

CLAIMS

~~1. (Cancelled)~~

~~2. (Cancelled)~~

~~31.~~ An antibody molecule capable of binding to complement component 5a receptor 1 (C5aR1), wherein the antibody molecule competes with a C5aR1 antibody molecule comprising:
an HCDR1 comprising [an amino acid sequence of](#) SEQ ID NO: 656, an HCDR2 comprising [an amino acid sequence of](#) SEQ ID NO: 776, and an HCDR3 comprising [an amino acid sequence of](#) SEQ ID NO: 896, an LCDR1 comprising [an amino acid sequence of](#) SEQ ID NO: 715, an LCDR2 comprising [an amino acid sequence of](#) SEQ ID NO: 835, and an LCDR3 comprising [an amino acid sequence of](#) SEQ ID NO: 955.

~~42.~~ ~~An~~The antibody molecule capable of [binding to C5aR1 claim 1](#), wherein the antibody molecule binds to an epitope on Site I of C5aR1, wherein the epitope on Site I comprises [amino acid residues](#) SEQ ID NO: 1449 or SEQ ID NO: 1452.

~~5.~~ ~~The antibody molecule of claim 4, wherein the antibody molecule binds to residues T8-D18 in SEQ ID NO: 1449 or SEQ ID NO: 1452.~~

~~6.~~ ~~The antibody molecule of claim 5, wherein the antibody molecule binds to residues T8-G12 in SEQ ID NO: 1449 or SEQ ID NO: 1452.~~

~~7.~~ ~~The antibody molecule of claim 5, wherein the antibody molecule binds to residues T8, D10, Y11, Y14, and/or D15 in SEQ ID NO: 1449 or SEQ ID NO: 1452.~~

~~8.~~ ~~An antibody molecule capable of binding to C5aR1, comprising a heavy chain variable region (VH) and a light chain variable region (VL),~~
~~wherein the VH has at least 80% identity with any of SEQ ID NOs: 481-541; and~~
~~wherein the VL has at least 70% identity with any of SEQ ID NOs: 542-600.~~

~~93.~~ ~~An~~The antibody molecule ~~capable of~~ [binding to complement C5aR1 claim 1](#), comprising a VH and/or a VL,

wherein the VH comprises:

- i. an HCDR1 comprising [an amino acid sequence of](#) SEQ ID NO: 656;
- ii. an HCDR2 comprising [an amino acid sequence of](#) SEQ ID NO: 776; and
- iii. an HCDR3 comprising [an amino acid sequence of](#) SEQ ID NO: 896; and

wherein the VL comprises:

- i. an LCDR1 comprising [an amino acid sequence of](#) SEQ ID NO: 715,
- ii. an LCDR2 comprising [an amino acid sequence of](#) SEQ ID NO: 835, and
- iii. an LCDR3 comprising [an amino acid sequence of](#) SEQ ID NO: 955.

~~10. An antibody molecule capable of binding to C5aR1, comprising a VH and/or a VL,
wherein the VH comprises:~~

- ~~i. an HCDR1 comprising SEQ ID NO: 1456;~~
- ~~ii. an HCDR2 comprising SEQ ID NO: 1457; and~~
- ~~iii. an HCDR3 comprising SEQ ID NO: 1458; and~~

~~wherein the VL comprises:~~

- ~~i. an LCDR1 comprising SEQ ID NO: 1459,~~
- ~~ii. an LCDR2 comprising SEQ ID NO: 1460, and~~
- ~~iii. an LCDR3 comprising SEQ ID NO: 1461.~~

~~11. An antibody molecule capable of binding to C5aR1, comprising a VH and/or a VL,
wherein the VH comprises at least 80% identity with SEQ ID NO: 536; and
wherein the VL comprises at least 70% identity with SEQ ID NO: 595.~~

~~12. The antibody molecule of any one of claims 9-11, wherein the VH comprises SEQ ID NO:
536 and the VL comprises SEQ ID NO: 595.~~

~~134. An~~The antibody molecule ~~capable of binding to complement C5aR1~~claim 1,
comprising a VH and/or a VL,

wherein the VH comprises:

- i. an HCDR1 comprising [an amino acid sequence of](#) SEQ ID NO: 603;
- ii. an HCDR2 comprising [an amino acid sequence of](#) SEQ ID NO: 723; and
- iii. an HCDR3 comprising [an amino acid sequence of](#) SEQ ID NO: 843; and

wherein the VL comprises:

- i. an LCDR1 comprising [an amino acid sequence of](#) SEQ ID NO: 663,
- ii. an LCDR2 comprising [an amino acid sequence of](#) SEQ ID NO: 783, and
- iii. an LCDR3 comprising [an amino acid sequence of](#) SEQ ID NO: 903.

~~14. The antibody molecule of claim 13, wherein the VH comprises SEQ ID NO: 483 and the VL comprises SEQ ID NO: 543.~~

~~155.~~ ~~An~~The antibody molecule ~~capable~~ of ~~binding to C5aR1~~claim 1, comprising a VH and/or a VL,

wherein the VH comprises:

- i. an HCDR1 comprising an amino acid sequence of SEQ ID NO: 611;
- ii. an HCDR2 comprising an amino acid sequence of SEQ ID NO: 731; and
- iii. an HCDR3 comprising an amino acid sequence of SEQ ID NO: 851; and

wherein the VL comprises:

- i. an LCDR1 comprising an amino acid sequence of SEQ ID NO: 671,
- ii. an LCDR2 comprising an amino acid sequence of SEQ ID NO: 792, and
- iii. an LCDR3 comprising an amino acid sequence of SEQ ID NO: 911.

~~16. The antibody molecule of claim 15, wherein the VH comprises SEQ ID NO: 491 and the VL comprises SEQ ID NO: 551.~~

~~176.~~ An antibody molecule capable of binding to complement component 5a receptor 1 (C5aR1), wherein the antibody molecule competes with a C5aR1 antibody molecule comprising:

an HCDR1 comprising an amino acid sequence of SEQ ID NO: 612, an HCDR2 comprising an amino acid sequence of SEQ ID NO: 732, and an HCDR3 comprising an amino acid sequence of SEQ ID NO: 852, an LCDR1 comprising an amino acid sequence of SEQ ID NO: 672, an LCDR2 comprising an amino acid sequence of SEQ ID NO: 792, and an LCDR3 comprising an amino acid sequence of SEQ ID NO: 912.

~~187.~~ ~~An~~The antibody molecule ~~capable~~ of ~~binding to C5aR1~~claim 6, wherein the antibody molecule binds to an epitope on Site II of C5aR1, wherein the epitope on Site II comprises amino residues of SEQ ID NO: 1450.

~~19. The antibody molecule of claim 18, wherein the antibody molecule binds to amino acid residues R175-G189 in SEQ ID NO: 1448.~~

~~20. The antibody molecule of claim 19, wherein the antibody molecule binds to amino acid residues E180-P183 in SEQ ID NO: 1448.~~

~~21. The antibody molecule of claim 19, wherein the antibody molecule binds to amino acid residues E180-P184 in SEQ ID NO: 1448.~~

~~22. The antibody molecule of claim 19, wherein the antibody molecule binds to amino acid residues E178-P183 in SEQ ID NO: 1448.~~

~~238. An~~The antibody molecule ~~capable of binding to C5aR1~~claim 6, comprising a VH and/or a VL,

wherein the VH comprises:

- i. an HCDR1 comprising an amino acid sequence of SEQ ID NO: 612;
- ii. an HCDR2 comprising an amino acid sequence of SEQ ID NO: 732; and
- iii. an HCDR3 comprising an amino acid sequence of SEQ ID NO: 852; and

wherein the VL comprises:

- i. an LCDR1 comprising an amino acid sequence of SEQ ID NO: 672,
- ii. an LCDR2 comprising an amino acid sequence of SEQ ID NO: 792, and
- iii. an LCDR3 comprising an amino acid sequence of SEQ ID NO: 912.

~~24. An antibody molecule capable of binding to complement component 5a receptor 1 (C5aR1), comprising a VH and/or a VL,~~

~~wherein the VH comprises:~~

- ~~i. an HCDR1 comprising an amino acid sequence of SEQ ID NO: 1462;~~
- ~~ii. an HCDR2 comprising an amino acid sequence of SEQ ID NO: 1463; and~~
- ~~iii. an HCDR3 comprising an amino acid sequence of SEQ ID NO: 1464; and~~

~~wherein the VL comprises:~~

- ~~i. an LCDR1 comprising an amino acid sequence of SEQ ID NO: 1465,~~
- ~~ii. an LCDR2 comprising an amino acid sequence of SEQ ID NO: 792, and~~
- ~~iii. an LCDR3 comprising an amino acid sequence of SEQ ID NO: 912.~~

~~25. An antibody molecule capable of binding to C5aR1, comprising a VH and/or a VL,~~

~~wherein the VH comprises:~~

- ~~i. an HCDR1 that differs no more than 1 or 2 amino acid residues from SEQ ID NO: 612;~~
- ~~ii. an HCDR2 that differs no more than 1 or 2 amino acid residues from SEQ ID NO: 732;~~
- ~~and~~
- ~~iii. an HCDR3 that differs no more than 1 or 2 amino acid residues from SEQ ID NO: 852;~~
- ~~and~~

~~wherein the VL comprises:~~

- i. ~~an LCDR1 that differs no more than 1 or 2 amino acid residues from SEQ ID NO: 672;~~
- ii. ~~an LCDR2 that differs no more than 1 or 2 amino acid residues from SEQ ID NO: 792; and~~
- iii. ~~an LCDR3 that differs no more than 1 or 2 amino acid residues from of SEQ ID NO: 912.~~

~~26. An antibody molecule capable of binding to C5aR1, comprising a VH and/or a VL, wherein the VH comprises at least 80% identity to SEQ ID NO: 492; and wherein the VL comprises at least 70% identity to SEQ ID NO: 552.~~

~~27. The antibody molecule of any one of claims 23-26, wherein the VH comprises SEQ ID NO: 492 and the VL comprises SEQ ID NO: 552.~~

~~289.~~ ~~An~~The antibody molecule ~~capable of binding to C5aR1~~claim 6, comprising a VH and/or a VL,

wherein the VH comprises:

- i. an HCDR1 comprising an amino acid sequence of SEQ ID NO: 602;
- ii. an HCDR2 comprising an amino acid sequence of SEQ ID NO: 722; and
- iii. an HCDR3 comprising an amino acid sequence of SEQ ID NO: 842; and

wherein the VL comprises:

- i. an LCDR1 comprising an amino acid sequence of SEQ ID NO: 662,
- ii. an LCDR2 comprising an amino acid sequence of SEQ ID NO: 782, and
- iii. an LCDR3 comprising an amino acid sequence of SEQ ID NO: 902.

~~29. The antibody molecule of claim 28, wherein the VH comprises SEQ ID NO: 482 and the VL comprises SEQ ID NO: 542.~~

~~3010.~~ ~~An~~The antibody molecule ~~capable of binding to C5aR1~~claim 6, comprising a VH and/or a VL,

wherein the VH comprises:

- i. an HCDR1 comprising an amino acid sequence of SEQ ID NO 617;
- ii. an HCDR2 comprising an amino acid sequence of SEQ ID NOs: 737; and
- iii. an HCDR3 comprising an amino acid sequence of SEQ ID NO: 857; and

wherein the VL comprises:

- i. an LCDR1 comprising [an amino acid sequence of](#) SEQ ID NO: 677,
- ii. an LCDR2 comprising [an amino acid sequence of](#) SEQ ID NO: 797, and
- iii. an LCDR3 comprising [an amino acid sequence of](#) SEQ ID NO: 917.

~~31. The antibody molecule of claim 30, wherein the VH comprises SEQ ID NO: 497 and the VL comprises SEQ ID NO: 557.~~

~~32. The antibody molecule of any one of the preceding claims, wherein the antibody molecule reduces (e.g., inhibits or blocks) localized enrichment of C5a to C5aR1.~~

~~33. The antibody molecule of any one of the preceding claims, wherein the antibody molecule binds to C5aR1 with a dissociation constant (K_D) of less than about 100 nM.~~

~~34. The antibody molecule of claim 33, wherein the antibody molecule binds to C5aR1 with a K_D of between 10 pM and 50 nM.~~

~~35. The antibody molecule of any one of the preceding claims, wherein the antibody molecule reduces C5a-induced chemotaxis.~~

~~36. The antibody molecule of any one of the preceding claims, wherein the antibody molecule is capable of binding to neutrophils.~~

~~37. The antibody molecule of any one of the preceding claims, wherein the antibody molecule does not, or does not substantially bind to C5aR2, or other GPCRs.~~

~~38~~11. A multispecific antibody molecule capable of binding to [complement component 5a receptor 1](#) (C5aR1), wherein the antibody molecule comprises:

a first immunoglobulin variable region that binds to a first epitope, and a second immunoglobulin variable region that binds to a second epitope,

wherein the first epitope is on Site II of C5aR1, comprising [amino acid residues of](#) SEQ ID NO: 1450; and

wherein the second epitope is on Site I of C5aR1 comprising [amino acid residues of](#) SEQ ID NO: 1449 or SEQ ID NO: 1452.

~~39. The multispecific antibody molecule of claim 38, wherein the first immunoglobulin variable region binds to amino acid residues R175-G189 in SEQ ID NO: 1450.~~

~~40. The multispecific antibody molecule of claim 38, wherein the second immunoglobulin variable region binds to amino acid residues T8-D18 in SEQ ID NO: 1449 or SEQ ID NO: 1452.~~

~~41~~12. The multispecific antibody molecule of claim ~~38~~11, wherein the first immunoglobulin variable region competes with a C5aR1 antibody molecule comprising:

a HCDR1 comprising [an amino acid sequence of](#) SEQ ID NO: 612, a HCDR2 comprising [an amino acid sequence of](#) SEQ ID NO: 732, and a HCDR3 comprising an amino acid sequence of SEQ ID NO: 852, a LCDR1 comprising [an amino acid sequence of](#) SEQ ID NO: 672, a LCDR2 comprising [an amino acid sequence of](#) SEQ ID NO: 792, and a LCDR3 comprising [an amino acid sequence of](#) SEQ ID NO: 912; and

wherein the second immunoglobulin variable region competes with a C5aR1 antibody molecule comprising:

a HCDR1 comprising [an amino acid sequence of](#) SEQ ID NO: 656, a HCDR2 comprising [an amino acid sequence of](#) SEQ ID NO: 776, and a HCDR3 comprising [an amino acid sequence of](#) SEQ ID NO: 896, a LCDR1 comprising [an amino acid sequence of](#) SEQ ID NO: 715, a LCDR2 comprising [an amino acid sequence of](#) SEQ ID NO: 835 and a LCDR3 comprising [an amino acid sequence of](#) SEQ ID NO: 955.

~~42~~13. ~~A~~The multispecific antibody molecule ~~capable of binding to complement component 5a-receptor 1 (C5aR1)~~claim 11, wherein the antibody molecule comprises:

a first immunoglobulin variable region that binds to a first epitope, and a second immunoglobulin variable region that binds to a second epitope,

wherein the first epitope is on Site II of C5aR1;

wherein the first immunoglobulin variable region comprises: a HCDR1 comprising [an amino acid sequence of](#) SEQ ID NO: 612, a HCDR2 comprising [an amino acid sequence of](#) SEQ ID NO: 732, and a HCDR3 comprising [an amino acid sequence of](#) SEQ ID NO: 852, a LCDR1 comprising [an amino acid sequence of](#) SEQ ID NO: 672, a LCDR2 comprising [an amino acid sequence of](#) SEQ ID NO: 792, and a LCDR3 comprising [an amino acid sequence of](#) SEQ ID NO: 912;

wherein the second epitope is on Site I of C5aR; and

wherein the second immunoglobulin variable region comprises: HCDR1 comprising [an amino acid sequence of](#) SEQ ID NO: 656, a HCDR2 comprising [an amino acid sequence of](#) SEQ ID NO: 776, and a HCDR3 comprising [an amino acid sequence of](#) SEQ ID NO: 896, a LCDR1 comprising an amino acid sequence of SEQ ID NO: 715, a LCDR2 comprising [an](#)

amino acid sequence of SEQ ID NO: 835 and a LCDR3 comprising an amino acid sequence of SEQ ID NO: 955.

- ~~43. A multispecific antibody molecule capable of binding to complement component 5a receptor 1 (C5aR1), wherein the antibody molecule comprises:~~
- ~~a first immunoglobulin variable region that binds to a first epitope, and a second immunoglobulin variable region that binds to a second epitope,~~
 - ~~wherein the first epitope is on Site II of C5aR1;~~
 - ~~wherein the first immunoglobulin variable region comprises: a HCDR1 comprising an amino acid sequence of SEQ ID NO: 1462, a HCDR2 comprising an amino acid sequence of SEQ ID NO: 1463, and a HCDR3 comprising an amino acid sequence of SEQ ID NO: 1464, a LCDR1 comprising an amino acid sequence of SEQ ID NO: 1465, a LCDR2 comprising an amino acid sequence of SEQ ID NO: 792, and a LCDR3 comprising an amino acid sequence of SEQ ID NO: 912;~~
 - ~~wherein the second epitope is on Site I of C5aR; and~~
 - ~~wherein the second immunoglobulin variable region comprises: HCDR1 comprising an amino acid sequence of SEQ ID NO: 1456, a HCDR2 comprising an amino acid sequence of SEQ ID NO: 1457, and a HCDR3 comprising an amino acid sequence of SEQ ID NO: 1458, a LCDR1 comprising an amino acid sequence of SEQ ID NO: 1459, a LCDR2 comprising an amino acid sequence of SEQ ID NO: 1460, and a LCDR3 comprising an amino acid sequence of SEQ ID NO: 1461.~~
- ~~44. The multispecific antibody molecule of any one of claims 38-43, wherein the antibody is a bispecific or a biparatopic antibody.~~
- ~~45. The multispecific antibody molecule of claim 44, wherein the bispecific or biparatopic antibody molecule comprises a half antibody, or fragment thereof, having binding specificity for the first epitope and a half antibody, or fragment thereof, having binding specificity for the second epitope.~~
- ~~46. The multispecific antibody of claim 45, wherein the bispecific or biparatopic antibody molecule comprises a scFv, or fragment thereof, having binding specificity for the first epitope.~~
- ~~47. The multispecific antibody of claim 45, wherein the bispecific or biparatopic antibody molecule comprises a scFv, or fragment thereof, having binding specificity for the second epitope.~~

~~48. The multispecific antibody molecule of any one of claims 38-47, wherein the antibody molecule reduces C5a-induced chemotaxis.~~

~~49. The multispecific antibody molecule of any one of claims 38-48, wherein the antibody molecule is capable of binding to neutrophils.~~

~~50. The multispecific antibody molecule of any one of claims 38-49, wherein the antibody molecule does not, or does not substantially bind to C5aR2, or other GPCRs.~~

~~51~~14. A pharmaceutical composition comprising the antibody molecule of ~~any one of the preceding claims~~claim 1, optionally further comprising a pharmaceutically acceptable carrier or excipient.

~~52~~15. A combination comprising the antibody molecule of ~~any of~~ claims ~~1-50~~ and a second therapeutic agent.

~~53. The combination of claim 52, wherein the second therapeutic agent comprises a small molecule (e.g., avacopan).~~

~~54. The combination of claim 52, wherein the second therapeutic agent comprises a second antibody molecule.~~

~~55. The combination of claim 54, wherein the second antibody molecule is an antibody molecule of any one of claims 1-50.~~

~~56. The combination of claim 55, wherein the second antibody molecule is antibodies 3C5, 7F3, or 7h3.~~

~~57~~16. A nucleic acid molecule comprising a nucleotide sequence encoding the antibody molecule of ~~any one of~~ claims ~~1-50~~.

~~58. A vector comprising the nucleic acid molecule of claim 57.~~

~~59~~17. A host cell comprising the nucleic acid molecule of claim ~~57~~16 ~~or the vector of claim 58~~.

~~60~~18. A method of producing an anti-C5aR1 antibody molecule, the method comprising culturing the host cell of claim ~~59~~17 under conditions that allow production of an antibody molecule, thereby producing the antibody molecule.

~~61. The method of claim 60, further comprising isolating the antibody molecule.~~

~~62~~19. ~~A method of treating a disease or disorder, the method comprising administering to a subject in need thereof an effective amount of the~~Use of a composition comprising an antibody molecule of ~~any of claims 1-50, the pharmaceutical composition of claim 51, or the combination of any of claims 52-56, thereby treating the disorder~~ in the preparation of a medicament for use in treating a disease or disorder.

~~63. The method of claim 62, wherein the disorder is a C5aR1-associated (e.g., associated with C5aR1 activation) disorder.~~

~~64. The method of claim 62 or 63, wherein the disorder is an autoimmune disorder.~~

~~65. The method of claim 64, wherein the disorder is rheumatoid arthritis.~~

~~66. The method of claim 62 or 63, wherein the disorder is a kidney disorder.~~

~~67. The method of claim 62 or 63, wherein the disorder is ANCA vasculitis or lupus.~~

~~68. The method of claim 62 or 63, wherein the disease or disorder is a cancer.~~

~~69. The method of any of claims 62-68, further comprising administering to the subject a second therapeutic agent.~~

~~70~~20. ~~A method of modulating (e.g., decreasing) a C5aR1 activity, the method comprising contacting a cell or a subject in need thereof an effective amount of the~~Use of a composition comprising an antibody molecule of ~~any of claims 1-50, the pharmaceutical composition of claim 51, or the combination of any of claims 52-56, thereby~~in the manufacture of a medication for modulating (e.g., decreasing) ~~the~~a C5aR1 activity, comprising contacting a cell or a subject in need thereof an effective amount of the antibody.

~~71. The method of claim 70, wherein the C5aR1 activity is modulated in vitro, ex vivo, or in vivo.~~