the polypeptide of sequence SEQ ID No: 114 wherein the fragment comprises epitope sequence(s) from domain D1 and from the site 2b of human CD127, the epitope sequences comprising or consisting of the sequence of SEQ ID No:86 (or SEQ ID No:116) and of SEQ ID No:110 (or SEQ ID No:115) and of

SEQ ID No:111 (or SEQ ID No:117), ,

- (i) wherein the epitope sequence of human CD127 comprising SEQ ID No:110 does not extend to comprise the amino acids adjacent to said sequence in the sequence of human CD127 by more than 1 N-terminal amino acid or by more than 7 C-terminal amino acids; and/or
- (ii) wherein the epitope sequence of human CD127 comprising SEQ ID No:111 does not extend to comprise the amino acids adjacent to said sequence in the sequence of human CD127 by more than 30 N-terminal amino acid or by more than 30 C-terminal amino acids.

18. An antigen according to claim 17, wherein the epitope sequences comprise or consist of the sequences of SEQ ID No:116, SEQ ID No:115 and SEQ ID No:117.

19. A method of manufacturing an antibody comprising immunizing a non-human animal against an antigen as defined in claim 17 or 18.

20. A method of selecting an antibody, in particular an antibody obtained as in claim 13, an antigen-binding fragment or mimetic of such an antibody or another macromolecule, comprising or consisting of at least one of the following steps:

- a. testing the binding capacity of the macromolecule to CD127;
- b. testing the internalization of CD127 in CD127-expressing cells induced by the presence of the macromolecule;
- c. testing the inhibition by the macromolecule of IL7-induced internalization of CD127 in CD127-expressing cells; and
- d. testing the increase of the maturation of DCs induced by TSLP in the presence of the macromolecule.

21. A method according to claim 20, further comprising one or more of the following steps:

- e. testing the inhibition by the macromolecule of IL-7 induced signalling, in particular STAT5 phosphorylation;
- f. testing the inhibition by the macromolecule of TSLP-induced production of TARC;
- g. testing the inhibition by the macromolecule of the expression of $\alpha 4$, $\beta 7$ and/or $\alpha 4/\beta 7$ integrin expression, in particular cell surface expression on T-lymphocytes.

22. An antibody or an antigen-binding fragment thereof which binds specifically to human CD127 and which recognizes an epitope comprising a sequence taken from domain D1 and from the 2b site of human CD127, which comprises a VH chain comprising at least one of the following amino acid sequences:

- VHCDR1 SEQ ID No:10;

- VHCDR2 SEQ ID No:12;
- VHCDR3 SEQ ID No:14 or SEQ ID No:48;

and/or a VL chain comprising at least one of the following amino acid sequences:

- VLCDR1 SEQ ID No:16 or SEQ ID No:50;
- VLCDR2 SEQ ID No:18 or SEQ ID No:52;
- VLCDR3 SEQ ID No:20;