pneumonia, acute and chronic graft rejection in transplant patients, graft versus host reactions, renal glomerular diseases such as glomerulonephritis and other entities of renal failure, rheumatoid arthritis and similar auto-immune diseases such as Bechterew's disease, lupus-type diseases, inflammatory bowel disease, Crohn's disease, tumor growth, or solid organ cancer in a patient in need thereof, the method comprising administering to the patient an effective amount of (a) a binding moiety according to the first aspect or (b) an antibody or antigen-binding fragment thereof according to the second aspect.

This summary of the invention does not necessarily describe all features of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Before the present invention is described in detail below, it is to be understood that this invention is not limited to the particular methodology, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

Preferably, the terms used herein are defined as described in "A multilingual glossary of biotechnological terms: (IUPAC Recommendations)", Leuenberger, H.G.W, Nagel, B. and Kölbl, H. eds. (1995), Helvetica Chimica Acta, CH-4010 Basel, Switzerland).

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integer or step.

~~Several documents are cited throughout the text of this specification. Each of the documents cited herein (including all patents, patent applications, scientific publications, manufacturer's specifications, instructions, GenBank Accession Number sequence submissions etc.), whether supra or infra, is hereby incorporated by reference in its entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.~~

As used herein, "human C5a" refers to the following 74 amino acid peptide:

portions are homologous to sequences of antibodies derived from another. One clear advantage to such chimeric forms is that the variable region can conveniently be derived from presently known sources using readily available B-cells or hybridomas from non-human host organisms in combination with constant regions derived from, for example, human cell preparations. While the variable region has the advantage of ease of preparation and the specificity is not affected by the source, the constant region being human is less likely to elicit an immune response from a human subject when the antibodies are injected than would the constant region from a non-human source. However, the definition is not limited to this particular example.

The term "humanized antibody" refers to a molecule having an antigen binding site that is substantially derived from an immunoglobulin from a non-human species, wherein the remaining immunoglobulin structure of the molecule is based upon the structure and/or sequence of a human immunoglobulin. The antigen binding site may either comprise complete variable domains fused onto constant domains or only the complementarity determining regions (CDR) grafted onto appropriate framework regions in the variable domains. Antigen-binding sites may be wild-type or modified by one or more amino acid substitutions, e.g. modified to resemble human immunoglobulins more closely. Some forms of humanized antibodies preserve all CDR sequences (for example a humanized mouse antibody which contains all six CDRs from the mouse antibody). Other forms have one or more CDRs which are altered with respect to the original antibody.

Different methods for humanizing antibodies are known to the skilled person, as reviewed by Almagro & Fransson, 2008, ~~the content of which is herein incorporated by reference in its entirety~~. The review article by Almagro & Fransson is briefly summarized in the following. Almagro & Fransson distinguish between rational approaches and empirical approaches. Rational approaches are characterized by generating few variants of the engineered antibody and assessing their binding or any other property of interest. If the designed variants do not produce the expected results, a new cycle of design and binding assessment is initiated. Rational approaches include CDR grafting, Resurfacing, Superhumanization, and Human String Content Optimization. In contrast, empirical approaches are based on the generation of large libraries of humanized variants and selection of the best clones using enrichment technologies or high-throughput screening. Accordingly, empirical approaches are dependent on a reliable selection and/or screening system that is able to search through a vast space of antibody variants. *In vitro* display technologies, such as phage display and ribosome display fulfill these requirements and are well-known to the

1. A binding moiety which binds to a conformational epitope formed by amino acid sequences ~~X_1X_2ETCEX_3RX_4 (SEQ ID NO: 18)~~ NDETCEQRA (SEQ ID NO: 2) and ~~X_5X_6K$X_7X_8X_9$L (SEQ ID NO: 19)~~ SHKDMQL (SEQ ID NO: 3) of C5a,

wherein the binding moiety binds to at least one amino acid within the amino acid sequence according to SEQ ID NO: 2 and to at least one amino acid within the amino acid sequence according to SEQ ID NO: 3;

wherein said binding moiety has a binding constant to C5a with a Kd value of 100 nM or less;

~~wherein~~

~~X_1 is selected from the group consisting of N, H, D, F, K, Y, and T;~~

~~X_2 is selected from the group consisting of D, L, Y, and H;~~

~~X_3 is selected from the group consisting of Q, E, and K;~~

~~X_4 is selected from the group consisting of A, V, and L;~~

~~X_5 is selected from the group consisting of S, H, P, and N;~~

~~X_6 is selected from the group consisting of H and N;~~

~~X_7 is selected from the group consisting of D, N, H, P, and G;~~

~~X_8 is selected from the group consisting of M, L, I, and V; and~~

~~X_9 is selected from the group consisting of Q, L, and I;~~

wherein said binding moiety is selected from the group consisting of:

(a) antibodies or antigen-binding fragments thereof; and

~~(b) oligonucleotides;~~

(eb) antibody-like proteins~~; and~~

~~(d) peptidomimetics.~~

~~2. The binding moiety of claim 1, wherein the binding moiety binds to at least one amino acid of the amino acid sequence X_2ETCEX_3R (SEQ ID NO: 20),~~
~~wherein X_2 and X_3 are defined as in claim 1.~~

~~3. The binding moiety of claims 1 or 2, wherein the binding moiety binds to at least one amino acid of the amino acid sequence X_6K$X_7X_8X_9$ (SEQ ID NO: 21), preferably KX_7X_8,~~
~~wherein X_6, X_7, X_8, and X_9 are defined as in claim 1.~~

~~4. The binding moiety of claim 1, 2, or 3, wherein the conformational epitope is formed by~~

~~(a) amino acid sequences NDETCEQRA (SEQ ID NO: 2) and SHKDMQL (SEQ ID NO: 3) of C5a;~~

~~(b) amino acid sequences HDETCEQRA (SEQ ID NO: 22) and SHKDLQL (SEQ ID NO: 23) of C5a;~~

~~(c) amino acid sequences DDETCEERA (SEQ ID NO: 24) and SHKNIQL (SEQ ID NO: 25) of C5a;~~

~~(d) amino acid sequences DLETCEQRA (SEQ ID NO: 26) and SHKHIQL (SEQ ID NO: 27) of C5a;~~

~~(e) amino acid sequences DDETCEQRA (SEQ ID NO: 28) and HHKNMQL (SEQ ID NO: 29) of C5a;~~

~~(f) amino acid sequences FYETCEERV (SEQ ID NO: 30) and PHKPVQL (SEQ ID NO: 31) of C5a;~~

~~(g) amino acid sequences KYETCEQRV (SEQ ID NO: 32) and HHKGMLL (SEQ ID NO: 33) of C5a;~~

~~(h) amino acid sequences YDETCEQRA (SEQ ID NO: 34) and SNKPLQL (SEQ ID NO: 35) of C5a; or~~

~~(i) amino acid sequences THETCEKRL (SEQ ID NO: 36) and NHKPVIL (SEQ ID NO: 37) of C5a.~~

~~5~~2. The binding moiety of ~~any one of~~ claims ~~1 to 4~~, wherein the binding moiety binds to at least one amino acid of an amino acid sequence ~~selected from the group consisting of~~according to

~~(a)~~ DETCEQR (SEQ ID NO: 4)~~;~~

~~(b) DETCEER (SEQ ID NO: 38);~~

~~(c) LETCEQR (SEQ ID NO: 39);~~

~~(e) YETCEER (SEQ ID NO: 40);~~

~~(f) YETCEQR (SEQ ID NO: 41); and~~

~~(g) HETCEKR (SEQ ID NO: 42)~~.

~~63~~63. The binding moiety of ~~any one of~~ claims ~~1 to 5~~ or 2, wherein the binding moiety binds to at least one amino acid of an amino acid sequence ~~selected from the group consisting of~~according to

~~(a) HKDMQ (SEQ ID NO: 5), preferably KDM;~~

~~(b) HKDLQ (SEQ ID NO: 43), preferably KDL;~~

~~(c) HKNIQ (SEQ ID NO: 44), preferably KNI;~~

~~(d) HKHIQ (SEQ ID NO: 45), preferably KHI;~~

~~(e) HKNMQ (SEQ ID NO: 46), preferably KNM;~~

~~(f) HKPVQ (SEQ ID NO: 47), preferably KPV;~~

~~(g) HKGML (SEQ ID NO: 48), preferably KGM;~~

~~(h) NKPLQ (SEQ ID NO: 49), preferably KPL; and~~

~~(i) HKPVI (SEQ ID NO: 50), preferablyKPV~~.

~~74~~74 The binding moiety of any one of claims 1 to ~~63~~63, wherein said binding moiety exhibits one or more of the following properties:

- said binding moiety has a binding constant to C5a with a K_d value of 10 nM or less;
- one binding moiety exhibits at least 80% blocking activity for biological effects induced by one molecule C5a;
- said binding moiety does not inhibit CH50 activity in human plasma;
- said binding moiety is capable of reducing *E. coli* induced IL-8 production in human whole blood.

~~85~~85. The binding moiety of any one of claims 1 to ~~74~~74, wherein the binding moiety is an antibody or an antigen-binding fragment thereof, said antibody being selected from the group consisting of polyclonal antibodies, monoclonal antibodies, chimeric antibodies, humanized antibodies, and human antibodies.

~~96~~96. The binding moiety of any one of claims 1 to ~~74~~74, wherein the binding moiety is an antigen-binding fragment of an antibody, said fragment being selected from the group consisting of Fab fragments, Fab' fragments, $F(ab')_2$ fragments, Fd fragments, Fv fragments, disulfide-linked Fvs (dsFv), single domain antibodies and single chain Fv (scFv) antibodies.

~~10~~7. An antibody or an antigen-binding fragment thereof comprising:

(i) a heavy chain CDR3 sequence as set forth in SEQ ID NO: 6; or

(ii) a heavy chain CDR3 sequence as set forth in SEQ ID NO: 7;

wherein the heavy chain CDR3 sequence optionally comprises 1, 2 or 3 amino acid exchanges, 1, 2, or 3 amino acid deletions and/or 1, 2, or 3 amino acid additions,

further comprising at least one of the following sequences:

(i) a heavy chain CDR2 sequence according to SEQ ID NO: 10;

(ii) a heavy chain CDR2 sequence according to SEQ ID NO: 11;

(iii) a light chain CDR2 sequence according to SEQ ID NO: 12;

(iv) a light chain CDR2 sequence according to SEQ ID NO: 13;

(v) a heavy chain CDR1 sequence according to SEQ ID NO: 14;

(vi) a heavy chain CDR1 sequence according to SEQ ID NO: 15;

(vii) a light chain CDR1 sequence according to SEQ ID NO: 16; or

(viii) a light chain CDR1 sequence according to SEQ ID NO: 17;

wherein the heavy chain CDR2 sequence optionally comprises 1, 2 or 3 amino acid exchanges, 1, 2, or 3 amino acid deletions and/or 1, 2, or 3 amino acid additions;

wherein the light chain CDR2 sequence optionally comprises 1, 2 or 3 amino acid exchanges, 1, 2, or 3 amino acid deletions and/or 1, 2, or 3 amino acid additions;

wherein the heavy chain CDR1 sequence optionally comprises 1, 2 or 3 amino acid exchanges, 1, 2, or 3 amino acid deletions and/or 1, 2, or 3 amino acid additions;

wherein the light chain CDR1 sequence optionally comprises 1, 2 or 3 amino acid exchanges, 1, 2, or 3 amino acid deletions and/or 1, 2, or 3 amino acid additions;

wherein the antibody or antigen-binding fragment thereof binds to a conformational epitope formed by amino acid sequences NDETCEQRA (SEQ ID NO: 2) and SHKDMQL (SEQ ID NO: 3) of C5a;

wherein the antibody or antigen-binding fragment thereof binds to at least one amino acid within the amino acid sequence according to SEQ ID NO: 2 and to at least one amino acid within the amino acid sequence according to SEQ ID NO: 3; and

wherein said antibody or antigen-binding fragment thereof has a binding constant to C5a with a Kd value of 100 nM or less.

~~11~~8. The antibody or fragment thereof according to claim ~~10~~ 7, further comprising:

(i) a light chain CDR3 sequence as set forth in SEQ ID NO: 8; or

(ii) a light chain CDR3 sequence as set forth in SEQ ID NO: 9;

wherein the light chain CDR3 sequence optionally comprises 1, 2 or 3 amino acid exchanges, 1, 2, or 3 amino acid deletions and/or 1, 2, or 3 amino acid additions.

~~12~~9. An antibody or an antigen-binding fragment thereof comprising:

(i) a light chain CDR3 sequence as set forth in SEQ ID NO: 8; or

(ii) a light chain CDR3 sequence as set forth in SEQ ID NO: 9;

wherein the light chain CDR3 sequence optionally comprises 1, 2 or 3 amino acid exchanges, 1, 2, or 3 amino acid deletions and/or 1, 2, or 3 amino acid additions;

wherein the antibody or antigen-binding fragment thereof binds to a conformational epitope formed by amino acid sequences NDETCEQRA (SEQ ID NO: 2) and SHKDMQL (SEQ ID NO: 3) of C5a;

wherein the antibody or antigen-binding fragment thereof binds to at least one amino acid within the amino acid sequence according to SEQ ID NO: 2 and to at least one amino acid within the amino acid sequence according to SEQ ID NO: 3; and

wherein said antibody or antigen-binding fragment thereof has a binding constant to C5a with a Kd value of 100 nM or less.

~~13~~10. The antibody or fragment thereof according to claim ~~12~~9, further comprising at least one of the following sequences:

(i) a heavy chain CDR2 sequence according to SEQ ID NO: 10;

(ii) a heavy chain CDR2 sequence according to SEQ ID NO: 11;

(iii) a light chain CDR2 sequence according to SEQ ID NO: 12;

(iv) a light chain CDR2 sequence according to SEQ ID NO: 13;

(v) a heavy chain CDR1 sequence according to SEQ ID NO: 14;

(vi) a heavy chain CDR1 sequence according to SEQ ID NO: 15;

(vii) a light chain CDR1 sequence according to SEQ ID NO: 16; or

(viii) a light chain CDR1 sequence according to SEQ ID NO: 17;

wherein the heavy chain CDR2 sequence optionally comprises 1, 2 or 3 amino acid exchanges, 1, 2, or 3 amino acid deletions and/or 1, 2, or 3 amino acid additions;

wherein the light chain CDR2 sequence optionally comprises 1, 2 or 3 amino acid exchanges, 1, 2, or 3 amino acid deletions and/or 1, 2, or 3 amino acid additions;

wherein the heavy chain CDR1 sequence optionally comprises 1, 2 or 3 amino acid exchanges, 1, 2, or 3 amino acid deletions and/or 1, 2, or 3 amino acid additions;
wherein the light chain CDR1 sequence optionally comprises 1, 2 or 3 amino acid exchanges, 1, 2, or 3 amino acid deletions and/or 1, 2, or 3 amino acid additions.

~~14~~11. An antibody or an antigen-binding fragment thereof comprising a set of heavy chain CDR3, heavy chain CDR2, and heavy chain CDR1 sequences selected from one of the following sets:

(i) a heavy chain CDR3 sequence according to SEQ ID NO: 6, a heavy chain CDR2 sequence according to SEQ ID NO: 10, and a heavy chain CDR1 sequence according to SEQ ID NO: 14;

(ii) a heavy chain CDR3 sequence according to SEQ ID NO: 6, a heavy chain CDR2 sequence according to SEQ ID NO: 10, and a heavy chain CDR1 sequence according to SEQ ID NO: 15;

(iii) a heavy chain CDR3 sequence according to SEQ ID NO: 6, a heavy chain CDR2 sequence according to SEQ ID NO: 11, and a heavy chain CDR1 sequence according to SEQ ID NO: 14;

(iv) a heavy chain CDR3 sequence according to SEQ ID NO: 6, a heavy chain CDR2 sequence according to SEQ ID NO: 11, and a heavy chain CDR1 sequence according to SEQ ID NO: 15;

(v) a heavy chain CDR3 sequence according to SEQ ID NO: 7, a heavy chain CDR2 sequence according to SEQ ID NO: 10, and a heavy chain CDR1 sequence according to SEQ ID NO: 14;

(vi) a heavy chain CDR3 sequence according to SEQ ID NO: 7, a heavy chain CDR2 sequence according to SEQ ID NO: 10, and a heavy chain CDR1 sequence according to SEQ ID NO: 15;

(vii) a heavy chain CDR3 sequence according to SEQ ID NO: 7, a heavy chain CDR2 sequence according to SEQ ID NO: 11, and a heavy chain CDR1 sequence according to SEQ ID NO: 14; or

(viii) a heavy chain CDR3 sequence according to SEQ ID NO: 7, a heavy chain CDR2 sequence according to SEQ ID NO: 11, and a heavy chain CDR1 sequence according to SEQ ID NO: 15;

wherein each heavy chain CDR3 sequence optionally comprises 1, 2 or 3 amino acid exchanges, 1, 2, or 3 amino acid deletions and/or 1, 2, or 3 amino acid additions;
wherein each heavy chain CDR2 sequence optionally comprises 1, 2 or 3 amino acid exchanges, 1, 2, or 3 amino acid deletions and/or 1, 2, or 3 amino acid additions; and
wherein each heavy chain CDR1 sequence optionally comprises 1, 2 or 3 amino acid exchanges, 1, 2, or 3 amino acid deletions and/or 1, 2, or 3 amino acid additions;
wherein the antibody or antigen-binding fragment thereof binds to a conformational epitope formed by amino acid sequences NDETCEQRA (SEQ ID NO: 2) and SHKDMQL (SEQ ID NO: 3) of C5a;
wherein the antibody or antigen-binding fragment thereof binds to at least one amino acid within the amino acid sequence according to SEQ ID NO: 2 and to at least one amino acid within the amino acid sequence according to SEQ ID NO: 3; and
wherein said antibody or antigen-binding fragment thereof has a binding constant to C5a with a Kd value of 100 nM or less.

~~15~~12. An antibody or an antigen-binding fragment thereof comprising a set of light chain CDR3, light chain CDR2, and light chain CDR1 sequences selected from one of the following sets:

(i) a light chain CDR3 sequence according to SEQ ID NO: 8, a light chain CDR2 sequence according to SEQ ID NO: 12, and a light chain CDR1 sequence according to SEQ ID NO: 16;

(ii) a light chain CDR3 sequence according to SEQ ID NO: 8, a light chain CDR2 sequence according to SEQ ID NO: 12, and a light chain CDR1 sequence according to SEQ ID NO: 17;

(iii) a light chain CDR3 sequence according to SEQ ID NO: 9, a light chain CDR2 sequence according to SEQ ID NO: 12, and a light chain CDR1 sequence according to SEQ ID NO: 16; or

(iv) a light chain CDR3 sequence according to SEQ ID NO: 9, a light chain CDR2 sequence according to SEQ ID NO: 12, and a light chain CDR1 sequence according to SEQ ID NO: 17;

wherein each light chain CDR3 sequence optionally comprises 1, 2 or 3 amino acid exchanges, 1, 2, or 3 amino acid deletions and/or 1, 2, or 3 amino acid additions;

wherein each light chain CDR2 sequence optionally comprises 1, 2 or 3 amino acid exchanges, 1, 2, or 3 amino acid deletions and/or 1, 2, or 3 amino acid additions; and wherein each light chain CDR1 sequence optionally comprises 1, 2 or 3 amino acid exchanges, 1, 2, or 3 amino acid deletions and/or 1, 2, or 3 amino acid additions;

wherein the antibody or antigen-binding fragment thereof binds to a conformational epitope formed by amino acid sequences NDETCEQRA (SEQ ID NO: 2) and SHKDMQL (SEQ ID NO: 3) of C5a;

wherein the antibody or antigen-binding fragment thereof binds to at least one amino acid within the amino acid sequence according to SEQ ID NO: 2 and to at least one amino acid within the amino acid sequence according to SEQ ID NO: 3; and

wherein said antibody or antigen-binding fragment thereof has a binding constant to C5a with a Kd value of 100 nM or less.

~~16~~13. Pharmaceutical composition comprising

(a) the binding moiety according to any one of claims 1 to ~~9~~6 or

(b) the antibody or antigen-binding fragment thereof according to any one of claims ~~10~~7 to ~~15~~12

and further comprising one or more pharmaceutically acceptable carriers, diluents, excipients, fillers, binders, lubricants, glidants, disintegrants, adsorbents, and/or preservatives.

~~17~~14. Use of

(a) a binding moiety according to any one of claims 1 to ~~9~~6 or

(b) an antibody or antigen-binding fragment thereof according to any one of claims ~~13~~7 to ~~18~~12

for the preparation of a pharmaceutical composition for the prevention and or treatment of various diseases involving acute inflammation such as systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, ischemia/reperfusion related injuries such as ischemic heart disease, acute lung injury, pneumonia, acute and chronic graft rejection in transplant patients, graft versus host reactions, as wells as diseases involving chronic types of inflammation such as renal glomerular diseases such as glomerulonephritis and other entities of renal failure, rheumatoid arthritis and similar auto-immune diseases such as Bechterew's disease,

lupus-type diseases, inflammatory bowel disease, Crohn´s disease, tumor growth, or solid organ cancer.