

and their functions have begun to be unveiled. Accordingly, a first plasma protein-derived chemoattractant named chemerin has been identified as a ligand for CMKLR1.

- [5] The second ligand of CMKLR1 is the lipid mediator Resolvin E1 (RvE1) that belongs to the Resolvin family. The anti-inflammatory lipid mediator Resolvin E1 inhibits leukocyte infiltration and pro-inflammatory gene expression.
- [6] Initially, the interest in the chemerin system (*i.e.* the signaling pathway(s) activated or not by Chemerin receptors by their ligands like Chemerin and Resolvin) was focused on its role in inflammation and chemotaxis of immune cells following its discovery in psoriasis disease. Most recently, in connection with its role in inflammation, in obesity, metabolic syndrome, its potential role in association with cardiovascular functions has been considered, as well as role in reproductive biology. Therefore, the chemerin system is of major interest for its role in the inflammation process, in particular for its role in the resolution of the inflammation. A number of diseases are related to delay or disruption of the resolution process. Most of the specialized pro-resolving factor mediators currently known are derived from polyunsaturated fatty acids, including lipoxins, the resolving family, including E-series resolvins and D-series resolvins, protectins, and maresins. Nonetheless, pro-resolving molecules are difficult to synthesize because of their lipidic nature. Production of pro-resolving molecules in sufficient quantities, for a clinical trial for example, is a burden, and very few SPM have gone through efficient production. Besides that, antibodies specifically targeting G-protein-coupled receptors are difficult to produce. There is therefore a need for molecules having the capability to take part, in particular to initiate or enhance the resolution stage of the inflammatory response like pro-resolving factors.

Summary of the invention

- [7] In a first ~~aspect example~~, the ~~invention disclosure~~ relates to a humanized anti-CMKLR1 antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic or modified antibody.
- [8] The inventors have sought to obtain improved humanized antibodies when compared to wild type anti-CMKLR1 antibody known in the prior art. While it is known that some residues in the variable domain CDR and framework (FR) sequences, including residues in the Vernier zone, canonical residues, residues at the variable heavy and variable light chains interface, etc, are critical in the structure of an antibody and should not be mutated in order to preserve the biochemical and biological activity of an antibody, the inventors have surprisingly discovered that some mutations within the heavy chain variable domain and/or the light chain variable domain sequence of wild type antibody, including some of such critical residues, allow increasing human residue content (up to 99% of humanization) while functional features are associated with these humanized antibodies, which are not shared by wild type anti-CMKLR1 in particular which are improved, and at the same time that

production of these humanized antibodies may be improved as compared to less or distinctly humanized anti-CMKLR1 antibodies. These humanized antibodies lead to the provision of compounds exhibiting functional features useful in the treatment of diseases, including diseases wherein inflammation is implicated, which can be produced on a large scale for candidate drug development. The combination of these two features leads to the provision of anti-CMKLR1 antibodies showing improved capabilities as compared to the antibodies of the prior art.

[9] Starting from a not humanized anti-CMKLR1 antibody and selecting human germline sequences, the inventors designed particular humanized heavy chain variable domains and light chain variable domains. The humanized heavy chain variable domain and light chain variable domain derived from non-humanized antibody allow a production of functional antibodies in different cell lines, like but not limited to Chinese Hamster Ovary (CHO) cell line, transformed African Green Monkey Kidney Fibroblast Cells (COS-7) cell line and Human Embryonic Kidney cell line (HEK 293) in conditions that enable recovering significant yield of antibodies that bind their target with an activity that may even be increased with respect to the binding activity of the wild type antibody. Some of the obtained humanized heavy chain variable domain and light chain variable domain were in particular further humanized with respect to a first humanization step carried out on framework regions of the heavy and light chains variable domains, leading to the provision of antibodies suitable for high yield production in different cell lines, with a reduced immunogenicity, and having at least the functional features of their parental antibody. The skilled artisan would not have expected that said mutations, particularly at such positions in the CDR domains and in framework regions of the heavy and/or light chain variable domain would lead to the provision of anti-CMKLR1 antibodies with a preserved binding capability in particular preserved affinity, a preserved stability, the preservation of the Resolvin-like agonist capability of these antibodies on CMKLR1, with a lowered immunogenicity index, while the production scale of these antibodies comprising a heavy variable domain and a light variable domain according to the ~~invention~~disclosure would be improved as compared to less or differently humanized antibodies. It was not foreseeable that the introduction of the disclosed mutations, and particularly in the CDR2 of the heavy chain would result in improved production, while still preserving binding features and advantageously other functional features of the anti-CMKLR1 antibodies of the prior art. Anti-CMKLR1 antibodies exhibiting the recited features (binding capability, in particular affinity, for CMKLR1, in particular for the particular third extra-loop of CMKLR1, low immunogenicity, good production scale and Resolvin-like agonist capability for CMKLR1) are useful for a potent treatment of several diseases, including diseases wherein inflammation is involved, and more particularly inflammatory diseases.

[10] Further, as will be explained later in the present application, several very advantageous biological effects have been reached, associated in particular to the apoptosis of neutrophils and to the reduction of migration and/or transmigration of neutrophils and/or macrophages notably, leading to strong benefic action in the resolution of inflammation.

5 The new compounds allow thus to combine the production capacity and the biological activity.

[11] Accordingly, in a first ~~aspect~~ example of the ~~invention~~ disclosure, it is disclosed an antibody or antigen-binding fragment thereof, which binds to Chemokine-like receptor 1 (CMKLR1), in particular human CMKLR1, comprising:

- 10 a) an antibody heavy chain variable (VH) domain comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3, wherein:
- VHCDR1 is selected from the group consisting of SEQ ID No.3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6 and SEQ ID No. 7;
 - VHCDR2 is selected from the group consisting of SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12 and SEQ ID No. 61;
 - VHCDR3 is selected from the group consisting of SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15 and SEQ ID No. 16;
- 15 b) an antibody light chain variable (VL) domain comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3, wherein:
- VLCDR1 is selected from the group consisting of SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22 and SEQ ID No. 23;
 - VLCDR2 is 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, SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32 and SEQ ID No. 33;
 - VLCDR3 is selected from the group consisting of SEQ ID No. 34, SEQ ID No. 35 and SEQ ID No. 36.
- 20
- 25

In a first aspect of the disclosure, it is disclosed an anti- Chemerin Like Receptor 1 (CMKLR1) antibody or antigen-binding fragment thereof which binds to CMKLR1, in particular human CMKLR1, said antibody or antigen-binding fragment thereof comprising:

- 30 a. an antibody heavy chain variable (VH) domain comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3, wherein:
- VHCDR1 is selected from the group consisting of SEQ ID No.3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6 and SEQ ID No. 7; and
 - VHCDR2 is selected from the group consisting of SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID NO: 12 and SEQ ID No. 61; and
- 35

- VHCDR3 is selected from the group consisting of SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15 and SEQ ID No. 16; and

b. an antibody light chain variable (VL) domain comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3, wherein:

5 - VLCDR1 is selected from the group consisting of SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22 and SEQ ID No. 23; and

- VLCDR2 is 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, SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32 and SEQ ID No. 33; and

10 - VLCDR3 is selected from the group consisting of SEQ ID No. 34, SEQ ID No. 35 and SEQ ID No. 36.

15 In another aspect of the disclosure, it is disclosed an antibody or antigen-binding fragment thereof, in particular selected from the group consisting of a chimeric, a modified and a humanized antibody, which specifically binds to CMKLR1, in particular human CMKLR1, which comprises an antibody heavy chain variable domain comprising (i) VHCDR2 comprising or consisting of an amino acid sequence set forth in SEQ ID No: 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12 and SEQ ID No. 61, and (ii) VHCDR3 comprising or consisting of an amino acid sequence set forth in SEQ ID No: 13, SEQ ID No. 14, SEQ ID No. 15 and SEQ ID No. 16 or a mutated sequence thereof wherein amino acid residue(s) is(are) substituted provided that amino acid residues at positions 1 and 2 of the mutated sequence are respectively L and I; and wherein the anti-CMKLR1 compound binds specifically to an epitope located within the third extra-cellular loop (EL3) of CMKLR1, in particular wherein the compound binds specifically to a polypeptide comprising or consisting of amino acid sequence SEQ ID No: 2 or SEQ ID No. 59 or to an epitope located within amino acid sequence SEQ ID No. 60 ; and

25 wherein said compound competes with an antibody comprising the heavy chain variable domain corresponding to SEQ ID No: 37 and the light chain variable domain corresponding to SEQ ID No: 49, for the binding to a polypeptide comprising or consisting of amino acid sequence of sequence SEQ ID No: 2 or SEQ ID No. 59 or of SEQ ID No. 60 or to a polypeptide comprising or consisting of the third loop (EL3) of the extracellular domain of CMKLR1.

30 In another aspect of the disclosure, it is disclosed the anti-CMKLR1 antibody or antigen-binding fragment thereof according to the disclosure for use in therapy.

In another aspect of the disclosure, it is disclosed a use of the anti-CMKLR1 antibody or antigen-binding fragment thereof according to the disclosure in the manufacture of a medicament for preventing or treating:

- an inflammatory disease, in particular acute inflammatory diseases, chronic inflammatory diseases such as chronic inflammatory pulmonary diseases, keratoconjunctivitis, periodontal disease, eczema, inflammatory bowel disease, in particular Crohn's disease or colitis, in particular ulcerative colitis or spontaneous colitis, cystic fibrosis, NASH (Nonalcoholic steatohepatitis), scleroderma, anti-neutrophil cytoplasm antibodies-related disease ANCA associated disease, in particular wherein, as a result of the administration of the treatment, the resolution of inflammation is enhanced;

- an autoimmune disease such as diabetes, in particular type I diabetes, psoriasis, lupus, rheumatoid arthritis, multiple sclerosis, Sjögren's syndrome, celiac disease, vasculitis, myasthenia gravis, or an infection disease such as sepsis, peritonitis, degenerative diseases, wound healing disorders or dry eye syndrome, in particular wherein, as a result of the administration of the treatment, the resolution of inflammation is enhanced;

- a cancer, in particular metastatic cancers, solid or liquid cancers such as carcinoma, more particularly hepatocarcinoma, in particular mammary carcinoma or colon carcinoma, colorectal cancer or lung cancer or mesothelioma or myeloid cancer such as leukemia, in particular a cancer wherein cancer cells express CMKLR1 or where the microenvironment of the tumor is invaded by cells expressing or overexpressing CMKLR1, in particular wherein, as a result of the administration of the treatment, the resolution of inflammation is enhanced.

In another aspect of the disclosure, it is disclosed a use of the anti-CMKLR1 antibody or antigen-binding fragment thereof according to the disclosure in the manufacture of a medicament for preventing or treating NASH (Nonalcoholic steatohepatitis), scleroderma, cystic fibrosis or anti-neutrophil cytoplasm antibodies-related disease (ANCA).

[12] In a particular ~~embodiment~~example, said antibody or antigen-binding fragment thereof, which binds to Chemokine-like receptor 1 (CMKLR1), in particular human CMKLR1, comprises:

a) an antibody heavy chain variable (VH) domain comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3, wherein:

- VHCDR1 is selected from the group consisting of SEQ ID No.3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6 and SEQ ID No. 7;

- VHCDR2 is selected from the group consisting of SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11 and SEQ 61; or VHCDR2 corresponds to the amino acid sequence of SEQ ID No. 12 or SEQ ID No. 63 with the proviso that VHCDR1 is not SEQ ID No. 3 or SEQ ID No. 4;

- VHCDR3 is selected from the group consisting of SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15 and SEQ ID No. 16;
- b) an antibody light chain variable (VL) domain comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3, wherein:
 - 5 - VLCDR1 is selected from the group consisting of SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22 and SEQ ID No. 23;
 - VLCDR2 is 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, SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32 and SEQ ID No. 33;
 - 10 - VLCDR3 is selected from the group consisting of SEQ ID No. 34, SEQ ID No. 35 and SEQ ID No. 36.

[13] In another particular embodiment example, said antibody or antigen-binding fragment thereof, which binds to Chemokine-like receptor 1 (CMKLR1), in particular human CMKLR1, comprises:

- a) an antibody heavy chain variable (VH) domain comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3, wherein:
 - VHCDR1 is selected from the group consisting of SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6 and SEQ ID No. 7;
 - 20 - VHCDR2 is selected from the group consisting of SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11 and SEQ ID No. 61,
 - o when VHCDR1 is SEQ ID No. 3 or SEQ ID No. 4 and VHCDR2 corresponds to the amino sequence of SEQ ID NO: 12 said heavy chain variable (VH) domain does not comprise a framework VHFR3 of SEQ ID No. 70, preferably with the proviso that said heavy chain variable (VH) domain comprises a framework FR3 of SEQ ID NO: 69,
 - 25 - VHCDR3 is selected from the group consisting of SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15 and SEQ ID No. 16;
- b) an antibody light chain variable (VL) domain comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3, wherein:
 - 30 - VLCDR1 is selected from the group consisting of SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22 and SEQ ID No. 23;
 - VLCDR2 is 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, SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32 and SEQ ID No. 33;
 - 35 - VLCDR3 is selected from the group consisting of SEQ ID No. 34, SEQ ID No. 35 and SEQ ID No. 36.

- VLCDR3 is selected from the group consisting of SEQ ID No. 34, SEQ ID No. 35 and SEQ ID No. 36.

In particular advantageously, the antibody or antigen-binding fragment thereof binds specifically to the third extra-cellular loop (EL3) of CMKLR1, in particular an epitope located within the third extra-cellular loop (EL3) of CMKLR1; more particularly the antibody or antigen-binding fragment thereof binds specifically to a polypeptide comprising amino acid sequence SEQ ID No: 2 or SEQ ID No. 59 or to an epitope located within amino acid sequence SEQ ID No. 60.

[14] An antibody or an antigen-binding fragment thereof according to this embodimentexample is suitable for production in different cell lines, including but not limited to mammalian cell lines, with a yield of production suitable for purposes of development of a drug candidate, while the specific binding capability to the extra cellular third loop of CMKLR1 and its Resolvin E1-like agonist capability on CMKLR1 are retained.

The humanized antibodies disclosed herein may therefore be efficiently produced and share the functional capabilities of their parental antibody.

[15] In a particular aspect-example of the inventiondisclosure, which may be distinguished from the definition of the antibodies of the inventiondisclosure solely by their CDR domains, but which may be combined with such a definition in particular embodimentexamples, it is disclosed an antibody or antigen-binding fragment thereof, which binds to Chemokine-like receptor 1 (CMKLR1), in particular human CMKLR1, suitable for the production in mammalian cells such as COS or CHO or HEK cells, in particular with a yield over 0.1mg/ml, in particular with a yield over 1 mg/ml, more particularly with a yield of at least 10 mg/ml, and again more particularly with a yield over 100 mg/ml wherein:

- a) the Variable Heavy (VH) domain comprises the amino acid sequence of the frameworks (FR1, FR2, FR3 and FR4) of a Heavy Chain variable domain wherein each framework harbors a sequence identity respectively with the framework of the same rank in the sequence of SEQ ID No. 41 that is 100 % for FR1, at least 60 % for FR2, at least 78 % for FR3 and at least 80 % for FR4; more particularly 100 % for FR1, at least 80 % for FR2, at least 85 % for FR3 and at least 90 % for FR4;
- b) the Variable Light (VL) domain comprises the amino acid sequence of the frameworks (FR1, FR2, FR3 and FR4) of a Light Chain Variable domain wherein each framework harbors a sequence identity respectively with the framework of the same rank in the sequence of SEQ ID No.50 that is at least 60 % for FR1, at least 70 % for FR2, at least 75 % for FR3 and at least 80 % for FR4, and more particularly of 100% for FR1, at least 90 % for FR2, at least 90% for FR3 and 100 % for FR4.

In particular, said humanized anti-CMKLR1 antibody or said antigen binding fragment thereof specifically binds to the third extra-cellular loop (EL3) of CMKLR1, in particular the antibody or antigen-binding fragment thereof binds specifically to a polypeptide comprising amino acid sequence SEQ ID No: 2 or SEQ ID No. 59 or to an epitope located within amino acid sequence SEQ ID No. 60.

[16] The inventors, starting from the anti-CMKLR1 antibody 2G1, synthesized various heavy chain variable domains and light chain variable domains. The humanized heavy chain variable domain of SEQ ID No. 41 and the humanized light chain variable domain of SEQ ID No. 50 were particularly suitable for the production of humanized anti-CMKLR1 antibodies in cell or cell line, including mammalian cell like CHO cells or COS cells or HEK Cells. Having selected a particular human germline sequence for the design of the heavy chain variable domain and light chain variable domain, humanized antibodies with the herein defined identities in framework regions were also able to be produced in decent amounts in cell or cell line for the purpose of developing an antibody that may give rise to a drug candidate. There is a high interest in the provision of humanized antibodies which are able to be produced in high amount in cell or cell line, in particular in mammalian cell or cell line, for developing therapeutic antibodies. The particular anti-CMKLR1 antibodies provided herein share a highly similar structure with their parental antibody comprising heavy chain variable domain of SEQ ID No. 41 and light chain variable domain of SEQ ID No. 50, allowing the correct production, conformation and secretion of the anti-CMKLR1 antibody, thereby allowing the provision of an antibody which binds to the particular epitope of the Chemerin-like receptor 1 and having a Resolvin E1-like agonist capability on this receptor in sufficient amount for therapeutic purposes.

[17] In a particular embodiment example of the invention disclosure, it is provided an antibody which is a humanized anti- Chemerin Like Receptor 1 (CMKLR1) antibody or an antigen-binding fragment thereof suitable for the production in mammalian cells such as COS or CHO cells, in particular with a yield over 0.1 mg/ml, more particularly with a yield over 1 mg/ml, more particularly with a yield over 10 mg/ml, again more particularly with a yield over 100 mg/ml, wherein :

- a) the Variable Heavy (VH) domain comprises the amino acid sequence of the frameworks (FR1, FR2, FR3 and FR4) of a Heavy Chain variable domain wherein each framework harbors a sequence identity respectively with the framework of the same rank in the sequence of SEQ ID No. 41 that is at least 90 % for FR1, at least 70 % for FR2, at least 80 % for FR3 and at least 80 % for FR4;
- b) the Variable Light (VL) domain comprises the amino acid sequence of the frameworks (FR1, FR2, FR3 and FR4) of a Light Chain Variable domain wherein each framework harbors a sequence identity respectively with the framework of the same rank in the

sequence of SEQ ID No.50 that is at least 60 % for FR1, at least 80 % for FR2, at least 75 % for FR3 and at least 70 % for FR4.

[18] In particular, said humanized anti-CMKLR1 antibody or said antigen binding fragment thereof specifically binds to the third extra-cellular loop (EL3) of CMKLR1; in particular the antibody or antigen-binding fragment thereof binds specifically to a polypeptide comprising amino acid sequence SEQ ID No: 2 or SEQ ID No. 59 or located within amino acid sequence SEQ ID No 60.

[19] In a particular embodimentexample of the humanized antibody or the antigen-binding fragment thereof defined above, such humanized antibody or the antigen-binding fragment thereof comprises

a) an antibody heavy chain variable (VH) domain comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3, wherein:

- VHCDR1 is selected from the group consisting of SEQ ID No.3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6 and SEQ ID No. 7; and

- VHCDR2 is selected from the group consisting of SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12 and SEQ 61; and

- VHCDR3 is selected from the group consisting of SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15 and SEQ ID No. 16; and

b) an antibody light chain variable (VL) domain comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3, wherein:

- VLCDR1 is selected from the group consisting of SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22 and SEQ ID No. 23; and

[20] In a particular embodimentexample, of the humanized antibody or the antigen-binding fragment thereof defined above, such humanized antibody or the antigen-binding fragment thereof comprises:

a) an antibody heavy chain variable (VH) domain comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3, wherein:

- VHCDR1 is selected from the group consisting of SEQ ID No.3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6 and SEQ ID No. 7; and

- VHCDR2 is selected from the group consisting of SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11 and SEQ 61; or VHCDR2 comprises or consists of the amino acid sequence of SEQ ID No. 12 or SEQ ID No. 63 with the proviso that VHCDR1 is not SEQ ID No.3 or SEQ ID No. 4; and

- VHCDR3 is selected from the group consisting of SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15 and SEQ ID No. 16; and

b) an antibody light chain variable (VL) domain comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3, wherein:

- VLCDR1 is selected from the group consisting of SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22 and SEQ ID No. 23; and

- VLCDR2 is 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, SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32 and SEQ ID No. 33; and

- VLCDR3 is selected from the group consisting of SEQ ID No. 34, SEQ ID No. 35 and SEQ ID No. 36.

[21] In another particular embodimentexample of the humanized antibody or the antigen-binding fragment thereof defined above, such humanized antibody or the antigen-binding fragment thereof comprises:

a) an antibody heavy chain variable (VH) domain comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3, wherein:

- VHCDR1 is selected from the group consisting of SEQ ID No.3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6 and SEQ ID No. 7; and

- VHCDR2 is selected from the group consisting of SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11 and SEQ 61;

when VHCDR1 is SEQ ID No. 3 or SEQ ID No. 4 and VHCDR2 comprises or consists of the amino acid sequence of SEQ ID No. 12 said heavy chain variable (VH) domain does not comprise a framework VHFR3 of SEQ ID No. 70, preferably with the proviso that said heavy chain variable (VH) domain comprises VHFR3 of SEQ ID No. 69 ; and

- VHCDR3 is selected from the group consisting of SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15 and SEQ ID No. 16; and

b) an antibody light chain variable (VL) domain comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3, wherein:

- VLCDR1 is selected from the group consisting of SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22 and SEQ ID No. 23; and

- VLCDR2 is 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, SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32 and SEQ ID No. 33; and

- VLCDR3 is selected from the group consisting of SEQ ID No. 34, SEQ ID No. 35 and SEQ ID No. 36.

[22] Such antibody presents the same advantageous features as the antibodies defined according to the first ~~aspect—example~~ and the second ~~aspect—example~~ of the ~~invention~~disclosure; i.e. high yield production, specific binding to an epitope located within the third extra loop of the chemerin-like Receptor 1, a Resolvin E1-like agonist capability.

5 [23] The disclosed antibodies are suitable for being used in the treatment of a condition wherein the resolution of the inflammation is delayed or disrupted. All antibodies described herein are suitable for inducing the resolution of the inflammation, and/or enhancing resolution of the inflammation, and/or initiating resolution of the inflammation.

[24] In the following disclosure, a humanized anti-CMKLR1 compound is considered as
10 being either a humanized anti-CMKLR1 antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic or modified antibody. In a particular ~~embodiment~~example of the ~~invention~~disclosure, said compound is defined by the sequences of its CDR. In a more particular ~~embodiment~~example of the ~~invention~~disclosure, the anti-CMKLR1 compound is an antibody defined by the sequences of its CDRs and its framework regions
15 (FR). An anti-CMKLR1 compound is a compound which binds specifically to the Chemokin-like receptor 1 (CMKLR1). In the following disclosure, the terms Chemokin-like receptor 1, CMKLR1 and ChemR23 are used interchangeably, and all designate the receptor encoded by gene *CMKLR1* in human or *cmklr1* in non-human animals. In a particular ~~embodiment~~example of the ~~invention~~disclosure, the anti-CMKLR1 compound binds
20 specifically to human CMKLR1 or, in other words, the ~~invention~~disclosure relates to an anti-human CMKLR1 compound. As used herein, the term “CMKLR1” refers to a Chemokin-Like Receptor 1 protein (also designated as chemR23), a member of the G-protein coupled receptor family from a mammal species, preferably a human CMKLR1. A reference sequence of the human CMKLR1 protein, used in the examples of the present application,
25 corresponds to the sequence associated to the Uniprot Accession number Q99788 (SEQ ID No: 1).

[25] In a particular ~~example~~aspect, the ~~invention~~disclosure relates to an anti-CMKLR1 antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic or modified antibody defined by at least one functional feature. In a preferred ~~embodiment~~example, said anti-CMKLR1 compound
30 is defined by its capability to inhibit secretion of pro-inflammatory cytokines, in particular IL12, and/or its capability to enhance secretion of anti-inflammatory cytokines, in particular IL10. In a more particular ~~embodiment~~example, the anti-CMKLR1 compound inhibits or enhances cytokine secretion by macrophages, in particular by pro-inflammatory macrophages and/or by pro-resolution of the inflammation macrophages. In a particular ~~embodiment~~example, the anti-CMKLR1 compound
35 of the ~~invention~~disclosure enhances the polarization of macrophages into anti-inflammatory macrophages, in particular pro-resolution macrophages. In a particular ~~embodiment~~example, the anti-CMKLR1 compound of the ~~invention~~disclosure enhances the apoptosis of neutrophils as compared to a control antibody.

[26] In a particular exampleaspect, the inventiondisclosure relates to an anti-CMKLR1 antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic that has agonist properties towards the Resolvin E1 (RvE1)/CMKLR1 interaction, thereby mimicking at least one of the effects induced by the binding of RvE1 to CMKLR1 on CMKLR1-positive cells. “*Agonist properties towards RvE1-CMKLR1 interaction*” means that the antibody or antigen-binding fragment thereof or antigen-binding antibody mimetic or modified antibody of the inventiondisclosure, which targets the CMKLR1, has the effect of mimicking at least one of the effects provided by the binding of RvE1 to CMKLR1, thereby activating the receptor signaling pathway normally activated by RvE1, especially the binding of human RvE1 to human CMKLR1, in particular on dendritic cells, neutrophils, monocytes and macrophages. As a result of binding and activation of the receptor to produce a biological response, the compounds of the inventiondisclosure may lead to the activation of the G protein signaling pathway, in particular $G\alpha_i$ signaling pathway and/or $G\alpha_o$, without activating the β -arrestin pathway. In particular, the compound of the inventiondisclosure may lead to the inhibition of the β -arrestin pathway. In particular, the binding of a compound according to the inventiondisclosure induces the activation of Akt and/or Erk protein(s) *in vitro* and/or *in vivo*. In a particular embodimentexample, the compound may be considered as an anti-CMKLR1 agonist having a Resolvin E1-like capability when the G-protein signaling pathway is activated in CMKLR1-positive cells stimulated with the compound of the inventiondisclosure, and in a more particular embodimentexample, also when the B-arrestin pathway is not activated, and in particular conditions, when the B-arrestin pathway is inhibited. In other words, a Resolvin-E1 like agonist antibody may be defined as an antibody able to bind CMKLR1, and thereby able to induce the phosphorylation of the Akt and/or Erk protein(s), as compared to a control antibody. A control antibody may be an antibody which does not specifically bind CMKLR1. Phosphorylation of a protein may be determined according to methods well known by the skilled artisan, for example by the method disclosed in the examples of the present description. In a particular embodimentexample, the compound of the inventiondisclosure enhances activation of the G protein pathway induced by CMKLR1. In another embodimentexample, the compound of the inventiondisclosure does not induce the activation of the β -arrestin pathway induced by CMKLR1. In another embodimentexample, the compound of the inventiondisclosure inhibits the β -arrestin pathway induced by CMKLR1. In another embodimentexample, since a compound of the inventiondisclosure induces at least one agonist effect of the binding of RvE1 to CMKLR1, and since RvE1 is a pro-resolution factor or pro-resolution mediator, a compound of the inventiondisclosure is a pro-resolution factor or a pro-resolution mediator; e.g. a pro-resolution factor may be defined as a compound which inhibits the β -arrestin pathway induced by CMKLR1 and/or enhances activation of the G protein pathway induced by CMKLR1 in CMKLR1-positive cells, as compared to a control compound, which is known for not specifically interacting with CMKLR1. The activation/inhibition of these

pathways may be assessed according to the methods disclosed in the working examples of the inventiondisclosure. In a particular embodimentexample, the effect of the agonist compound is assessed in human cells.

[27] In a particular embodimentexample, a compound of the inventiondisclosure does not interfere with the binding of Chemerin to CMKLR1. Chemerin is one of the natural ligand of CMKLR1. In other words, a compound according to the inventiondisclosure is not an agonist and/or not an antagonist of the interaction between Chemerin and CMKLR1. The absence of such an agonist and/or antagonist capability may be assessed according to the examples of the inventiondisclosure, wherein a competition assay to measure Chemerin-dependent Beta-arrestin recruitment by CMKLR1 receptor in presence of anti-CMKLR1 antibody of the inventiondisclosure is disclosed. In a preferred embodimentexample, the anti-CMKLR1 compound of the inventiondisclosure does not compete with Chemerin for the binding to CMKLR1. The absence of competition between an anti-CMKLR1 compound of the inventiondisclosure and chemerin may be determined when, in presence of the CMKLR1 compound of the inventiondisclosure, the binding of Chemerin to CMKLR1 is at least 50%, more preferably at least 80%, still more preferably at least 90% and most preferably similar, to the binding of Chemerin to CMKLR1, under the same experimental conditions but without the presence of the anti-CMKLR1 of the inventiondisclosure. Alternatively, the absence of competition between an anti-CMKLR1 compound of the inventiondisclosure and Chemerin may be determined according to the method illustrated in example 9.

[28] In a particular embodimentexample, the anti-CMKLR1 compound has the capability *in vitro* and/or *in vivo* to activate at least one of the Akt signaling pathway proteins (also known as PI3K-Akt Pathway) and/or Erk signaling pathway proteins, preferably Akt protein and/or Erk protein, preferably both the Akt and the Erk proteins. Activation of a pathway may be assessed according to methods known in the art, and in particular with methods disclosed in the examples of the present inventiondisclosure.

Detailed description of the invention

[29] The present invention relates to an agonist of CMKLR1 having a Resolvin E1-like capability for use in the therapeutic treatment of an inflammatory condition in a patient, in particular an inflammatory condition wherein the resolution phase of the inflammation is delayed or disrupted, in particular in a chronic inflammation, in particular said agonist being selected from the group consisting of an antibody or antigen-binding fragment thereof, a peptide, a polypeptide and a protein.

[30] In the following description, without any contrary mention, agonist of CMKLR1 having a Resolvin E1-like capability may be identified as the or a “agonist”; both terms include an antibody or antigen-bind fragment thereof (also reference anti-CMKLR1 antibody), a

CLAIMS

1. An anti- Chemerin Like Receptor 1 (CMKLR1) antibody or antigen-binding fragment thereof which binds to CMKLR1, in particular human CMKLR1, said antibody of antigen-binding fragment thereof comprising:

 - a. an antibody heavy chain variable (VH) domain comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3, wherein:

 - VHCDR1 is selected from the group consisting of SEQ ID No.3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6 and SEQ ID No. 7; and
 - VHCDR2 is selected from the group consisting of SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID NO: 12 and SEQ ID No. 61; and
 - VHCDR3 is selected from the group consisting of SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15 and SEQ ID No. 16; and
 - b. an antibody light chain variable (VL) domain comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3, wherein:

 - VLCDR1 is selected from the group consisting of SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22 and SEQ ID No. 23; and
 - VLCDR2 is 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, SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32 and SEQ ID No. 33; and
 - VLCDR3 is selected from the group consisting of SEQ ID No. 34, SEQ ID No. 35 and SEQ ID No. 36.
2. The anti-CMKLR1 antibody or antigen-binding fragment thereof according to claim 1 wherein the antibody or antigen-binding fragment thereof binds specifically to the third extra-cellular loop (EL3) of CMKLR1, in particular to an epitope located within third extra-cellular loop (EL3) of CMKLR1, or within the polypeptide comprising amino acid sequence SEQ ID No: 2 or SEQ ID No. 59 or to an epitope located within amino acid sequence SEQ ID No. 60.
3. The anti-CMKLR1 antibody or antigen-binding fragment thereof according to claim 1 or 2, which is a Resolvin E1-like agonist of CMKLR1, in particular wherein the anti-CMKLR1 antibody or antigen-binding fragment thereof has an effect of a pro-resolution factor of inflammation, in particular has such an effect by interacting with myeloid cell.

4. The anti-CMKLR1 antibody or antigen-binding fragment thereof according to any one of claims 1 to 3, wherein:
- VHCDR1 is selected from the group consisting of SEQ ID No. 3 and SEQ ID No. 4; and/or
 - 5 - VHCDR2 is selected from the group consisting of SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11 and SEQ ID No. 61; and/or
 - VHCDR3 is selected from the group consisting of SEQ ID No. 13, SEQ ID No. 14 and SEQ ID No. 15.
- 10 5. The anti-CMKLR1 antibody or antigen-binding fragment thereof according to any one of claims 1 to 4, wherein:
- VLCDR1 is selected from the group consisting of SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19 and SEQ ID No. 23, and/or
 - VLCDR2 is selected from the group consisting of SEQ ID No. 24, SEQ ID No. 25, 15 SEQ ID No. 26, SEQ ID No. 27 and SEQ ID No. 33; and/or
 - VLCDR3 is selected from the group consisting of SEQ ID No. 34, SEQ ID No. 35 and SEQ ID No. 36.
- 20 6. The anti-CMKLR1 antibody or antigen-binding fragment thereof according to any one of claims 1 to 5 which comprises a heavy chain variable domain comprising or consisting of an amino acid sequence selected from the group consisting of SEQ ID No. 38, SEQ ID No. 39, SEQ ID No. 40 and SEQ ID No. 62.
- 25 7. The anti-CMKLR1 antibody or antigen-binding fragment thereof according to any one of claims 1 to 6, which comprises a light chain variable domain comprising or consisting of an amino acid sequence selected from the group consisting of SEQ ID No. 49, SEQ ID No. 50, SEQ ID No. 51, SEQ ID No. 52, SEQ ID No. 53, SEQ ID No. 54, SEQ ID No. 55, SEQ ID No. 56, SEQ ID No. 57 and, SEQ ID No. 58.
- 30 8. The anti-CMKLR1 antibody or antigen-binding fragment thereof according to any one of claims 1 to 7, which comprises a heavy chain variable domain comprising or consisting of the amino acid sequence selected from the group consisting of SEQ ID No. 38, SEQ ID No. 39, SEQ ID No. 40 and, SEQ ID No. 62; and a light chain variable domain comprising or consisting of an amino acid sequence selected from the group 35 consisting of SEQ ID No. 54, SEQ ID No. 55 and SEQ ID No. 56.

9. The anti-CMKLR1 antibody or antigen-binding fragment thereof according to any one of claims 1 to 3, which comprises the following CDRs: VHCDR1 of SEQ ID No. 4; VHCDR2 of SEQ ID No. 12; VHCDR3 of SEQ ID No. 13, VLCDR1 of SEQ ID No. 19, VLCDR2 of SEQ ID No. 26, and VLCDR3 of SEQ ID No. 35.

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10. The anti-CMKLR1 antibody or antigen-binding fragment thereof according to any one of claims 1 to 9, which comprises the following frameworks: VHFR1 of SEQ ID No. 65, VHFR2 of SEQ ID No. 67, VHFR3 of SEQ ID No. 69, VHFR4 of SEQ ID No. 71, VLFR1 of SEQ ID No. 72, VLFR2 of SEQ ID No. 73, VLFR3 of SEQ ID No. 76 and VLFR4 of SEQ ID No. 77.

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11. The anti-CMKLR1 antibody or antigen-binding fragment thereof according to claim 9 or 10, which comprises a heavy chain variable domain comprising or consisting of the amino acid sequence SEQ ID No. 91 and a light chain variable domain comprising or consisting of the amino acid sequence SEQ ID No. 93.

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12. The anti-CMKLR1 antibody or antigen-binding fragment thereof according to any one of claims 1 to 11, which does not activate the beta-arrestin signaling pathway in CMKLR1-positive cells *in vitro* and/or *in vivo*.

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13. The anti-CMKLR1 antibody or antigen-binding fragment thereof according to any one of claims 1 to 12, which does not exhibit a significant depletion of CMKLR1-positive cells *in vitro* and/or *in vivo*

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14. The anti-CMKLR1 antibody or antigen-binding fragment thereof according to any one of claims 1 to 13, which does not compete with Chemerin for the binding to CMKLR1, and/or which does not interfere with the binding of Chemerin to CMKLR1.

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15. The anti-CMKLR1 antibody or antigen-binding fragment according to any one of claims 1 to 14 which is a humanized monoclonal antibody or antigen-binding fragment thereof, in particular wherein the antibody light chain constant domain is derived from a human kappa light chain constant domain, in particular wherein the light chain constant domain comprises or consists of the sequence of SEQ ID No: 79, and wherein the antibody heavy chain constant domain is derived from a human IgG1, IgG2, IgG3, or IgG4 heavy chain constant domain, in particular wherein the antibody heavy chain constant domain comprises or consists of the amino acid sequence of SEQ ID 80, SEQ ID No. 81, SEQ ID No. 82, SEQ ID No. 83 or SEQ ID No. 84, in particular from a human IgG1 heavy

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chain constant domain, in particular wherein the antibody heavy chain constant domain comprises or consists of the amino acid sequence of SEQ ID No:80 or SEQ ID No. 83.

16. An antibody or antigen-binding fragment thereof, in particular selected from the group consisting of a chimeric, a modified and a humanized antibody, which specifically binds to CMKLR1, in particular human CMKLR1, which comprises an antibody heavy chain variable domain comprising (i) VHCDR2 comprising or consisting of an amino acid sequence set forth in SEQ ID No: 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12 and SEQ ID No. 61, and (ii) VHCDR3 comprising or consisting of an amino acid sequence set forth in SEQ ID No: 13, SEQ ID No. 14, SEQ ID No. 15 and SEQ ID No. 16 or a mutated sequence thereof wherein amino acid residue(s) is(are) substituted provided that amino acid residues at positions 1 and 2 of the mutated sequence are respectively L and I; and wherein the anti-CMKLR1 compound binds specifically to an epitope located within the third extra-cellular loop (EL3) of CMKLR1, in particular wherein the compound binds specifically to a polypeptide comprising or consisting of amino acid sequence SEQ ID No: 2 or SEQ ID No. 59 or to an epitope located within amino acid sequence SEQ ID No. 60 ; and wherein said compound competes with an antibody comprising the heavy chain variable domain corresponding to SEQ ID No: 37 and the light chain variable domain corresponding to SEQ ID No: 49, for the binding to a polypeptide comprising or consisting of amino acid sequence of sequence SEQ ID No: 2 or SEQ ID No. 59 or of SEQ ID No. 60 or to a polypeptide comprising or consisting of the third loop (EL3) of the extracellular domain of CMKLR1.

17. The anti-CMKLR1 antibody or antigen-binding fragment thereof according to claim 16, which comprises the following CDRs:

- VHCDR1 of SEQ ID No. 4;
- VHCDR2 of SEQ ID No. 12;
- VHCDR3 of SEQ ID No. 13,
- VLCDR1 of SEQ ID No. 19,
- VLCDR2 of SEQ ID No. 26, and
- VLCDR3 of SEQ ID No. 35.

18. The anti-CMKLR1 antibody or antigen-binding fragment thereof according to any one of claims 16 or 17, which comprises the following frameworks: VHFR1 of SEQ ID No. 65, VHFR2 of SEQ ID No. 67, VHFR3 of SEQ ID No. 69, VHFR4 of SEQ ID No. 71,

VLFR1 of SEQ ID No. 72, VLFR2 of SEQ ID No. 73, VLFR3 of SEQ ID No. 76, and VLFR4 of SEQ ID No. 77.

19. The anti-CMKLR1 antibody or antigen-binding fragment thereof according to claim 18, which comprises a heavy chain variable domain comprising or consisting of the amino acid sequence SEQ ID No. 91 and a light chain variable domain comprising or consisting of the amino acid sequence SEQ ID No. 93.

20. The anti-CMKLR1 antibody or antigen-binding fragment thereof according to any one of claims 1 to 19 for use in therapy.

20.21. Use of the anti-CMKLR1 antibody or antigen-binding fragment thereof according to any one of claims 1 to 19 ~~for use in the preventive or the therapeutic treatment of~~ in the manufacture of a medicament for preventing or treating:

- an inflammatory disease, in particular acute inflammatory diseases, chronic inflammatory diseases such as chronic inflammatory pulmonary diseases, keratoconjunctivitis, periodontal disease, eczema, inflammatory bowel disease, in particular Crohn's disease or colitis, in particular ulcerative colitis or spontaneous colitis, cystic fibrosis, NASH (Nonalcoholic steatohepatitis), scleroderma, anti-neutrophil cytoplasm antibodies-related disease ANCA associated disease, in particular wherein, as a result of the administration of the treatment, the resolution of inflammation is enhanced;
- an autoimmune disease such as diabetes, in particular type I diabetes, psoriasis, lupus, rheumatoid arthritis, multiple sclerosis, Sjögren's syndrome, celiac disease, vasculitis, myasthenia gravis, or an infection disease such as sepsis, peritonitis, degenerative diseases, wound healing disorders or dry eye syndrome, in particular wherein, as a result of the administration of the treatment, the resolution of inflammation is enhanced;
- a cancer, in particular metastatic cancers, solid or liquid cancers such as carcinoma, more particularly hepatocarcinoma, in particular mammary carcinoma or colon carcinoma, colorectal cancer or lung cancer or mesothelioma or myeloid cancer such as leukemia, in particular a cancer wherein cancer cells express CMKLR1 or where the microenvironment of the tumor is invaded by cells expressing or overexpressing CMKLR1, in particular wherein, as a result of the administration of the treatment, the resolution of inflammation is enhanced.

21.22. Use of the anti-CMKLR1 antibody or antigen-binding fragment thereof according to any one of claims 1 to 20 in the manufacture of a medicament for preventing or treating ~~for use in the preventive or the therapeutic treatment~~ NASH (Nonalcoholic steatohepatitis), scleroderma, cystic fibrosis or anti-neutrophil cytoplasm antibodies-related disease (ANCA).