

TECHNICAL PROBLEMS UNDERLYING THE PRESENT INVENTION

As explained above, there existed a need in the prior art for effective therapies for the treatment of neutrophilic dermatoses, such as Hidradenitis suppurativa (HS), and cutaneous neutrophilic autoimmune diseases.

5 The present inventors have now surprisingly found that molecules inhibiting C5a signaling, e.g. an anti-C5a antibody, are exceptionally well-suited for the treatment of Hidradenitis suppurativa. The present inventors have additionally studied the physiological mechanism leading to neutrophil activation and found out that C5a is the key driver of neutrophil activation.

10 Thus, the present inventors expect that inhibiting C5a activity will be a suitable therapy approach for the treatment of various neutrophilic disorders, especially cutaneous, neutrophilic, inflammatory diseases.

SUMMARY

15 In one aspect the present disclosure refers to the use of a compound in the manufacture of a medicament for treating a cutaneous, neutrophilic, inflammatory disease in a subject, wherein the compound is an inhibitor of C5a activity, and wherein the cutaneous, neutrophilic, inflammatory disease is selected from the group consisting of hidradenitis suppurativa (HS); Pyoderma gangrenosum (PG); PAPA (pyogenic arthritis, PG and acne); PASH (PG, acne and
20 hidradenitis suppurativa); PAPASH (pyogenic arthritis, acne, PG and hidradenitis suppurativa); Sweet syndrome (SS); subcorneal pustular dermatosis (SPD); epidermolysis bullosa acquisita, erythema elevatum diutinum (EED); neutrophilic panniculitis; bowel-associated dermatosis-arthritis syndrome (BADAS); SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome; rheumatoid neutrophilic dermatosis; familial Mediterranean fever, cryopyrin-associated disorders, gout, and Schnitzler syndrome, wherein the inhibitor of C5a activity: (a)
25 inhibits the activity or lowers the concentration of a C5a receptor; or (b) inhibits binding between C5a and a C5a receptor, inhibits cleavage of C5 into C5a and C5b or lowers the concentration of C5a.

30 In one example, there is disclosed a method for the treatment of a cutaneous, neutrophilic, inflammatory disease in a subject, comprising the step of:

administering to a subject in need thereof a therapeutic amount of a compound, wherein the compound is an inhibitor of C5a activity, and wherein the cutaneous, neutrophilic, inflammatory disease is selected from the group consisting of hidradenitis suppurativa (HS); Pyoderma gangrenosum (PG); PAPA (pyogenic arthritis, PG and acne); PASH (PG, acne and
35 hidradenitis suppurativa); PAPASH (pyogenic arthritis, acne, PG and hidradenitis suppurativa); Sweet syndrome (SS); subcorneal pustular dermatosis (SPD); epidermolysis bullosa acquisita,

erythema elevatum diutinum (EED); neutrophilic panniculitis; bowel-associated dermatosis-arthritis syndrome (BADAS); SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome; rheumatoid neutrophilic dermatosis; familial Mediterranean fever, cryopyrin-associated disorders, gout, and Schnitzler syndrome.

5 In a further example, there is disclosed a use of a compound for the preparation of a pharmaceutical composition for the treatment of a cutaneous, neutrophilic, inflammatory disease, wherein the compound is an inhibitor of C5a activity, and wherein the cutaneous, neutrophilic, inflammatory disease is selected from the group consisting of hidradenitis suppurativa (HS);
 10 Pyoderma gangrenosum (PG); PAPA (pyogenic arthritis, PG and acne); PASH (PG, acne and hidradenitis suppurativa); PAPASH (pyogenic arthritis, acne, PG and hidradenitis suppurativa);
 Sweet syndrome (SS); subcorneal pustular dermatosis (SPD); epidermolysis bullosa acquisita, erythema elevatum diutinum (EED); neutrophilic panniculitis; bowel-associated dermatosis-arthritis syndrome (BADAS); SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome; rheumatoid neutrophilic dermatosis; familial Mediterranean fever, cryopyrin-
 15 associated disorders, gout, and Schnitzler syndrome.

This summary of the invention does not necessarily describe all features of the present invention. Other embodiments will become apparent from a review of the ensuing detailed description.

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BRIEF DESCRIPTION OF THE FIGURES

Figure 1. Blocking activity of IFX-1 to recombinant human C5a (rhC5a)-induced CD11b upregulation on blood neutrophils. IFX-1-004 and IFX-1-012 represent two different production batches. Human whole blood was incubated with buffer, antibody alone, rhC5a alone,
 25 or combinations of different antibody concentration and rhC5a. After incubation, cells were stained with anti-mouse CD11b:FITC and CD11b MFI was analysed by flow cytometry. Results are presented as mean $\pm$ SD. The percentage of IFX-1 blocking activity of C5a-induced CD11b expression is marked (arrow). Statistical differences were calculated by One-Way-ANOVA, p values of $p < 0.05$ were statistically significant.

30 **Figure 2. Blocking activity of IFX-1 on endogenous C5a (eC5a)-driven CD11b upregulation on neutrophils.** Zymosan-activated human plasma (ZAP) was used as the source of eC5a. Whole blood was incubated with buffer, IFX-1 alone, ZAP alone, or combinations of IFX-1 and ZAP. After incubation, cells were stained with anti-mouse CD11b:FITC and analysed by flow cytometry. Results are presented as mean $\pm$ SD. The percentage of IFX-1

CLAIMS

1. Use of a compound in the manufacture of a medicament for treating a cutaneous, neutrophilic, inflammatory disease in a subject, wherein the compound is an inhibitor of C5a activity, and
5 wherein the cutaneous, neutrophilic, inflammatory disease is selected from the group consisting of hidradenitis suppurativa (HS); Pyoderma gangrenosum (PG); PAPA (pyogenic arthritis, PG and acne); PASH (PG, acne and hidradenitis suppurativa); PAPASH (pyogenic arthritis, acne, PG and hidradenitis suppurativa); Sweet syndrome (SS); subcorneal pustular dermatosis (SPD); epidermolysis bullosa acquisita, erythema elevatum diutinum (EED); neutrophilic panniculitis; bowel-associated dermatosis-arthritis syndrome (BADAS); SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome; rheumatoid neutrophilic dermatosis; familial Mediterranean fever, cryopyrin-associated disorders, gout, and Schnitzler syndrome, wherein the inhibitor of C5a activity:
15 (a) inhibits the activity or lowers the concentration of a C5a receptor; or
(b) inhibits binding between C5a and a C5a receptor, inhibits cleavage of C5 into C5a and C5b or lowers the concentration of C5a.
- 20 2. The use of claim 1, wherein the inhibitor of C5a activity is a protein ligand that specifically binds to C5, or to C5a, or to a C5a receptor.
3. The use of claim 2, wherein the protein ligand is selected from the group consisting of
25 (i) antibodies,
(ii) antigen-binding fragments of antibodies,
(iii) antibody-like proteins,
(iv) inhibitory variants of C5a,
(v) inhibitory variants of a C5a receptor,
(vi) proteins acting on the complement pathway; and
30 (vii) peptides.
4. The use of claim 1, wherein the inhibitor of C5a activity is an oligonucleotide that specifically binds to C5, or to C5a, or to a C5a receptor.

5. The use of claim 4, wherein the oligonucleotide is selected from the group consisting of DNA-aptamers, D-RNA aptamers, and L-RNA aptamers.
6. The use of claim 1, wherein the inhibitor of C5a activity reduces expression of C5 protein or a C5a receptor protein.
7. The use of claim 6, wherein said inhibitor of C5a activity is an oligonucleotide selected from the group consisting of antisense DNA, antisense RNA, siRNA, and miRNA.
8. The use of any one of claims 1 to 7, wherein the C5a receptor is C5aR and/or C5L2.
9. The use of any one of claims 1 to 8, wherein the inhibitor of C5a activity is selected from the group consisting of:
 - (a) IFX-1, INab708, MEDI-7814, ALXN-1007, or NOX-D21, or an antigen-binding fragment thereof;
 - (b) an antibody or an antigen-binding fragment thereof, wherein said antibody or antigen-binding fragment thereof competes with one of the antibodies indicated under (a) for binding to C5a;
 - (c) Eculizumab, ALXN1210, ALXN5500, or LFG316, or an antigen-binding fragment thereof;
 - (d) an antibody or an antigen-binding fragment thereof, wherein said antibody or antigen-binding fragment thereof competes with one of the antibodies indicated under (c) for binding to C5;
 - (e) Coversin or RA101495;
 - (f) an antibody or an antigen-binding fragment thereof or a protein or a macrocyclic peptide wherein said antibody or antigen-binding fragment thereof or protein or macrocyclic peptide competes with one of the proteins or peptides indicated under (e) for binding to C5;
 - (g) Zimura;
 - (h) an antibody or an antigen-binding fragment thereof or an aptamer, wherein said antibody or antigen-binding fragment thereof or aptamer competes with Zimura for binding to C5;
 - (i) AMY-201 or Mirococept;

- (j) an antibody or an antigen-binding fragment thereof or a protein wherein said antibody or antigen-binding fragment thereof or protein competes with one of the proteins indicated under (i) for binding to C3b;
 - (k) Bikaciomab;
 - 5 (l) an antibody or an antigen-binding fragment thereof, wherein said antibody or antigen-binding fragment thereof competes with Bikaciomab for binding to Factor B;
 - (m) Lampalizumab;
 - 10 (n) an antibody or an antigen-binding fragment thereof, wherein said antibody or antigen-binding fragment thereof competes with Lampalizumab for binding to Factor D;
 - (o) ALN-CC5;
 - (p) Avacopan or a compound according to formula II or formula III; or PMX-53 or a compound according to formula IV;
 - 15 (q) an antibody or an antigen-binding fragment thereof, wherein said antibody or antigen-binding fragment thereof competes with avacopan or PMX-53 for binding to C5aR;
 - (r) clone S5/1 or clone 7H110, or an antigen-binding fragment thereof; and
 - (s) an antibody or an antigen-binding fragment thereof, wherein said antibody or
20 antigen-binding fragment thereof competes with one of the antibodies indicated under (r) for binding to C5aR.
10. The use of any one of claims 1 to 9, wherein the cutaneous, neutrophilic, inflammatory disease is an auto-inflammatory disease selected from the group consisting of
25 hidradenitis suppurativa (HS); Pyoderma gangrenosum (PG); PAPA (pyogenic arthritis, PG and acne); PASH (PG, acne and hidradenitis suppurativa); PAPASH (pyogenic arthritis, acne, PG and hidradenitis suppurativa); Sweet syndrome (SS); subcorneal pustular dermatosis (SPD); epidermolysis bullosa acquisita, erythema elevatum diutinum (EED); neutrophilic panniculitis; bowel-associated dermatosis-arthritis syndrome (BADAS); and SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome;.
- 30 11. The use of any one of claims 1 to 9, wherein the cutaneous, neutrophilic, inflammatory disease is HS or a HS-related disease selected from the group consisting of Pyoderma

gangrenosum (PG); PAPA (pyogenic arthritis, PG and acne); PASH (PG, acne and hidradenitis suppurativa); PAPASH (pyogenic arthritis, acne, PG and hidradenitis suppurativa); Sweet syndrome (SS); and subcorneal pustular dermatosis (SPD).

- 5 12. The use of any one of claims 1 to 9, wherein the cutaneous, neutrophilic, inflammatory disease is an autoimmune disease with cutaneous inflammation selected from the group consisting of rheumatoid neutrophilic dermatosis; familial Mediterranean fever, cryopyrin-associated disorders, gout, and Schnitzler syndrome.
- 10 13. The use of any one of claims 1 to 12, wherein the compound is to be administered at a dose of 800 mg once per week or at a dose of 800 mg twice per week.