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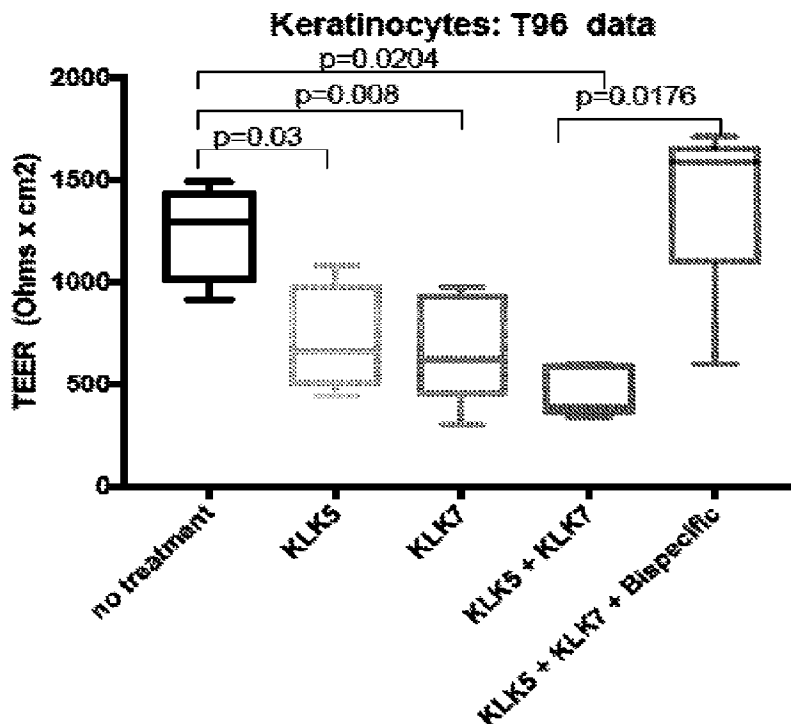
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(54) Titre : ANTICORPS ANTI-KLK7, ANTICORPS ANTI-KLK5, ANTICORPS MULTISPECIFIQUES ANTI-KLK5/KLK7, ET LEURS PROCEDES D'UTILISATION

(54) Title: ANTI-KLK7 ANTIBODIES, ANTI-KLK5 ANTIBODIES, MULTISPECIFIC ANTI-KLK5/KLK7 ANTIBODIES, AND METHODS OF USE

FIG. 19B



(57) Abrégé/Abstract:

The invention provides anti-KLK7 antibodies, anti-KLK5 antibodies, anti-KLK5/KLK7 multispecific antibodies, and methods of using the same.

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Abstract:

The invention provides anti-KLK7 antibodies, anti-KLK5 antibodies, anti-KLK5/KLK7 multispecific antibodies, and methods of using the same.

ANTI-KLK7 ANTIBODIES, ANTI-KLK5 ANTIBODIES, MULTISPECIFIC ANTI-KLK5/KLK7 ANTIBODIES, AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims the benefit of priority of US Provisional Application No. 62/901,990, filed September 18, 2019, which is incorporated by reference herein in its entirety for any purpose.

FIELD

[002] The present invention relates to anti-KLK7 antibodies, anti-KLK5 antibodies, anti-KLK5/KLK7 multispecific antibodies, and methods of using the same.

BACKGROUND

[003] Human kallikrein-related peptidases (KLKs) are (chymo)-trypsin-like serine proteases that are expressed in a variety of tissues such as prostate, ovary, breast, testis, brain, and skin. KLKs belong to a subgroup of the chymotrypsin-like serine protease family S1A of clan PA(S). The 15 human KLK genes are located on chromosome 19q13.4 and constitute the largest contiguous serine protease cluster in the human genome. These genes, generally composed of five coding exons and in some cases one or two 5' non-coding exons, encode the kallikrein-related peptidases KLK1 to KLK15. All KLK genes encode single-chain pre-pro-proteins containing a chymotrypsin- or trypsin-like catalytic domain of 224-237 residues with an amino acid sequence identity of approximately 40% among KLK4 to KLK15. KLK1 and its close homologs KLK2 and KLK3 form a clade of their own, KLK4, 5, and 7 belong to another subgroup, whereas KLK6 shares more similarity with KLK13 and KLK14. See Debela et al., *Biol Chem* 389, 623-632 (2008).

[004] KLK5 is a secreted trypsin-like serine protease that appears to be most abundantly expressed in human skin, specifically in the upper spinous and granular layers of the skin, where keratinocytes undergo terminal differentiation and are transformed into flattened brick-like structures that form the stratum corneum, the outermost epidermal layer and the barrier to the outside environment. See Debela et al., *J Mol Biol*, 373, 1017-1031 (2007); and Tan et al., *J Med Chem*. 2015 Jan 22;58(2):598-612 (2014). KLK7 is a chymotrypsin-like serine protease also expressed in skin. KLK5 is described to play pathological roles in skin disorders such as Netherton Syndrome. See Furio et al., *PLOS Genet* 11(9), e1005389 (2015). Netherton Syndrome is caused by loss-of-function mutations in the SPINK5 gene, encoding the serine

protease inhibitor Kazal-type 5 (SPINK5). See Descargues et al., Nat Genet. 2005 Jan;37(1):56-65 (2004). SPINK5 has been shown to inhibit several members of the KLK serine protease family (e.g. KLK5 and KLK7). See Wang et al., Exp Dermatol. Jul;23(7):524-6 (2014). The absence of SPINK5 in Netherton Syndrome results in unopposed KLKs activities. KLK5 hyperactivity is thought to be a key element in the pathophysiology of Netherton Syndrome as KLK5 is a regulator of proteolysis in the epidermis. Ablation of KLK5 and KLK7 rescues lethality of Netherton Syndrome-like phenotype. See Briot et al., J Exp Med. May 11;206(5):1135-47 (2009); Furio et al., J Exp Med. Mar 10;211(3):499-513 (2014); and Kasparek et al., PLoS Genet. 2017 Jan 17;13(1):e1006566 (2017). Netherton Syndrome is a complex systemic disease with multiple effects for which currently no satisfactory treatment is available.

[005] Asthma is a clinically heterogeneous disorder associated with both genetic and environmental risk factors. Estimates of heritability from asthma twin studies vary from 35% to 80%, indicating an important role for genetic risk. See e.g., Ullemar et al., Allergy 71, 230-238 (2016). Several large scale GWAS have been performed for asthma and asthma related phenotypes, and many of the loci identified such as those near ORMDL3, IL13, IL1RL1 and TSLP genes have been confirmed in multiple study populations. See e.g., Bonnelykke et al., Nat Genet 46, 51-55 (2014). Recent studies identified a SNP at the KLK4/5 locus which is protective for the risk regarding periostin low, or type 2 low inflammation asthma. In the same study, KLK5 levels were found to be elevated in bronchoalveolar lavage of severe asthma patients supporting the hypothesis that KLK5 plays a role in bronchial obstruction and asthma pathogenesis.

[006] Despite the advances in the field of diseases such as Netherton Syndrome and asthma, there remains a need to identify targets and develop means that can supplement or enhance the efficacy of existing therapies.

SUMMARY

[007] The invention provides anti-KLK7 antibodies, anti-KLK5 antibodies, anti-KLK5/KLK7 multispecific antibodies, and methods of using the same.

Embodiment 1. An isolated antibody that binds to human kallikrein related peptidase 7 (KLK7), wherein the antibody:

- a) inhibits human KLK7-mediated cleavage of a substrate comprising the amino acid sequence RPKPVE-Nval-WRK (SEQ ID NO: 121), wherein Nval is norvaline;
- b) binds human KLK7 with an K_D of less than 10 pM, or less than 9 pM, or less than 8 pM, or less than 7 pM, or less than 6 pM, or less than 5 pM as measured by surface plasmon resonance;
- c) binds an epitope within amino acids R71-N82, K152-S158, and/or Q211-K222 of KLK7 (SEQ ID NO: 4); and/or
- d) binds an epitope comprising one or more of amino acids H72, P73, G74, S76, Q78, N82, N157, K211, and/or T213 of KLK7 (SEQ ID NO: 4), or an epitope comprising one or more of amino acids H91, P92, G93, S95, Q97, N101, N178, K233, and/or T235 of KLK7, by chymotrypsin numbering.

Embodiment 2. An antibody that binds to human KLK7, wherein the antibody comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12.

Embodiment 3. The antibody of embodiment 1, comprising a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12.

Embodiment 4. The antibody of any one of embodiments 1 to 3, which is a monoclonal antibody.

Embodiment 5. The antibody of any one of embodiments 1 to 4, which is a humanized, or chimeric antibody.

Embodiment 6. The antibody of any one of embodiments 1 to 5, which is an antibody fragment that binds to human KLK7.

Embodiment 7. The antibody of any of embodiments 1 to 6, wherein the antibody binds human KLK7 with a K_D of less than 10 pM, or less than 9 pM, or less than 8 pM, or less than 7 pM, or less than 6 pM, or less than 5 pM as measured by surface plasmon resonance; and/or

binds to cynomolgus monkey KLK7 with a K_D of less than 10 pM, or less than 9 pM, or less than 8 pM, or less than 7 pM, or less than 6 pM, or less than 5 pM as measured by surface plasmon resonance.

Embodiment 8. The antibody of any one of embodiments 1 to 7, wherein the heavy chain variable region comprises an FR1 comprising an amino acid sequence selected from SEQ ID NO: 123-128, an FR2 comprising an amino acid sequence selected from SEQ ID NO: 130-133, an FR3 comprising an amino acid sequence of SEQ ID NO: 135-143, and/or an FR4 comprising an amino acid sequence selected from SEQ ID NO: 144-145.

Embodiment 9. The antibody of any one of embodiments 1 to 8, wherein the light chain variable region comprises an FR1 comprising an amino acid sequence selected from SEQ ID NO: 147-150, an FR2 comprising an amino acid sequence selected from SEQ ID NO: 152-154, an FR3 comprising an amino acid sequence selected from SEQ ID NO: 156-158, and/or an FR4 comprising an amino acid sequence selected from SEQ ID NO: 160.

Embodiment 10. The antibody of any of embodiments 1 to 9, comprising a sequence selected from:

- (a) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 15-30;
- (b) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NO:31-38; and
- (c) a VH sequence as defined in (a) and a VL sequence as defined in (b).

Embodiment 11. The antibody of any of embodiments 1 to 10, comprising a sequence selected from:

- (a) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 15-30;
- (b) a VL sequence comprising an amino acid sequence selected from SEQ ID NO:31-38; and
- (c) a VH sequence as defined in (a) and a VL sequence as defined in (b).

Embodiment 12. The antibody of any of embodiments 1 to 11, comprising a VH sequence of SEQ ID NO: 29 and a VL sequence of SEQ ID NO: 32.

Embodiment 13. The antibody of any of embodiments 1 to 11, comprising a VH sequence of SEQ ID NO: 30 and a VL sequence of SEQ ID NO: 38.

Embodiment 14. An antibody that specifically binds to human KLK7 comprising a VH sequence of SEQ ID NO: 29 and a VL sequence of SEQ ID NO: 32.

Embodiment 15. An antibody that specifically binds to human KLK7 comprising a VH sequence of SEQ ID NO: 30 and a VL sequence of SEQ ID NO: 38.

Embodiment 16. The antibody of any one of embodiments 1 to 15, wherein the antibody comprises a heavy chain constant region and a light chain constant region, wherein the heavy chain constant region comprises a S183K substitution (EU numbering) and/or an S183E substitution (EU numbering); and/or the light chain constant region comprises a V133K substitution (EU numbering) and/or a V133E substitution (EU numbering).

Embodiment 17. The antibody of any of embodiments 1 to 16, which is a full length IgG1 antibody.

Embodiment 18. The antibody of embodiment 17, wherein the antibody comprises a N297G substitution (EU numbering).

Embodiment 19. The antibody of any one of embodiments 16 to 18, wherein the antibody comprises a M428L substitution (EU numbering) and/or an N434S substitution (EU numbering).

Embodiment 20. The antibody of any one of embodiments 1 to 19, wherein the antibody binds human KLK7 with a K_D of less than 20 pM, or less than 15 pM, or less than 10 pM, less than 5 pM, or less than 3 pM, or less than 2 pM, or less than 1 pM, as measured by surface plasmon resonance.

Embodiment 21. The antibody of any one of embodiments 1 to 20, wherein the antibody inhibits human KLK7 protease activity with an IC_{50} of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM.

Embodiment 22. The antibody of any one of embodiments 1 to 21, wherein the antibody binds human KLK7 with a K_D of less than 20 pM, or less than 15 pM, or less than 10 pM, less than 5 pM, or less than 3 pM, or less than 2 pM, or less than 1 pM, as measured by surface plasmon resonance; and wherein the antibody inhibits human KLK7 protease activity with an IC_{50} of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM.

Embodiment 23. The antibody of embodiment 21 or embodiment 22, wherein inhibition of human KLK7 protease activity is inhibition of human KLK7-mediated cleavage of a substrate comprising the amino acid sequence RPKPVE- Nval-WRK (SEQ ID NO: 121), wherein Nval is norvaline.

Embodiment 24. The antibody of any of embodiments 1 to 23, wherein the antibody is a multispecific antibody.

Embodiment 25. The antibody of embodiment 24, which is a bispecific antibody.

Embodiment 26. An antibody that specifically binds human KLK7, which competes for binding to human KLK7 with the antibody of any one of embodiments 1 to 25.

Embodiment 27. The antibody of embodiment 26, wherein the antibody:

- a) inhibits human KLK7-mediated cleavage of a substrate comprising the amino acid sequence RPKPVE-Nval-WRK (SEQ ID NO: 121), wherein Nval is norvaline with an IC₅₀ of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM; and/or
- b) binds human KLK7 with a K_D of less than 10 pM, or less than 9 pM, or less than 8 pM, or less than 7 pM, or less than 6 pM, or less than 5 pM as measured by surface plasmon resonance.

Embodiment 28. An isolated nucleic acid encoding the antibody of any of embodiments 1 to 27.

Embodiment 29. An isolated host cell comprising the nucleic acid of embodiment 28.

Embodiment 30. An isolated host cell that expresses the antibody of any one of embodiments 1 to 27.

Embodiment 31. A method of producing an antibody that binds to human KLK7 comprising culturing the host cell of embodiment 29 or embodiment 30 under conditions suitable for the expression of the antibody.

Embodiment 32. The method of embodiment 31, further comprising recovering the antibody from the host cell.

Embodiment 33. An antibody produced by the method of embodiment 32.

Embodiment 34. An antibody that binds to human KLK5, wherein the antibody comprises:

- a) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 43 and 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49; or
- b) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 39 and 107, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising an amino acid sequence selected

from SEQ ID NOs: 43 and 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49; or

c) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 39 and 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NOs: 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49; or

d) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 39 and 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 43 and 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 47-49; or

e) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 70, and (c) CDR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 71 and 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 75-78; or

f) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 69 and 70, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 75-78; or

g) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 69 and 70, and (c) CDR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 71 and 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 76-78.

Embodiment 35. The antibody of embodiment 34, wherein the antibody comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NOs: 43, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 47.

Embodiment 36. The antibody of embodiment 34, wherein the antibody comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 70, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 76.

Embodiment 37. The antibody of any one of embodiments 34 to 36, which is a monoclonal antibody.

Embodiment 38. The antibody of any one of embodiments 34 to 37, which is a humanized, or chimeric antibody.

Embodiment 39. The antibody of any one of embodiments 34 to 38, which is an antibody fragment that binds human KLK5.

Embodiment 40. The antibody of any of embodiments 34 to 39, wherein the antibody binds human KLK5 with a K_D of less than 1 nM, or less than 500 pM, or less than 300 pM, or less than 200 pM, or less than 100 pM, or less than 50 pM as measured by surface plasmon resonance; and/or binds to cynomolgus monkey KLK5 with a K_D of less than 1 nM, or less than 500 pM, or less than 300 pM, or less than 200 pM, or less than 100 pM, or less than 50 pM as measured by surface plasmon resonance.

Embodiment 41. The antibody of any one of embodiments 34 to 40, wherein the heavy chain variable region comprises:

- a) an FR1 comprising the amino acid sequence selected of SEQ ID NO: 161, an FR2 comprising the amino acid sequence of SEQ ID NO: 162-163, an FR3 comprising the amino acid sequence of SEQ ID NO: 164, and/or an FR4 comprising the amino acid sequence of SEQ ID NO: 165; or
- b) an FR1 comprising the amino acid sequence of SEQ ID NO: 171, an FR2 comprising an amino acid sequence selected from SEQ ID NO: 172-173, an FR3 comprising the amino acid sequence of SEQ ID NO: 174, and/or an FR4 comprising the amino acid sequence of SEQ ID NO: 175.

Embodiment 42. The antibody of any one of embodiments 34 to 41, wherein the light chain variable region comprises:

- a) an FR1 comprising the amino acid sequence of SEQ ID NO: 166, an FR2 comprising an amino acid sequence selected from SEQ ID NO: 167-168, an FR3 comprising the amino acid sequence of SEQ ID NO: 169, and/or an FR4 comprising the amino acid sequence of SEQ ID NO: 170; or
- b) an FR1 comprising the amino acid sequence of SEQ ID NO: 176, an FR2 comprising an amino acid sequence selected from SEQ ID NO: 177-178, an FR3 comprising the amino acid sequence of SEQ ID NO: 179, and/or an FR4 comprising the amino acid sequence of SEQ ID NO: 180.

Embodiment 43. The antibody of any of embodiments 34 to 42, comprising a sequence selected from:

- a) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 50, 52, 53, 105, and 106;
- b) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 51 and 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 79 and 81-87;
- e) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 80 and 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

Embodiment 44. The antibody of any of embodiments 34 to 43, comprising a sequence selected from:

- a) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 50, 52, 53, 105, and 106;
- b) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 51 and 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 79 and 81-87;
- e) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 80 and 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

Embodiment 45. The antibody of any of embodiments 34 to 44, comprising a VH sequence of SEQ ID NO: 52 and a VL sequence of SEQ ID NO: 55.

Embodiment 46. The antibody of any of embodiments 34 to 44, comprising a VH sequence of SEQ ID NO: 53 and a VL sequence of SEQ ID NO: 62.

Embodiment 47. An antibody that specifically binds to human KLK5 comprising a VH sequence of SEQ ID NO: 52 and a VL sequence of SEQ ID NO: 55.

Embodiment 48. An antibody that specifically binds to human KLK5 comprising a VH sequence of SEQ ID NO: 53 and a VL sequence of SEQ ID NO: 62.

Embodiment 49. The antibody of any of embodiments 34 to 44, comprising a VH sequence of SEQ ID NO: 83 and a VL sequence of SEQ ID NO: 88.

Embodiment 50. The antibody of any of embodiments 34 to 44, comprising a VH sequence of SEQ ID NO: 87 and a VL sequence of SEQ ID NO: 92.

Embodiment 51. An antibody that specifically binds to human KLK5 comprising a VH sequence of SEQ ID NO: 83 and a VL sequence of SEQ ID NO: 88.

Embodiment 52. An antibody that specifically binds to human KLK5 comprising a VH sequence of SEQ ID NO: 87 and a VL sequence of SEQ ID NO: 92.

Embodiment 53. The antibody of any one of embodiments 34 to 52, wherein the antibody comprises a heavy chain constant region and a light chain constant region, wherein the heavy chain constant region comprises a S183K substitution (EU numbering) and/or an S183E substitution (EU numbering); and/or the light chain constant region comprises a V133K substitution (EU numbering) and/or a V133E substitution (EU numbering).

Embodiment 54. The antibody of any of embodiments 34 to 53, which is a full length IgG1 antibody.

Embodiment 55. The antibody of embodiment 54, wherein the antibody comprises a N297G substitution (EU numbering).

Embodiment 56. The antibody of any one of embodiments 53 to 55, wherein the antibody comprises a M428L substitution (EU numbering) and/or an N434S substitution (EU numbering).

Embodiment 57. The antibody of any of embodiments 34 to 56, wherein the antibody binds human KLK5 with a K_D of less than 60 pM, less than 30 pM, less than 20 pM, less than 10 pM, or less than 5 pM, as measured by surface plasmon resonance.

Embodiment 58. The antibody of any one of embodiments 34 to 57, wherein the antibody inhibits human KLK5 protease activity with an IC_{50} of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM.

Embodiment 59. The antibody of any one of embodiments 34 to 58, wherein the antibody binds human KLK5 with a K_D of less than 60 pM, less than 30 pM, less than 20 pM, less than 10 pM, or less than 5 pM, as measured by surface plasmon resonance; and wherein the antibody inhibits human KLK5 protease activity with an IC_{50} of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM.

Embodiment 60. The antibody of embodiment 58 or embodiment 59, wherein inhibition of human KLK5 protease activity is inhibition of human KLK5-mediated cleavage of the substrate Boc-Val-Pro-Arg-AMC.

Embodiment 61. The antibody of any of embodiments 34 to 60, wherein the antibody is a multispecific antibody.

Embodiment 62. The antibody of embodiment 61, wherein the antibody is a bispecific antibody.

Embodiment 63. An isolated nucleic acid encoding the antibody of any of embodiments 34 to 62.

Embodiment 64. An isolated host cell comprising the nucleic acid of embodiment 63.

Embodiment 65. An isolated host cell that expresses the antibody of any one of embodiments 34 to 62.

Embodiment 66. A method of producing an antibody that binds to human KLK5 comprising culturing the host cell of embodiment 64 or embodiment 65 under conditions suitable for the expression of the antibody.

Embodiment 67. The method of embodiment 66, further comprising recovering the antibody from the host cell.

Embodiment 68. An antibody produced by the method of embodiment 67.

Embodiment 69. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12.

Embodiment 70. The bispecific antibody of embodiment 69, wherein the first binding domain is humanized.

Embodiment 71. The bispecific antibody of embodiment 69 or embodiment 70, wherein the first binding domain comprises a sequence selected from:

- (a) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 15-30;
- (b) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NO:31-38; and
- (c) a VH sequence as defined in (a) and a VL sequence as defined in (b).

Embodiment 72. The bispecific antibody of any one of embodiments 69 to 71, wherein the first binding domain comprises a sequence selected from:

- (a) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 15-30;
- (b) a VL sequence comprising an amino acid sequence selected from SEQ ID NO: 31-38; and
- (c) a VH sequence as defined in (a) and a VL sequence as defined in (b).

Embodiment 73. The bispecific antibody of any one of embodiments 69 to 72, wherein the first binding domain comprises a VH sequence of SEQ ID NO: 29 and a VL sequence of SEQ ID NO: 32.

Embodiment 74. The bispecific antibody of any one of embodiments 69 to 72, wherein the first binding domain comprises a VH sequence of SEQ ID NO: 30 and a VL sequence of SEQ ID NO: 38.

Embodiment 75. The bispecific antibody of any one of embodiments 69 to 74, wherein the second binding domain comprises:

- a) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 39 and 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 43 and 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49; or
- b) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 69 and 70, and (c) CDR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 71 and 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 75-78.

Embodiment 76. The bispecific antibody of any one of embodiments 69 to 75, wherein the second binding domain comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NOs: 43, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 47.

Embodiment 77. The bispecific antibody of any one of embodiments 69 to 75, wherein the second binding domain comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 70, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 76.

Embodiment 78. The bispecific antibody of any one of embodiments 69 to 77, wherein the second binding domain is humanized.

Embodiment 79. The bispecific antibody of any one of embodiments 75 to 78, wherein the second binding domain comprises a sequence selected from:

- a) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 50, 52, 53, 105, and 106;
- b) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 51 and 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 79 and 81-87;
- e) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 80 and 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

Embodiment 80. The bispecific antibody of any one of embodiments 75 to 78, wherein the second binding domain comprises a sequence selected from:

- a) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 52, 53, 105, and 106;
- b) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 81-87;
- e) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

Embodiment 81. The bispecific antibody of any one of embodiments 69 to 78, wherein the second binding domain comprises a sequence selected from:

- a) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 50, 52, 53, 105, and 106;
- b) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 51 and 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 79 and 81-87;

- e) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 80 and 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

Embodiment 82. The bispecific antibody of any one of embodiments 69 to 78, wherein the second binding domain comprises a sequence selected from:

- a) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 52, 53, 105, and 106;
- b) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 81-87;
- e) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

Embodiment 83. The bispecific antibody of any one of embodiments 69 to 79, wherein the first binding domain comprises a VH amino acid sequence of SEQ ID NO: 29 or SEQ ID NO: 30 and a VL amino acid sequence of SEQ ID NO: 32 or SEQ ID NO: 38, and the second binding domain comprises a VH sequence of SEQ ID NO: 52 or SEQ ID NO: 53 and a VL amino acid sequence of SEQ ID NO: 55 or SEQ ID NO: 62.

Embodiment 84. The bispecific antibody of embodiment 83, wherein (i) the first binding domain comprises a VH amino acid sequence of SEQ ID NO: 29 and a VL amino acid sequence of SEQ ID NO: 32, or a VH amino acid sequence of SEQ ID NO: 30 and a VL amino acid sequence of SEQ ID NO: 38; and (ii) the second binding domain comprises a VH sequence of SEQ ID NO: 52 and a VL amino acid sequence of SEQ ID NO: 55; or a VH sequence of SEQ ID NO: 53 and a VL amino acid sequence of SEQ ID NO: 62.

Embodiment 85. The bispecific antibody of any one of embodiments 69 to 79, wherein the first binding domain comprises a VH sequence of SEQ ID NO: 30 and a VL sequence of SEQ ID NO: 38, and the second binding domain comprises a VH sequence of SEQ ID NO: 53 and a VL sequence of SEQ ID NO: 62.

Embodiment 86. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain variable domain (VH) amino acid sequence of SEQ ID NO: 30 and a light chain variable domain

(VL) amino acid sequence of SEQ ID NO: 38, and the second binding domain comprises a VH amino acid sequence of SEQ ID NO: 53 and a VL amino acid sequence of SEQ ID NO: 62.

Embodiment 87. The bispecific antibody of any one of embodiments 69 to 86, wherein the first binding domain comprises a first heavy chain variable domain and a first light chain variable domain, wherein the first heavy chain variable domain is linked to a first heavy chain constant region and the first light chain variable domain is linked to a first light chain constant region; and the second binding domain comprises a second heavy chain variable domain and a second light chain variable domain, wherein the second heavy chain variable domain is linked to a second heavy chain constant region and the second light chain variable domain is linked to a second light chain constant region.

Embodiment 88. The bispecific antibody of embodiment 87, wherein the first heavy chain constant region comprises a knob mutation and the second heavy chain constant region comprises a hole mutation; or wherein the first heavy chain constant region comprises a hole mutation and the second heavy chain constant region comprises a knob mutation.

Embodiment 89. The bispecific antibody of embodiment 88, wherein the antibody is an IgG1 antibody and wherein the knob mutation comprises a T366W substitution.

Embodiment 90. The bispecific antibody of embodiment 88 or embodiment 89, wherein the antibody is an IgG1 antibody and wherein the hole mutation comprises at least one, at least two, or three substitutions selected from T366S, L368A, and Y407V.

Embodiment 91. The bispecific antibody of embodiment 90, wherein the antibody is an IgG1 antibody and wherein the hole mutation comprises T366S, L368A, and Y407V substitutions.

Embodiment 92. The bispecific antibody of any one of embodiments 87 to 91, wherein the first heavy chain constant region and/or the second heavy chain constant region comprises a N297G substitution (EU numbering).

Embodiment 93. The bispecific antibody of embodiment 92, wherein the first heavy chain constant region and the second heavy chain constant region each comprises a N297G substitution (EU numbering).

Embodiment 94. The bispecific antibody of any one of embodiments 87 to 93, wherein:

- a) the first heavy chain constant region further comprises a S183K substitution (EU numbering) and the first light chain constant region comprises a V133E substitution (EU numbering), and the second heavy chain constant region further

comprises a S183E substitution (EU numbering) and the second light chain constant region comprises a V133K substitution (EU numbering); or

b) the first heavy chain constant region further comprises a S183E substitution (EU numbering) and the first light chain constant region comprises a V133K substitution (EU numbering), and the second heavy chain constant region further comprises a S183K substitution (EU numbering) and the second light chain constant region comprises a V133E substitution (EU numbering).

Embodiment 95. The bispecific antibody of any one of embodiments 87 to 94, wherein the first heavy chain constant region and/or the second heavy chain constant region further comprises at least one substitution selected from M428L and N434S (EU numbering).

Embodiment 96. The bispecific antibody of embodiment 95, wherein the first heavy chain constant region and the second heavy chain constant region each further comprises at least one substitution selected from M428L and N434S (EU numbering).

Embodiment 97. The bispecific antibody of embodiment 96, wherein the first heavy chain constant region and the second heavy chain constant region each further comprises M428L and N434S substitutions (EU numbering).

Embodiment 98. The bispecific antibody of any one of embodiments 87 to 97, wherein:

a) the first heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 96, 184, 98, 186, 117, 188, 119, and 190 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103; and the heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 97, 185, 99, 187, 118, 189, 120, and 191 and the second light chain constant region comprising the amino acid sequence of SEQ ID NO: 104; or

b) the second heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 96, 184, 98, 186, 117, 188, 119, and 190 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 103; and the first heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 97, 185, 99, 187, 118, 189, 120, and 191 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104.

Embodiment 99. The bispecific antibody of embodiment 98, wherein:

a) the first heavy chain constant region comprises the amino acid sequence of SEQ ID NOs: 96 or 184 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the second heavy chain constant region comprises the

amino acid sequence of SEQ ID NO: 97 or 185 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

b) the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 98 or 186 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 99 or 187 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

c) the second heavy chain constant region comprises the amino acid sequence of SEQ ID NOs: 96 or 184 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 97 or 185 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

d) the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 98 or 186 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 99 or 187 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

e) the first heavy chain constant region comprises the amino acid sequence of SEQ ID NOs: 118 or 189 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 117 or 188 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

f) the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 120 or 191 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 119 or 190 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

g) the second heavy chain constant region comprises the amino acid sequence of SEQ ID NOs: 118 or 189 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 117 or 188 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

h) the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 120 or 191 and the second light chain constant region comprises the amino

acid sequence of SEQ ID NO: 103, and the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 119 or 190 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104.

Embodiment 100. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 108 or 192, and a light chain amino acid sequence of SEQ ID NO: 109, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 110 or 193, and a light chain amino acid sequence of SEQ ID NO: 111.

Embodiment 101. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 112 or 194, and a light chain amino acid sequence of SEQ ID NO: 113, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 114 or 195, and a light chain amino acid sequence of SEQ ID NO: 115.

Embodiment 102. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 108 and a light chain amino acid sequence of SEQ ID NO: 109, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 110 and a light chain amino acid sequence of SEQ ID NO: 111.

Embodiment 103. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 112 and a light chain amino acid sequence of SEQ ID NO: 113, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 114 and a light chain amino acid sequence of SEQ ID NO: 115.

Embodiment 104. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the second binding domain comprises

- a) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL)

comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NOs: 43 or 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49; or

b) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 39 and 107, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 43 and 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49; or

c) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39 or 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NOs: 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49; or

d) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 39 and 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 43 and 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 47-49; or

e) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 70, and (c) CDR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 71 and 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 75-78; or

f) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 69 and 70, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 75-78; or
g) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 69 and 70, and (c) CDR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 71 and 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 76-78.

Embodiment 105. The bispecific antibody of embodiment 104, wherein the second binding domain comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NOs: 43, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 47.

Embodiment 106. The bispecific antibody of embodiment 104, wherein the second binding domain comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 70, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 76.

Embodiment 107. The bispecific antibody of any one of embodiments 104 to 106, wherein the second binding domain is humanized.

Embodiment 108. The bispecific antibody of any one of embodiments 104 to 107, wherein the second binding domain comprises a sequence selected from:

- a) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 50, 52, 53, 105, and 106;
- b) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 51 and 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 79 and 81-87;
- e) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 80 and 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

Embodiment 109. The bispecific antibody of any one of embodiments 104 to 107, wherein the second binding domain comprises a sequence selected from:

- a) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 52, 53, 105, and 106;
- b) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 81-87;
- e) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

Embodiment 110. The bispecific antibody of any one of embodiments 104 to 107, wherein the second binding domain comprises a sequence selected from:

- a) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 50, 52, 53, 105, and 106;
- b) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 51 and 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 79 and 81-87;
- e) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 80 and 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

Embodiment 111. The bispecific antibody of any one of embodiments 104 to 107, wherein the second binding domain comprises a sequence selected from:

- a) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 52, 53, 105, and 106;
- b) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 81-87;
- e) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

Embodiment 112. The bispecific antibody of any one of embodiments 104 to 107, wherein the second half amino acid antibody comprises a VH sequence of SEQ ID NO: 52 or SEQ ID NO: 53 and a VL amino acid sequence of SEQ ID NO: 55 or SEQ ID NO: 62.

Embodiment 113. The bispecific antibody of embodiment 112, wherein the second half amino acid antibody comprises a VH sequence of SEQ ID NO: 52 and a VL amino acid sequence of SEQ ID NO: 55; or a VH sequence of SEQ ID NO: 53 and a VL amino acid sequence of SEQ ID NO: 62.

Embodiment 114. The bispecific antibody of any one of embodiments 104 to 113, wherein the first binding domain is humanized.

Embodiment 115. The bispecific antibody of any one of embodiments 104 to 114, wherein the first binding domain comprises a first heavy chain variable domain and a first light chain variable domain, wherein the first heavy chain variable domain is linked to a first heavy chain constant region and the first light chain variable domain is linked to a first light chain constant region; and the second binding domain comprises a second heavy chain variable domain and a second light chain variable domain, wherein the second heavy chain variable domain is linked to a second heavy chain constant region and the second light chain variable domain is linked to a second light chain constant region.

Embodiment 116. The bispecific antibody of embodiment 115, wherein the first heavy chain constant region comprises a knob mutation and the second heavy chain constant region comprises a hole mutation; or wherein the first heavy chain constant region comprises a hole mutation and the second heavy chain constant region comprises a knob mutation.

Embodiment 117. The bispecific antibody of embodiment 116, wherein the antibody is an IgG1 antibody and wherein the knob mutation comprises a T366W mutation.

Embodiment 118. The bispecific antibody of embodiment 116 or embodiment 117, wherein the antibody is an IgG1 antibody and wherein the hole mutation comprises at least one, at least two, or three mutations selected from T366S, L368A, and Y407V.

Embodiment 119. The bispecific antibody of embodiment 118, wherein the antibody is an IgG1 antibody and wherein the hole mutation comprises T366S, L368A, and Y407V mutations.

Embodiment 120. The bispecific antibody of any one of embodiments 115 to 119, wherein the first heavy chain constant region and/or the second heavy chain constant region comprises a N297G substitution (EU numbering).

Embodiment 121. The bispecific antibody of embodiment 120, wherein the first heavy chain constant region and the second heavy chain constant region each comprises a N297G substitution (EU numbering).

Embodiment 122. The bispecific antibody of any one of embodiments 115 to 121, wherein:

a) the first heavy chain constant region further comprises a S183K substitution (EU numbering) and the first light chain constant region comprises a V133E substitution (EU numbering), and the second heavy chain constant region further comprises a S183E substitution (EU numbering) and the second light chain constant region comprises a V133K substitution (EU numbering); or

b) the first heavy chain constant region further comprises a S183E substitution (EU numbering) and the first light chain constant region comprises a V133K substitution (EU numbering), and the second heavy chain constant region further comprises a S183K substitution (EU numbering) and the second light chain constant region comprises a V133E substitution (EU numbering).

Embodiment 123. The bispecific antibody of any one of embodiments 115 to 122, wherein the first heavy chain constant region and/or the second heavy chain constant region further comprises at least one substitution selected from M428L and N434S (EU numbering).

Embodiment 124. The bispecific antibody of embodiment 123, wherein the first heavy chain constant region and the second heavy chain constant region each further comprises at least one substitution selected from M428L and N434S (EU numbering).

Embodiment 125. The bispecific antibody of embodiment 124, wherein the first heavy chain constant region and the second heavy chain constant region each further comprises M428L and N434S substitutions (EU numbering).

Embodiment 126. The bispecific antibody of any one of embodiments 115 to 125, wherein:

a) the first heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 96, 184, 98, 186, 117, 188, 119, and 190 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103; and the heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 97, 185, 99, 187, 118, 189, 120, and 191 and the second light chain constant region comprising the amino acid sequence of SEQ ID NO: 104; or

b) the second heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 96, 184, 98, 186, 117, 188, 119, and 190 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 103; and the first heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 97, 185, 99, 187, 118, 189, 120, and 191 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104.

Embodiment 127. The bispecific antibody of embodiment 126, wherein:

a) the first heavy chain constant region comprises the amino acid sequence of SEQ ID NOs: 96 or 184 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 97 or 185 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

b) the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 98 or 186 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 99 or 187 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

c) the second heavy chain constant region comprises the amino acid sequence of SEQ ID NOs: 96 or 184 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 97 or 185 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

d) the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 98 or 186 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the first heavy chain constant region comprises the

amino acid sequence of SEQ ID NO: 99 or 187 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

e) the first heavy chain constant region comprises the amino acid sequence of SEQ ID NOs: 118 or 189 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 117 or 188 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

f) the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 120 or 191 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 119 or 190 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

g) the second heavy chain constant region comprises the amino acid sequence of SEQ ID NOs: 118 or 189 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 117 or 188 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

h) the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 120 or 191 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 119 or 190 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104.

Embodiment 128. The bispecific antibody of any one of embodiments 69 to 127, wherein the antibody binds human KLK5 with a K_D of less than 60 pM, less than 30 pM, less than 20 pM, less than 10 pM, or less than 5 pM, as measured by surface plasmon resonance.

Embodiment 129. The bispecific antibody of any one of embodiments 69 to 128, wherein the antibody inhibits human KLK5 protease activity with an IC_{50} of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM.

Embodiment 130. The antibody of any one of embodiments 69 to 129, wherein the antibody binds human KLK5 with a K_D of less than 60 pM, less than 30 pM, less than 20 pM, less than 10 pM, or less than 5 pM, as measured by surface plasmon resonance; and wherein the antibody inhibits human KLK5 protease activity with an IC_{50} of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM.

Embodiment 131. The bispecific antibody of embodiment 129 or embodiment 130, wherein inhibition of human KLK5 protease activity is inhibition of human KLK5-mediated cleavage of the substrate Boc-Val-Pro-Arg-AMC.

Embodiment 132. The bispecific antibody of any one of embodiments 69 to 131, wherein the antibody binds human KLK7 with a K_D of less than 20 pM, or less than 15 pM, or less than 10 pM, less than 5 pM, or less than 3 pM, or less than 2 pM, or less than 1 pM, as measured by surface plasmon resonance.

Embodiment 133. The bispecific antibody of any one of embodiments 69 to 132, wherein the antibody inhibits human KLK7 protease activity with an IC_{50} of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM.

Embodiment 134. The bispecific antibody of any one of embodiments 69 to 133, wherein the antibody binds human KLK7 with a K_D of less than 20 pM, or less than 15 pM, or less than 10 pM, less than 5 pM, or less than 3 pM, or less than 2 pM, or less than 1 pM, as measured by surface plasmon resonance; and wherein the antibody inhibits human KLK7 protease activity with an IC_{50} of less than less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM.

Embodiment 135. The bispecific antibody of embodiment 133 or embodiment 134, wherein inhibition of human KLK7 protease activity is inhibition of human KLK7-mediated cleavage of a substrate comprising the amino acid sequence RPKPVE- Nval-WRK (SEQ ID NO: 121), wherein Nval is norvaline.

Embodiment 136. The bispecific antibody of any one of embodiments 69 to 135, wherein the K_D of the bispecific antibody for human KLK5 and the K_D of the antibody for human KLK7 are within 3-fold, or within 2.5-fold, or within 2-fold, or within 1.5-fold of one another.

Embodiment 137. An isolated nucleic acid encoding the bispecific antibody of any one of embodiments 69 to 136.

Embodiment 138. An isolated nucleic acid encoding the first binding domain of the bispecific antibody of any one of embodiments 69 to 136.

Embodiment 139. An isolated nucleic acid encoding the second binding domain of the bispecific antibody of any one of embodiments 69 to 136.

Embodiment 140. An isolated host cell comprising the isolated nucleic acid of embodiment 137.

Embodiment 141. An isolated host cell comprising the isolated nucleic acid of embodiment 138.

Embodiment 142. An isolated host cell comprising the isolated nucleic acid of embodiment 139.

Embodiment 143. An isolated host cell that expresses the bispecific antibody of any one of embodiments 69 to 136.

Embodiment 144. An isolated host cell that expresses the first binding domain of the bispecific antibody of any one of embodiments 69 to 136.

Embodiment 145. An isolated host cell that expresses the second binding domain of the bispecific antibody of any one of embodiments 69 to 136.

Embodiment 146. A method of producing a bispecific antibody that binds to human KLK5 and human KLK7, comprising culturing the host cell of embodiment 140 or embodiment 143 under conditions suitable for the expression of the antibody.

Embodiment 147. The method of embodiment 146, further comprising recovering the antibody from the host cell.

Embodiment 148. A method of producing a bispecific antibody that binds to human KLK5 and human KLK7, comprising (i) culturing the host cell of embodiment 141 or embodiment 144 under conditions suitable for the expression of the first binding domain; and (ii) culturing the host cell of embodiment 142 or embodiment 145 under conditions suitable for expression of the second binding domain.

Embodiment 149. The method of embodiment 148, further comprising recovering the first binding domain and the second binding domain and assembling the bispecific antibody.

Embodiment 150. A pharmaceutical composition comprising the antibody of any of embodiments 1 to 27 and a pharmaceutically acceptable carrier.

Embodiment 151. The pharmaceutical composition of embodiment 150, further comprising an additional therapeutic agent.

Embodiment 152. The pharmaceutical composition of embodiment 151, wherein the additional therapeutic agent is a KLK5 inhibitor.

Embodiment 153. The pharmaceutical composition of embodiment 152, wherein the KLK5 inhibitor is an anti-KLK5 antibody.

Embodiment 154. The pharmaceutical composition of embodiment 153, wherein the anti-KLK5 antibody comprises:

- a) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 39 and 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain

variable domain (VL) comprising (d) CDR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 43 and 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49; or

b) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 69 and 70, and (c) CDR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 71 and 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 75-78.

Embodiment 155. The pharmaceutical composition of embodiment 153 or embodiment 154, wherein the anti-KLK5 antibody comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NOs: 43, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 47.

Embodiment 156. The pharmaceutical composition of embodiment 153 or embodiment 154, wherein the anti-KLK5 antibody comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 70, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 76.

Embodiment 157. The pharmaceutical composition of any one of embodiments 153 to 156, wherein the anti-KLK5 antibody is a monoclonal antibody.

Embodiment 158. The pharmaceutical composition of any one of embodiments 153 to 157, wherein the anti-KLK5 antibody is a humanized, or chimeric antibody.

Embodiment 159. The pharmaceutical composition of any one of embodiments 153 to 158, wherein the anti-KLK5 antibody is an antibody fragment that binds human KLK5.

Embodiment 160. The pharmaceutical composition of any one of embodiments 153-159, wherein the anti-KLK5 antibody comprises a sequence selected from:

- a) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 50, 52, 53, 105 and 106;
- b) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 51 and 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 79 and 81-87;
- e) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 80 and 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

Embodiment 161. The pharmaceutical composition of any one of embodiments 153-159, wherein the anti-KLK5 antibody comprises a sequence selected from:

- a) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 52, 53, 105 and 106;
- b) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 81-87;
- e) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

Embodiment 162. The pharmaceutical composition of any one of embodiments 153-159, wherein the anti-KLK5 antibody comprises a sequence selected from:

- a) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 50, 52, 53, 105, and 106;
- b) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 51 and 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 79 and 81-87;

- e) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 80 and 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

Embodiment 163. The pharmaceutical composition of any one of embodiments 153-159, wherein the anti-KLK5 antibody comprises a sequence selected from:

- a) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 52, 53, 105, and 106;
- b) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 81-87;
- e) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

Embodiment 164. The pharmaceutical composition of embodiment 153, wherein the anti-KLK5 antibody is an antibody of any one of embodiments 34 to 62.

Embodiment 165. The pharmaceutical composition of embodiment 153, wherein the anti-KLK5 antibody is an antibody of any one of embodiments 47, 48, 51, and 52.

Embodiment 166. A pharmaceutical composition comprising the antibody of any of embodiments 34 to 62 and a pharmaceutically acceptable carrier.

Embodiment 167. The pharmaceutical composition of embodiment 166, further comprising an additional therapeutic agent.

Embodiment 168. The pharmaceutical composition of embodiment 167, wherein the additional therapeutic agent is a KLK7 inhibitor.

Embodiment 169. The pharmaceutical composition of embodiment 168, wherein the KLK7 inhibitor is an anti-KLK7 antibody.

Embodiment 170. The pharmaceutical composition of embodiment 169, wherein the anti-KLK7 antibody is an antibody of any one of embodiments 1 to 27.

Embodiment 171. A pharmaceutical composition comprising the antibody of any of embodiments 1 to 27 and an antibody of any one of embodiments 34 to 62, and a pharmaceutically acceptable carrier.

Embodiment 172. The pharmaceutical composition of any one of embodiments 150 to 171, comprising an additional therapeutic agent selected from an anti-inflammatory agent and an antibiotic.

Embodiment 173. A pharmaceutical composition comprising the bispecific antibody of any one of embodiments 69 to 136.

Embodiment 174. The pharmaceutical composition of embodiment 173, further comprising an additional therapeutic agent.

Embodiment 175. The pharmaceutical composition of embodiment 174, wherein the additional therapeutic agent is an anti-inflammatory agent.

Embodiment 176. The pharmaceutical composition of any one of embodiments 150 to 175, wherein the pharmaceutical composition is for topical administration.

Embodiment 177. The pharmaceutical composition of any one of embodiments 150 to 175, wherein the pharmaceutical composition is for subcutaneous or intravenous administration.

Embodiment 178. The antibody of any one of embodiments 1 to 27 and 34 to 62, the bispecific antibody of any one of embodiments 69 to 136, or the pharmaceutical composition of any one of embodiments 150 to 177 for use as a medicament.

Embodiment 179. The antibody of any one of embodiments 1 to 27 and 34 to 62, the bispecific antibody of any one of embodiments 69 to 136, or the pharmaceutical composition of any one of embodiments 150 to 177 for use in treating disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea.

Embodiment 180. The antibody, bispecific antibody, or pharmaceutical composition for use of embodiment 179, wherein the asthma is selected from atopic asthma, allergic asthma, non-allergic asthma, exercise-induced asthma, aspirin sensitive/exacerbated asthma, mild asthma, moderate to severe asthma, corticosteroid naïve asthma, chronic asthma, corticosteroid resistant asthma, corticosteroid refractory asthma, newly diagnosed and untreated asthma, asthma due to smoking, asthma uncontrolled on corticosteroids, T helper lymphocyte type 2 (Th2) or type 2 (Th2) high, or Type 2 (T2)-driven asthma, eosinophilic asthma, periostin-high asthma, eosinophil-high asthma, Th2-low asthma or nonTh2-driven asthma, periostin-low asthma, and eosinophil-low asthma.

Embodiment 181. The antibody, bispecific antibody, or pharmaceutical composition for use of embodiment 180, wherein the asthma is eosinophil-low asthma.

Embodiment 182. A combination of an antibody of any one of embodiments 1 to 27 and an antibody of any one of embodiments 34 to 62, for use as a medicament.

Embodiment 183. A combination of an antibody of any one of embodiments 1 to 27 and an antibody of any one of embodiments 34 to 62, for use in treating disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea.

Embodiment 184. The combination of embodiment 183, wherein the asthma is selected from atopic asthma, allergic asthma, non-allergic asthma, exercise-induced asthma, aspirin sensitive/exacerbated asthma, mild asthma, moderate to severe asthma, corticosteroid naïve asthma, chronic asthma, corticosteroid resistant asthma, corticosteroid refractory asthma, newly diagnosed and untreated asthma, asthma due to smoking, asthma uncontrolled on corticosteroids, T helper lymphocyte type 2 (Th2) or type 2 (Th2) high, or Type 2 (T2)-driven asthma, eosinophilic asthma, periostin-high asthma, eosinophil-high asthma, Th2-low asthma or nonTh2-driven asthma, periostin-low asthma, and eosinophil-low asthma.

Embodiment 185. The combination of embodiment 184, wherein the asthma is eosinophil-low asthma.

Embodiment 186. Use of the antibody of any one of embodiments 1 to 27 and 34 to 62, the bispecific antibody of any one of embodiments 69 to 136, or the pharmaceutical composition of any one of embodiments 150 to 177 in the manufacture of a medicament for treating disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea.

Embodiment 187. The use of embodiment 186, wherein the asthma is selected from atopic asthma, allergic asthma, non-allergic asthma, exercise-induced asthma, aspirin sensitive/exacerbated asthma, mild asthma, moderate to severe asthma, corticosteroid naïve asthma, chronic asthma, corticosteroid resistant asthma, corticosteroid refractory asthma, newly diagnosed and untreated asthma, asthma due to smoking, asthma uncontrolled on corticosteroids, T helper lymphocyte type 2 (Th2) or type 2 (Th2) high, or Type 2 (T2)-driven asthma, eosinophilic asthma, periostin-high asthma, eosinophil-high asthma, Th2-low asthma or nonTh2-driven asthma, periostin-low asthma, and eosinophil-low asthma.

Embodiment 188. The use of embodiment 187, wherein the asthma is eosinophil-low asthma.

Embodiment 189. Use of a combination of the antibody of any one of embodiments 1 to 27 and the antibody of any one of embodiments 34 to 62 in the manufacture of a medicament for treating disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea.

Embodiment 190. The use of embodiment 189, wherein the asthma is selected from atopic asthma, allergic asthma, non-allergic asthma, exercise-induced asthma, aspirin sensitive/exacerbated asthma, mild asthma, moderate to severe asthma, corticosteroid naïve asthma, chronic asthma, corticosteroid resistant asthma, corticosteroid refractory asthma, newly diagnosed and untreated asthma, asthma due to smoking, asthma uncontrolled on

corticosteroids, T helper lymphocyte type 2 (Th2) or type 2 (Th2) high, or Type 2 (T2)-driven asthma, eosinophilic asthma, periostin-high asthma, eosinophil-high asthma, Th2-low asthma or nonTh2-driven asthma, periostin-low asthma, and eosinophil-low asthma.

Embodiment 191. The use of embodiment 190, wherein the asthma is eosinophil-low asthma.

Embodiment 192. Use of the antibody of any one of embodiments 1 to 27 and 34 to 62, the bispecific antibody of any one of embodiments 69 to 136, or the pharmaceutical composition of any one of embodiments 150 to 177 in the manufacture of a medicament for reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines.

Embodiment 193. Use of a combination of the antibody of any one of embodiments 1 to 27 and the antibody of any one of embodiments 34 to 62 in the manufacture of a medicament for reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines.

Embodiment 194. A method of treating an individual having a disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea, comprising administering to the individual an effective amount of the antibody of any one of embodiments 1 to 27 and 34 to 62, the bispecific antibody of any one of embodiments 69 to 136, or the pharmaceutical composition of any one of embodiments 150 to 177.

Embodiment 195. A method of treating an individual having a disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea, comprising administering to the individual a) an effective amount of the antibody of any one of embodiments 1 to 27; and b) an effective amount of the antibody of any one of embodiments 34 to 62.

Embodiment 196. The method of embodiment 195, wherein the antibody of (a) and the antibody of (b) are administered simultaneously.

Embodiment 197. The method of embodiment 195, wherein the antibody of (a) and the antibody of (b) are administered sequentially.

Embodiment 198. A method of treating an individual having a disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea, comprising administering to the individual an effective amount of the bispecific antibody of any

one of embodiments 69 to 136, or an effective amount of the pharmaceutical composition of any one of embodiments 150 to 177.

Embodiment 199. The method of any one of embodiments 194 to 198, wherein the asthma is selected from atopic asthma, allergic asthma, non-allergic asthma, exercise-induced asthma, aspirin sensitive/exacerbated asthma, mild asthma, moderate to severe asthma, corticosteroid naïve asthma, chronic asthma, corticosteroid resistant asthma, corticosteroid refractory asthma, newly diagnosed and untreated asthma, asthma due to smoking, asthma uncontrolled on corticosteroids, T helper lymphocyte type 2 (Th2) or type 2 (Th2) high, or Type 2 (T2)-driven asthma, eosinophilic asthma, periostin-high asthma, eosinophil-high asthma, Th2-low asthma or nonTh2-driven asthma, periostin-low asthma, and eosinophil-low asthma.

Embodiment 200. The method of embodiment 199, wherein the asthma is eosinophil-low asthma.

Embodiment 201. The method of any one of embodiments 194 to 198, wherein the individual has Netherton Syndrome.

Embodiment 202. The method of any one of embodiments 194 to 198, wherein the individual has rosacea.

Embodiment 203. The method of any one of embodiments 194 to 202, further comprising administering an additional therapeutic agent to the individual.

Embodiment 204. The method of embodiment 203 wherein the additional therapeutic agent is an anti-inflammatory agent.

Embodiment 205. A method of reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines in an individual comprising administering to the individual an effective amount of the antibody of any one of embodiments 1 to 27 and 34 to 62, the bispecific antibody of any one of embodiments 69 to 136, or the pharmaceutical composition of any one of embodiments 150 to 177 to reduce epithelium inflammation, reduce epithelium permeability, reduce transepidermal water loss, reduce dermal infiltrates, reduce parakeratosis, and/or restore the epithelial barrier.

Embodiment 206. A method of reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines in an individual comprising administering to the individual a) an effective amount of the antibody of any one of embodiments 1 to 27; and b) an effective amount of the antibody of any one of embodiments 34 to 62, to reduce epithelium inflammation, reduce epithelium

permeability, reduce transepidermal water loss, reduce dermal infiltrates, reduce parakeratosis, and/or restore the epithelial barrier.

Embodiment 207. The method of embodiment 206, wherein the antibody of (a) and the antibody of (b) are administered simultaneously.

Embodiment 208. The method of embodiment 206, wherein the antibody of (a) and the antibody of (b) are administered sequentially.

Embodiment 209. A method of reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines in an individual comprising administering to the individual the bispecific antibody of any one of embodiments 69 to 136, or an effective amount of the pharmaceutical composition of any one of embodiments 150 to 177, to reduce epithelium inflammation, reduce epithelium permeability, reduce transepidermal water loss, reduce dermal infiltrates, reduce parakeratosis, and/or restore the epithelial barrier.

Embodiment 210. The method of any one of embodiments 194 to 209, wherein the administering is subcutaneous or intravenous administration.

Embodiment 211. The method of any one of embodiments 194 to 209, wherein the administering is topical administration.

Embodiment 212. The method of any one of embodiments 194 to 209, wherein the administering is intravenous administration.

Embodiment 213. An isolated antibody that binds human KLK7, wherein when bound to human KLK7 results in a conformational change of human KLK7, wherein the conformational change allosterically results in the disruption of the substrate binding site and/or the active site of human KLK7.

Embodiment 214. The isolated antibody of embodiment 213, which is a bispecific antibody.

Embodiment 215. The isolated antibody of embodiment 214, wherein the bispecific antibody binds human KLK7 and human KLK5.

Embodiment 216. The isolated antibody of embodiment 215, wherein when bound to human KLK5 results in a conformational change of human KLK5, wherein the conformational change allosterically results in the disruption of the substrate binding site and/or the active site of human KLK5.

Embodiment 217. The isolated antibody of embodiment 216, wherein the antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from

Pro130, Ser131, Ala132, Gly133, Val162, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Tyr172, Pro173, Arg174, Gln174A, Ile176, Asp177, Asp178, Gly184, Asp185, Lys186, Ala186A, Arg188, Asn223, Arg224, Pro225, and Lys233 according to standard protease numbering.

Embodiment 218. The isolated antibody of embodiment 217, wherein the antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from the group consisting of Pro130, Ser131, Ala132, Val162, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Tyr172, Pro173, Arg174, Gln174A, Ile176, Asp177, Asp178, Arg224, and Lys233 according to standard protease numbering.

Embodiment 219. The isolated antibody of embodiment 217, wherein the antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from Pro130, Ser131, Ala132, Gly133, Val162, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Tyr172, Pro173, Arg174, Gln174A, Ile176, Asp177, and Lys233 according to standard protease numbering.

Embodiment 220. The isolated antibody of embodiment 217, wherein the antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from Ser131, Ala132, Gly133, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Pro173, Arg174, Gly184, Asp185, Lys186, Ala186A, Arg188, Asn223, Arg224, and Pro225 according to standard protease numbering.

Embodiment 221. The isolated antibody of any one of embodiments 213 to 220, wherein the antibody binds an epitope within amino acids R71-N82, K152-S158, and/or Q211-K222 of KLK7 (SEQ ID NO: 4).

Embodiment 222. The isolated antibody of any one of embodiments 213 to 221, wherein the antibody binds an epitope comprising one or more of amino acids H72, P73, G74, S76, Q78, N82, N157, K211, and/or T213 of KLK7 (SEQ ID NO: 4).

Embodiment 223. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein when bound to human KLK7 results in a conformational change of human KLK7, wherein the conformational change allosterically results in the disruption of the substrate binding site and/or the active site of human KLK7.

Embodiment 224. The bispecific antibody of embodiment 223, wherein when bound to human KLK5 results in a conformational change of human KLK5, wherein the conformational change allosterically results in the disruption of the substrate binding site and/or the active site of human KLK5.

Embodiment 225. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein when bound to human KLK5 results in a conformational change of human KLK5, wherein the conformational change allosterically results in the disruption of the substrate binding site and/or the active site of human KLK5.

Embodiment 226. The bispecific antibody of embodiment 224 or embodiment 225, wherein the antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from Pro130, Ser131, Ala132, Gly133, Val162, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Tyr172, Pro173, Arg174, Gln174A, Ile176, Asp177, Asp178, Gly184, Asp185, Lys186, Ala186A, Arg188, Asn223, Arg224, Pro225, and Lys233 according to standard protease numbering.

Embodiment 227. The isolated antibody of embodiment 226, wherein the antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from the group consisting of Pro130, Ser131, Ala132, Val162, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Tyr172, Pro173, Arg174, Gln174A, Ile176, Asp177, Asp178, Arg224, and Lys233 according to standard protease numbering.

Embodiment 228. The isolated antibody of embodiment 226, wherein the antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from Pro130, Ser131, Ala132, Gly133, Val162, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Tyr172, Pro173, Arg174, Gln174A, Ile176, Asp177, and Lys233 according to standard protease numbering.

Embodiment 229. The isolated antibody of embodiment 226, wherein the antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from Ser131, Ala132, Gly133, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Pro173, Arg174, Gly184, Asp185, Lys186, Ala186A, Arg188, Asn223, Arg224, and Pro225 according to standard protease numbering.

Embodiment 230. The bispecific antibody of any one of embodiments 223 to 229, wherein the antibody binds an epitope within amino acids R71-N82, K152-S158, and/or Q211-K222 of KLK7 (SEQ ID NO: 4).

Embodiment 231. The bispecific antibody of any one of embodiments 223 to 230, wherein the antibody binds an epitope comprising one or more of amino acids H72, P73, G74, S76, Q78, N82, N157, K211, and/or T213 of KLK7 (SEQ ID NO: 4).

Embodiment 232. A pharmaceutical composition comprising the antibody of any one of embodiments 213 to 222 and a pharmaceutically acceptable carrier.

Embodiment 233. A pharmaceutical composition comprising the bispecific antibody of any one of embodiments 223 to 231 and a pharmaceutically acceptable carrier.

Embodiment 234. The antibody of any one of embodiments 213 to 222, the bispecific antibody of any one of embodiments 223 to 231, or the pharmaceutical composition of embodiment 232 or embodiment 233 for use as a medicament.

Embodiment 235. The antibody of any one of embodiments 213 to 222, the bispecific antibody of any one of embodiments 223 to 231, or the pharmaceutical composition of embodiment 232 or embodiment 233 for use in treating disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea.

Embodiment 236. The antibody, bispecific antibody, or pharmaceutical composition for use of embodiment 235, wherein the asthma is selected from atopic asthma, allergic asthma, non-allergic asthma, exercise-induced asthma, aspirin sensitive/exacerbated asthma, mild asthma, moderate to severe asthma, corticosteroid naïve asthma, chronic asthma, corticosteroid resistant asthma, corticosteroid refractory asthma, newly diagnosed and untreated asthma, asthma due to smoking, asthma uncontrolled on corticosteroids, T helper lymphocyte type 2 (Th2) or type 2 (Th2) high, or Type 2 (T2)-driven asthma, eosinophilic asthma, periostin-high asthma, eosinophil-high asthma, Th2-low asthma or nonTh2-driven asthma, periostin-low asthma, and eosinophil-low asthma.

Embodiment 237. The antibody of any one of embodiments 213 to 222, the bispecific antibody of any one of embodiments 223 to 231, or the pharmaceutical composition of embodiment 232 or embodiment 233 for use in reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines.

Embodiment 238. Use of the antibody of any one of embodiments 213 to 222, the bispecific antibody of any one of embodiments 223 to 231, or the pharmaceutical composition of embodiment 232 or embodiment 233 in the manufacture of a medicament for treating disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea.

Embodiment 239. The use of embodiment 238, wherein the asthma is selected from atopic asthma, allergic asthma, non-allergic asthma, exercise-induced asthma, aspirin sensitive/exacerbated asthma, mild asthma, moderate to severe asthma, corticosteroid naïve asthma, chronic asthma, corticosteroid resistant asthma, corticosteroid refractory asthma, newly diagnosed and untreated asthma, asthma due to smoking, asthma uncontrolled on

corticosteroids, T helper lymphocyte type 2 (Th2) or type 2 (Th2) high, or Type 2 (T2)-driven asthma, eosinophilic asthma, periostin-high asthma, eosinophil-high asthma, Th2-low asthma or nonTh2-driven asthma, periostin-low asthma, and eosinophil-low asthma.

Embodiment 240. Use of the antibody of any one of embodiments 213 to 222, the bispecific antibody of any one of embodiments 223 to 231, or the pharmaceutical composition of embodiment 232 or embodiment 233 in the manufacture of a medicament for reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines.

Embodiment 241. A method of treating an individual having a disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea, comprising administering to the individual an effective amount of the antibody of any one of 213 to 222, the bispecific antibody of any one of embodiments 223 to 231, or the pharmaceutical composition of embodiment 232 or embodiment 233.

Embodiment 242. The method of embodiment 241, wherein the asthma is selected from atopic asthma, allergic asthma, non-allergic asthma, exercise-induced asthma, aspirin sensitive/exacerbated asthma, mild asthma, moderate to severe asthma, corticosteroid naïve asthma, chronic asthma, corticosteroid resistant asthma, corticosteroid refractory asthma, newly diagnosed and untreated asthma, asthma due to smoking, asthma uncontrolled on corticosteroids, T helper lymphocyte type 2 (Th2) or type 2 (Th2) high, or Type 2 (T2)-driven asthma, eosinophilic asthma, periostin-high asthma, eosinophil-high asthma, Th2-low asthma or nonTh2-driven asthma, periostin-low asthma, and eosinophil-low asthma.

Embodiment 243. A method of reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines in an individual comprising administering to the individual an effective amount of the antibody of any one of 213 to 222, the bispecific antibody of any one of embodiments 223 to 231, or the pharmaceutical composition of embodiment 232 or embodiment 233 to reduce epithelium inflammation, reduce epithelium permeability, reduce transepidermal water loss, reduce dermal infiltrates, reduce parakeratosis, and/or restore the epithelial barrier.

Embodiment 244. The antibody, bispecific antibody, or pharmaceutical composition for use of embodiment 179 or embodiment 235, wherein the disease is Netherton Syndrome.

Embodiment 245. The combination for use of embodiment 183, wherein the disease is Netherton Syndrome.

Embodiment 246. The use of any one of embodiments 186, 189, and 238, wherein the disease is Netherton Syndrome.

Embodiment 247. The use of any one of embodiments 192, 193, and 240, wherein the medicament is for reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines in an individual with Netherton Syndrome.

Embodiment 248. A bispecific antibody for use in treating Netherton Syndrome, wherein the bispecific antibody comprises a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 112 or 194, and a light chain amino acid sequence of SEQ ID NO: 113, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 114 or 195, and a light chain amino acid sequence of SEQ ID NO: 115.

Embodiment 249. An anti-KLK5 antibody for use in treating Netherton Syndrome, wherein the anti-KLK5 antibody comprises (a) a VH sequence of SEQ ID NO: 52 and a VL sequence of SEQ ID NO: 55; or (b) a VH sequence of SEQ ID NO: 53 and a VL sequence of SEQ ID NO: 62.

Embodiment 250. An anti-KLK7 antibody for use in treating Netherton Syndrome, wherein the anti-KLK7 antibody comprises (a) a VH sequence of SEQ ID NO: 29 and a VL sequence of SEQ ID NO: 32; or (b) a VH sequence of SEQ ID NO: 30 and a VL sequence of SEQ ID NO: 38.

Embodiment 251. An antibody combination for use in treating Netherton Syndrome, wherein the antibody combination comprises an anti-KLK5 antibody and an anti-KLK7 antibody, wherein the anti-KLK5 antibody comprises a VH sequence of SEQ ID NO: 52 and a VL sequence of SEQ ID NO: 55, or a VH sequence of SEQ ID NO: 53 and a VL sequence of SEQ ID NO: 62; and wherein the anti-KLK7 antibody comprises a VH sequence of SEQ ID NO: 29 and a VL sequence of SEQ ID NO: 32, or a VH sequence of SEQ ID NO: 30 and a VL sequence of SEQ ID NO: 38.

Embodiment 252. A method of treating an individual having a disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea, comprising administering to the individual an effective amount of the bispecific antibody, wherein the bispecific antibody comprises a first binding domain and second binding domain,

wherein the first binding domain binds human KLK7 and inhibits KLK7 protease activity and the second binding domain binds human KLK5 and inhibits KLK5 protease activity.

Embodiment 253. A method of treating an individual having a disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea, comprising administering to the individual an anti-KLK5 antibody and an anti-KLK7 antibody, wherein the anti-KLK5 antibody inhibits KLK5 protease activity, and wherein the anti-KLK7 antibody inhibits KLK7 protease activity.

Embodiment 254. A method of reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier and/or reducing skin inflammatory cytokines in an individual comprising administering to the individual a KLK5 antagonist and a KLK7 antagonist.

Embodiment 255. The method of embodiment 254, wherein the KLK5 antagonist is an anti-KLK5 antibody and/or the KLK7 antagonist is an anti-KLK7 antibody.

Embodiment 256. A method of reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier and/or reducing skin inflammatory cytokines in an individual comprising administering to the individual an effective amount of the bispecific antibody, wherein the bispecific antibody comprises a first binding domain and second binding domain, wherein the first binding domain binds human KLK7 and inhibits KLK7 protease activity and the second binding domain binds human KLK5 and inhibits KLK5 protease activity.

Embodiment 257. A method of reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier and/or reducing skin inflammatory cytokines in an individual comprising administering to the individual an anti-KLK5 antibody and an anti-KLK7 antibody, wherein the anti-KLK5 antibody inhibits KLK5 protease activity, and wherein the anti-KLK7 antibody inhibits KLK7 protease activity.

Embodiment 258. A method of ameliorating skin rash and/or scaling in an individual with Netherton Syndrome comprising administering to the individual an effective amount of the bispecific antibody, wherein the bispecific antibody comprises a first binding domain and second binding domain, wherein the first binding domain binds human KLK7 and inhibits KLK7 protease activity and the second binding domain binds human KLK5 and inhibits KLK5 protease activity.

Embodiment 259. A method of ameliorating skin rash and/or scaling in an individual with Netherton Syndrome comprising administering to the individual an anti-KLK5 antibody and an anti-KLK7 antibody, wherein the anti-KLK5 antibody inhibits KLK5 protease activity, and wherein the anti-KLK7 antibody inhibits KLK7 protease activity.

Embodiment 260. The use of any one of embodiments 192, 193, 240, or 247 or the method of any one of embodiments 205, 206, 209, 243, or 254-257, or the antibody, bispecific antibody, or pharmaceutical composition for use of embodiment 237, wherein the skin inflammatory cytokines are one or more of IL-8, TNF α , IL-6, IL-4, and/or G-CSF.

Embodiment 261. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 194, and a light chain amino acid sequence of SEQ ID NO: 113, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 195, and a light chain amino acid sequence of SEQ ID NO: 115.

Embodiment 262. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 112, and a light chain amino acid sequence of SEQ ID NO: 113, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 195, and a light chain amino acid sequence of SEQ ID NO: 115.

Embodiment 263. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 194, and a light chain amino acid sequence of SEQ ID NO: 113, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 114, and a light chain amino acid sequence of SEQ ID NO: 115.

BRIEF DESCRIPTION OF THE FIGURES

[008] Figures 1A-1B show an alignment of anti-KLK7 antibody rb.14H11c-LC light chain variable region with certain humanized versions of the light chain variable regions (1A) and anti-KLK7 antibody rb.14H11c-HC heavy chain variable region with certain humanized versions of the heavy chain variable regions (1B). CDRs according to Chothia, Kabat, and contact residues are indicated. Differences in the humanized versions relative to the rabbit parental variable regions are shown in white with a black background.

[0009] Figures 2A-2B show an alignment of humanized anti-KLK5 antibody hu.10C5-H28L5 light chain variable region with certain modified humanized versions of the light chain variable regions (2A) and humanized anti-KLK5 antibody hu.10C5-H28L5 heavy chain variable region with certain modified humanized versions of the heavy chain variable regions (2B). CDRs according to Chothia, Kabat, and contact residues are indicated. Differences in the humanized versions relative to the parental variable regions are shown in white with a black background.

[0010] Figures 3A-3B show an alignment of humanized anti-KLK5 antibody hu.9H5-H14L4 light chain variable region with certain modified humanized versions of the light chain variable regions (3A) and humanized anti-KLK5 antibody hu.9H5-H14L4 heavy chain variable region with certain modified humanized versions of the heavy chain variable regions (3B). CDRs according to Chothia, Kabat, and contact residues are indicated. Differences in the humanized versions relative to the parental variable regions are shown in white with a black background.

[0011] Figure 4 shows the affinity of humanized anti-KLK5 antibody hu.10C5.L5H28 heavy chain and light chain variants and parental hu.10C5.L5H28.

[0012] Figure 5 shows a scatter plot of the on rates (k_a) and off-rates (k_d) of humanized anti-KLK5 antibody hu.9H5.L4H14 heavy chain and light chain variants.

[0013] Figures 6A-6B show surface plasmon resonance traces for the indicated hu.10C5.L5H28 variants for human KLK5 (Figure 6A) and cynomolgus monkey KLK5 (Figure 6B).

[0014] Figures 7A-7B show surface plasmon resonance traces for the indicated hu.9H5.L4H14 variants for human KLK5 (Figure 7A) and cynomolgus monkey KLK5 (Figure 7B).

[0015] Figure 8 shows representative KLK5 protein expression in human normal skin, atopic dermatitis, and rosacea.

[0016] Figure 9 shows representative KLK7 mRNA staining in human normal skin, atopic dermatitis, rosacea, and psoriasis.

[0017] Figures 10A-10C show KLK5 expression depth (10A), KLK7 expression depth (10B), and SPINK5 expression depth (10C) in human normal skin, atopic dermatitis, rosacea, and psoriasis.

[0018] Figure 11 shows transepidermal water loss in mice administered saline, KLK5, or KLK7.

[0019] Figures 12A-12C show daily clinical score (12A), total terminal atopic dermatitis score (12B), and AUC skin score (12C) in SDS/*S. Aureus* protein A atopic dermatitis model mice administered isotype control antibody, anti-murine KLK5 antibody, anti-murine KLK7 antibody, a combination of anti-KLK5 and anti-KLK7 antibodies, or SPINK5-Fc.

[0020] Figure 13 shows total terminal atopic dermatitis score, transepidermal water loss, and histological disease severity score in SDS/*S. Aureus* protein A atopic dermatitis model mice administered isotype control antibody, anti-murine KLK5 antibody, anti-murine KLK7 antibody, a combination of anti-KLK5 and anti-KLK7 antibodies, or anti-IL-13 antibody.

[0021] Figure 14 shows representative hematoxylin and eosin staining of skin from SDS/*S. Aureus* protein A atopic dermatitis model mice administered isotype control antibody, a combination of anti-KLK5 and anti-KLK7 antibodies, or anti-IL-13 antibody.

[0022] Figure 15 shows a schematic of an exemplary bispecific anti-KLK5/KLK7 antibody provided herein, including substitutions to promote proper heavy chain/light chain pairing and/or substitutions to reduce effector functions. In an alternative format, the knob may be present on the anti-KLK5 arm, and the hole may be present on the anti-KLK7 arm.

[0023] Figures 16A-16D show reduction of skin rash and scaling in Spink5 deficient mice treated with anti-mKLK5/mKLK7 bispecific antibody. Spink5 f/f Cre-ERT2-negative control mice were treated with 16 mg/kg tamoxifen (16A), and Spink5 f/f Cre-ERT2+ mice were injected with 16 mg/kg (16B), 8 mg/kg (16C), or 4 mg/kg (16D) tamoxifen, then treated with 2.5 mg anti-gp120 isotype control antibody or 2.5 mg anti-mKLK5/mKLK7 bispecific antibody every other day. Back skin was analyzed 6 days post-injection.

[0024] Figures 17A-17E show reduction of cytokines IL-8 (17A), TNF- α (17B), IL-6 (17C), IL-4 (17D), and G-CSF (17E) in lysates prepared from back skin of Spink5 deficient mice following anti-mKLK5/mKLK7 bispecific antibody treatment compared to isotype control antibody treatment.

[0025] Figure 18 shows representative cross-sections of hematoxylin and eosin stained skin from Spink5 f/f Cre-ERT2-negative control mice treated with 16mg/kg tamoxifen and Spink5 f/f Cre-ERT2+ mice treated with 16 mg/kg tamoxifen and isotype control antibody or anti-mKLK5/mKLK7 bispecific antibody.

[0026] Figures 19A-19B show epithelial permeability as measured by trans-epithelial electrical resistance (TEER) in human epidermal keratinocytes treated with KLK5, KLK7, KLK5+KLK7, and KLK5+KLK7+anti-KLK5/KLK7 bispecific antibody.

[0027] Figures 20A-20C show the crystal structure of anti-KLK7 rb.14H11c Fab bound to KLK7. The complete Fab bound to KLK7 is shown in Figure 20A, with an overlay of KLK7

alone. Figure 20B shows the KLK7-Fab interface. Figure 20C shows an overlay of KLK7 in its native conformation (yellow) and KLK7 bound to rb.14H11c Fab (cyan). Portions of the rb14H11c heavy chain are shown in dark blue.

DETAILED DESCRIPTION

I. DEFINITIONS

[0028] An “acceptor human framework” for the purposes herein is a framework comprising the amino acid sequence of a light chain variable domain (VL) framework or a heavy chain variable domain (VH) framework derived from a human immunoglobulin framework or a human consensus framework, as defined below. An acceptor human framework “derived from” a human immunoglobulin framework or a human consensus framework may comprise the same amino acid sequence thereof, or it may contain amino acid sequence changes. In some aspects, the number of amino acid changes are 10 or less, 9 or less, 8 or less, 7 or less, 6 or less, 5 or less, 4 or less, 3 or less, or 2 or less. In some aspects, the VL acceptor human framework is identical in sequence to the VL human immunoglobulin framework sequence or human consensus framework sequence.

[0029] “Affinity” refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). Unless indicated otherwise, as used herein, “binding affinity” refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured by common methods known in the art, including those described herein. Specific illustrative and exemplary methods for measuring binding affinity are described in the following.

[0030] An “affinity matured” antibody refers to an antibody with one or more alterations in one or more complementary determining regions (CDRs), compared to a parent antibody which does not possess such alterations, such alterations resulting in an improvement in the affinity of the antibody for antigen.

[0031] The terms “anti-KLK7 antibody” and “an antibody that binds to KLK7” refer to an antibody that is capable of binding KLK7, such as human KLK7, with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting KLK7. In one aspect, the extent of binding of an anti-KLK7 antibody to an unrelated, non-KLK7 protein is less than about 10% of the binding of the antibody to KLK7 as measured, e.g., by surface plasmon resonance (SPR). In certain aspects, an antibody that binds to KLK7 has a dissociation constant

(K_D) of $\leq 1\mu\text{M}$, $\leq 100\text{ nM}$, $\leq 10\text{ nM}$, $\leq 1\text{ nM}$, $\leq 0.1\text{ nM}$, $\leq 0.01\text{ nM}$, or $\leq 0.001\text{ nM}$ (e.g., 10^{-8} M or less, e.g., from 10^{-8} M to 10^{-13} M , e.g., from 10^{-9} M to 10^{-13} M). An antibody is said to “specifically bind” to KLK7 when the antibody has a K_D of $1\mu\text{M}$ or less. In certain aspects, an anti-KLK7 antibody binds to an epitope of KLK7 that is conserved among KLK7 from different species.

[0032] The terms “anti-KLK5 antibody” and “an antibody that binds to KLK5” refer to an antibody that is capable of binding KLK5, such as human KLK5, with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting KLK5. In one aspect, the extent of binding of an anti-KLK5 antibody to an unrelated, non-KLK5 protein is less than about 10% of the binding of the antibody to KLK5 as measured, e.g., by surface plasmon resonance (SPR). In certain aspects, an antibody that binds to KLK5 has a dissociation constant (K_D) of $\leq 1\mu\text{M}$, $\leq 100\text{ nM}$, $\leq 10\text{ nM}$, $\leq 1\text{ nM}$, $\leq 0.1\text{ nM}$, $\leq 0.01\text{ nM}$, or $\leq 0.001\text{ nM}$ (e.g., 10^{-8} M or less, e.g., from 10^{-8} M to 10^{-13} M , e.g., from 10^{-9} M to 10^{-13} M). An antibody is said to “specifically bind” to KLK5 when the antibody has a K_D of $1\mu\text{M}$ or less. In certain aspects, an anti-KLK5 antibody binds to an epitope of KLK5 that is conserved among KLK5 from different species.

[0033] The terms “anti-KLK5/KLK7 antibody” and “an antibody that binds to KLK5 and KLK7” refer to a multispecific antibody that is capable of binding KLK7 and KLK5 with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting KLK7 and/or KLK5. In one aspect, the extent of binding of an anti-KLK5/KLK7 antibody to an unrelated, non-KLK7/non-KLK5 protein is less than about 10% of the binding of the antibody to KLK7 or KLK5 as measured, e.g., by surface plasmon resonance (SPR). In certain aspects, a multispecific antibody that binds to KLK7 and KLK5 has a dissociation constant (K_D) of $\leq 1\mu\text{M}$, $\leq 100\text{ nM}$, $\leq 10\text{ nM}$, $\leq 1\text{ nM}$, $\leq 0.1\text{ nM}$, $\leq 0.01\text{ nM}$, or $\leq 0.001\text{ nM}$ (e.g., 10^{-8} M or less, e.g., from 10^{-8} M to 10^{-13} M , e.g., from 10^{-9} M to 10^{-13} M) for each of KLK5 and KLK7. An antibody is said to “specifically bind” to a target protein when the antibody has a K_D of $1\mu\text{M}$ or less. In certain aspects, an anti-KLK5/KLK7 antibody binds to an epitope of KLK7 that is conserved among KLK7 from different species. In certain aspects, an anti-KLK5/KLK7 antibody binds to an epitope of KLK5 that is conserved among KLK5 from different species.

[0034] The term “antibody” herein is used in the broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments so long as they exhibit the desired antigen-binding activity.

[0035] An “antibody fragment” refers to a molecule other than an intact antibody that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of antibody fragments include but are not limited to Fv, Fab, Fab', Fab'-SH, F(ab')₂; diabodies; linear antibodies; single-chain antibody molecules (e.g., scFv, and scFab); single domain antibodies (dAbs); and multispecific antibodies formed from antibody fragments. For a review of certain antibody fragments, see Holliger and Hudson, *Nature Biotechnology* 23:1126-1136 (2005).

[0036] A “binding domain” of an antibody, as used herein, refers to a portion of a variable domain that is sufficient to bind antigen. In some embodiments, a binding domain comprises heavy chain (HC) CDR1, CDR2, and CDR3 and light chain (LC) CDR1, CDR2, and CDR3. In some embodiments, a binding domain comprises heavy chain (HC) CDR1, FR2, CDR2, FR3, and CDR3 and light chain (LC) CDR1, FR2, CDR2, FR3, and CDR3.

[0037] The term “epitope” denotes the site on an antigen, either proteinaceous or non-proteinaceous, to which an anti-KLK7 antibody or anti-KLK5 antibody binds. Epitopes can be formed both from contiguous amino acid stretches (linear epitope) or comprise non-contiguous amino acids (conformational epitope), e.g., coming in spatial proximity due to the folding of the antigen, i.e. by the tertiary folding of a proteinaceous antigen. Linear epitopes are typically still bound by an antibody after exposure of the proteinaceous antigen to denaturing agents, whereas conformational epitopes are typically destroyed upon treatment with denaturing agents. An epitope comprises at least 3, at least 4, at least 5, at least 6, at least 7, or 8-10 amino acids in a unique spatial conformation.

[0038] Screening for antibodies binding to a particular epitope (i.e., those binding to the same epitope) can be done using methods routine in the art such as, e.g., without limitation, alanine scanning, peptide blots (see *Meth. Mol. Biol.* 248 (2004) 443-463), peptide cleavage analysis, epitope excision, epitope extraction, chemical modification of antigens (see *Prot. Sci.* 9 (2000) 487-496), and cross-blocking (see “Antibodies”, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harb., NY).

[0039] Antigen Structure-based Antibody Profiling (ASAP), also known as Modification-Assisted Profiling (MAP), allows to bin a multitude of monoclonal antibodies specifically binding to KLK7 or KLK5 based on the binding profile of each of the antibodies from the multitude to chemically or enzymatically modified antigen surfaces (see, e.g., US 2004/0101920). The antibodies in each bin bind to the same epitope which may be a unique epitope either distinctly different from or partially overlapping with epitope represented by another bin.

[0040] Also competitive binding can be used to easily determine whether an antibody binds to the same epitope of KLK7 as, or competes for binding with, an anti-KLK7 antibody. For example, an “antibody that binds to the same epitope” as a reference anti-KLK7 antibody refers to an antibody that blocks binding of the reference anti-KLK7 antibody, respectively, to its antigen in a competition assay by 50% or more, and conversely, the reference antibody blocks binding of the antibody to its antigen in a competition assay by 50% or more. Also for example, to determine if an antibody binds to the same epitope as a reference anti-KLK7 antibody, the reference antibody is allowed to bind to KLK7 under saturating conditions. After removal of the excess of the reference anti-KLK7 antibody, the ability of an anti-KLK7 antibody in question to bind to KLK7 is assessed. If the anti-KLK7 antibody is able to bind to KLK7 after saturation binding of the reference anti-KLK7 antibody, it can be concluded that the anti-KLK7 antibody in question binds to a different epitope than the reference anti-KLK7 antibody. But, if the anti-KLK7 antibody in question is not able to bind to KLK7 after saturation binding of the reference anti-KLK7 antibody, then the anti-KLK7 antibody in question may bind to the same epitope as the epitope bound by the reference anti-KLK7 antibody. To confirm whether the antibody in question binds to the same epitope or is just hampered from binding by steric reasons routine experimentation can be used (e.g., peptide mutation and binding analyses using ELISA, RIA, surface plasmon resonance, flow cytometry or any other quantitative or qualitative antibody-binding assay available in the art). This assay should be carried out in two set-ups, i.e. with both of the antibodies being the saturating antibody. If, in both set-ups, only the first (saturating) antibody is capable of binding to KLK7, then it can be concluded that the anti-KLK7 antibody in question and the reference anti-KLK7 antibody compete for binding to KLK7.

[0041] Similarly, competitive binding can be used to easily determine whether an antibody binds to the same epitope of KLK5 as, or competes for binding with, an anti-KLK5 antibody. For example, an “antibody that binds to the same epitope” as a reference anti-KLK5 antibody refers to an antibody that blocks binding of the reference anti-KLK5 antibody, respectively, to its antigen in a competition assay by 50% or more, and conversely, the reference antibody blocks binding of the antibody to its antigen in a competition assay by 50% or more. Also for example, to determine if an antibody binds to the same epitope as a reference anti-KLK5 antibody, the reference antibody is allowed to bind to KLK5 under saturating conditions. After removal of the excess of the reference anti-KLK5 antibody, the ability of an anti-KLK5 antibody in question to bind to KLK5 is assessed. If the anti-KLK5 antibody is able to bind to KLK5 after saturation binding of the reference anti-KLK5 antibody, it can be concluded that the

anti-KLK5 antibody in question binds to a different epitope than the reference anti-KLK5 antibody. But, if the anti-KLK5 antibody in question is not able to bind to KLK5 after saturation binding of the reference anti- KLK5 antibody, then the anti-KLK5 antibody in question may bind to the same epitope as the epitope bound by the reference anti- KLK5 antibody. To confirm whether the antibody in question binds to the same epitope or is just hampered from binding by steric reasons routine experimentation can be used (e.g., peptide mutation and binding analyses using ELISA, RIA, surface plasmon resonance, flow cytometry or any other quantitative or qualitative antibody-binding assay available in the art). This assay should be carried out in two set-ups, i.e. with both of the antibodies being the saturating antibody. If, in both set-ups, only the first (saturating) antibody is capable of binding to KLK5, then it can be concluded that the anti-KLK5 antibody in question and the reference anti- KLK5 antibody compete for binding to KLK5.

[0042] In some aspects, two antibodies are deemed to bind to the same or an overlapping epitope if a 1-, 5-, 10-, 20- or 100-fold excess of one antibody inhibits binding of the other by at least 50%, at least 75%, at least 90% or even 99% or more as measured in a competitive binding assay (see, e.g., Junghans et al., Cancer Res. 50 (1990) 1495-1502).

[0043] In some aspects, two antibodies are deemed to bind to the same epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antibody also reduce or eliminate binding of the other. Two antibodies are deemed to have “overlapping epitopes” if only a subset of the amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

[0044] The term “chimeric” antibody refers to an antibody in which a portion of the heavy and/or light chain is derived from a particular source or species, while the remainder of the heavy and/or light chain is derived from a different source or species.

[0045] The “class” of an antibody refers to the type of constant domain or constant region possessed by its heavy chain. There are five major classes of antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG₁, IgG₂, IgG₃, IgG₄, IgA₁, and IgA₂. In certain aspects, the antibody is of the IgG₁ isotype. In certain aspects, the antibody is of the IgG₁ isotype with the P329G, L234A and L235A mutation to reduce Fc-region effector function. In other aspects, the antibody is of the IgG₂ isotype. In certain aspects, the antibody is of the IgG₄ isotype with the S228P mutation in the hinge region to improve stability of IgG₄ antibody. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called α , δ , ϵ , γ , and μ , respectively. The light chain of

an antibody may be assigned to one of two types, called kappa (κ) and lambda (λ), based on the amino acid sequence of its constant domain.

[0046] “Effector functions” refer to those biological activities attributable to the Fc region of an antibody, which vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g., B cell receptor); and B cell activation.

[0047] An “effective amount” of an agent, e.g., a pharmaceutical composition, refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or prophylactic result.

[0048] The term “Fc region” herein is used to define a C-terminal region of an immunoglobulin heavy chain that contains at least a portion of the constant region. The term includes native sequence Fc regions and variant Fc regions. In one aspect, a human IgG heavy chain Fc region extends from Cys226, or from Pro230, to the carboxyl-terminus of the heavy chain. However, antibodies produced by host cells may undergo post-translational cleavage of one or more, particularly one or two, amino acids from the C-terminus of the heavy chain. Therefore, an antibody produced by a host cell by expression of a specific nucleic acid molecule encoding a full-length heavy chain may include the full-length heavy chain, or it may include a cleaved variant of the full-length heavy chain. This may be the case where the final two C-terminal amino acids of the heavy chain are glycine (G446) and lysine (K447, numbering according to EU index). Therefore, the C-terminal lysine (Lys447), or the C-terminal glycine (Gly446) and lysine (Lys447), of the Fc region may or may not be present. Thus, a “full-length IgG1” for example, includes an IgG1 with Gly446 and Lys447, or without Lys447, or without both Gly446 and Lys447. Amino acid sequences of heavy chains including an Fc region are denoted herein without C-terminal glycine-lysine dipeptide if not indicated otherwise. In one aspect, a heavy chain including an Fc region as specified herein, comprised in an antibody according to the invention, may comprise Gly446 and Lys447 (numbering according to EU index). In one aspect, a heavy chain including an Fc region as specified herein, comprised in an antibody according to the invention, may comprise Gly446 (numbering according to EU index). Unless otherwise specified herein, numbering of amino acid residues in the Fc region or constant region is according to the EU numbering system, also called the EU index, as described in Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991.

[0049] “Framework” or “FR” refers to variable domain residues other than complementary determining regions (CDRs). The FR of a variable domain generally consists of four FR domains: FR1, FR2, FR3, and FR4. Accordingly, the CDR and FR sequences generally appear in the following sequence in VH (or VL): FR1-CDR-H1(CDR-L1)-FR2-CDR-H2(CDR-L2)-FR3- CDR-H3(CDR-L3)-FR4.

[0050] The terms “full length antibody”, “intact antibody”, and “whole antibody” are used herein interchangeably to refer to an antibody having a structure substantially similar to a native antibody structure or having heavy chains that contain an Fc region as defined herein.

[0051] The terms “host cell”, “host cell line”, and “host cell culture” are used interchangeably and refer to cells into which exogenous nucleic acid has been introduced, including the progeny of such cells. Host cells include “transformants” and “transformed cells”, which include the primary transformed cell and progeny derived therefrom without regard to the number of passages. Progeny may not be completely identical in nucleic acid content to a parent cell, but may contain mutations. Mutant progeny that have the same function or biological activity as screened or selected for in the originally transformed cell are included herein.

[0052] A “human antibody” is one which possesses an amino acid sequence which corresponds to that of an antibody produced by a human or a human cell or derived from a non-human source that utilizes human antibody repertoires or other human antibody-encoding sequences. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues.

[0053] A “human consensus framework” is a framework which represents the most commonly occurring amino acid residues in a selection of human immunoglobulin VL or VH framework sequences. Generally, the selection of human immunoglobulin VL or VH sequences is from a subgroup of variable domain sequences. Generally, the subgroup of sequences is a subgroup as in Kabat et al., *Sequences of Proteins of Immunological Interest*, Fifth Edition, NIH Publication 91-3242, Bethesda MD (1991), vols. 1-3. In one aspect, for the VL, the subgroup is subgroup kappa I as in Kabat et al., *supra*. In one aspect, for the VH, the subgroup is subgroup III as in Kabat et al., *supra*.

[0054] A “humanized” antibody refers to a chimeric antibody comprising amino acid residues from non-human CDRs and amino acid residues from human FRs. In certain aspects, a humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDRs correspond to those of a non-human antibody, and all or substantially all of the FRs correspond to those of a human antibody. A humanized antibody optionally may comprise at least a portion of an antibody constant region

derived from a human antibody. A “humanized form” of an antibody, e.g., a non-human antibody, refers to an antibody that has undergone humanization.

[0055] The term “hypervariable region” or “HVR” as used herein refers to each of the regions of an antibody variable domain which are hypervariable in sequence and which determine antigen binding specificity, for example “complementarity determining regions” (“CDRs”).

[0056] Generally, antibodies comprise six CDRs: three in the VH (CDR-H1, CDR-H2, CDR-H3), and three in the VL (CDR-L1, CDR-L2, CDR-L3). Exemplary CDRs herein include:

(a) hypervariable loops occurring at amino acid residues 26-32 (L1), 50-52 (L2), 91-96 (L3), 26-32 (H1), 53-55 (H2), and 96-101 (H3) (Chothia and Lesk, *J. Mol. Biol.* 196:901-917 (1987));

(b) CDRs occurring at amino acid residues 24-34 (L1), 50-56 (L2), 89-97 (L3), 31-35b (H1), 50-65 (H2), and 95-102 (H3) (Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991)); and

(c) antigen contacts occurring at amino acid residues 27c-36 (L1), 46-55 (L2), 89-96 (L3), 30-35b (H1), 47-58 (H2), and 93-101 (H3) (MacCallum et al. *J. Mol. Biol.* 262: 732-745 (1996)).

[0057] Unless otherwise indicated, the CDRs are determined according to Kabat et al., *supra*. One of skill in the art will understand that the CDR designations can also be determined according to Chothia, *supra*, McCallum, *supra*, or any other scientifically accepted nomenclature system. In one aspect, CDR residues comprise those identified in Figures 1-3, or elsewhere in the specification.

[0058] An “immunoconjugate” is an antibody conjugated to one or more heterologous molecule(s), including but not limited to a cytotoxic agent.

[0059] An “individual” or “subject” is a mammal. Mammals include, but are not limited to, domesticated animals (e.g., cows, sheep, cats, dogs, and horses), primates (e.g., humans and non-human primates such as monkeys), rabbits, and rodents (e.g., mice and rats). In certain aspects, the individual or subject is a human.

[0060] An “isolated” antibody is one which has been separated from a component of its natural environment. In some aspects, an antibody is purified to greater than 95% or 99% purity as determined by, for example, electrophoretic (e.g., SDS-PAGE, isoelectric focusing (IEF), capillary electrophoresis) or chromatographic (e.g., ion exchange or reverse phase HPLC) methods. For a review of methods for assessment of antibody purity, see, e.g., Flatman et al., *J. Chromatogr. B* 848:79-87 (2007).

[0061] The term “linked” when used in the context of two polypeptides, means that the polypeptides are part of the same sequence of amino acids. Two polypeptides that are linked may be separated by additional amino acid sequence; that is, they need not be contiguous or directly linked to one another.

[0062] The term “nucleic acid molecule” or “polynucleotide” includes any compound and/or substance that comprises a polymer of nucleotides. Each nucleotide is composed of a base, specifically a purine- or pyrimidine base (i.e. cytosine (C), guanine (G), adenine (A), thymine (T) or uracil (U)), a sugar (i.e. deoxyribose or ribose), and a phosphate group. Often, the nucleic acid molecule is described by the sequence of bases, whereby said bases represent the primary structure (linear structure) of a nucleic acid molecule. The sequence of bases is typically represented from 5' to 3'. Herein, the term nucleic acid molecule encompasses deoxyribonucleic acid (DNA) including e.g., complementary DNA (cDNA) and genomic DNA, ribonucleic acid (RNA), in particular messenger RNA (mRNA), synthetic forms of DNA or RNA, and mixed polymers comprising two or more of these molecules. The nucleic acid molecule may be linear or circular. In addition, the term nucleic acid molecule includes both, sense and antisense strands, as well as single stranded and double stranded forms. Moreover, the herein described nucleic acid molecule can contain naturally occurring or non-naturally occurring nucleotides. Examples of non-naturally occurring nucleotides include modified nucleotide bases with derivatized sugars or phosphate backbone linkages or chemically modified residues. Nucleic acid molecules also encompass DNA and RNA molecules which are suitable as a vector for direct expression of an antibody of the invention *in vitro* and/or *in vivo*, e.g., in a host or patient. Such DNA (e.g., cDNA) or RNA (e.g., mRNA) vectors, can be unmodified or modified. For example, mRNA can be chemically modified to enhance the stability of the RNA vector and/or expression of the encoded molecule so that mRNA can be injected into a subject to generate the antibody *in vivo* (see e.g., Stadler et al, Nature Medicine 2017, published online 12 June 2017, doi:10.1038/nm.4356 or EP 2 101 823 B1).

[0063] An “isolated” nucleic acid refers to a nucleic acid molecule that has been separated from a component of its natural environment. An isolated nucleic acid includes a nucleic acid molecule contained in cells that ordinarily contain the nucleic acid molecule, but the nucleic acid molecule is present extrachromosomally or at a chromosomal location that is different from its natural chromosomal location.

[0064] “Isolated nucleic acid encoding an anti-KLK7 antibody” refers to one or more nucleic acid molecules encoding anti-KLK7 antibody heavy and light chains (or fragments

thereof), including such nucleic acid molecule(s) in a single vector or separate vectors, and such nucleic acid molecule(s) present at one or more locations in a host cell.

[0065] “Isolated nucleic acid encoding an anti-KLK5 antibody” refers to one or more nucleic acid molecules encoding anti-KLK5 antibody heavy and light chains (or fragments thereof), including such nucleic acid molecule(s) in a single vector or separate vectors, and such nucleic acid molecule(s) present at one or more locations in a host cell.

[0066] “Isolated nucleic acid encoding an anti-KLK5/KLK7 bispecific antibody” refers to one or more nucleic acid molecules encoding anti- KLK5/KLK7 bispecific antibody heavy and light chains (or fragments thereof), including such nucleic acid molecule(s) in a single vector or separate vectors, and such nucleic acid molecule(s) present at one or more locations in a host cell.

[0067] The term “monoclonal antibody” as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical and/or bind the same epitope, except for possible variant antibodies, e.g., containing naturally occurring mutations or arising during production of a monoclonal antibody preparation, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen. Thus, the modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies in accordance with the present invention may be made by a variety of techniques, including but not limited to the hybridoma method, recombinant DNA methods, phage-display methods, and methods utilizing transgenic animals containing all or part of the human immunoglobulin loci, such methods and other exemplary methods for making monoclonal antibodies being described herein.

[0068] A “naked antibody” refers to an antibody that is not conjugated to a heterologous moiety (e.g., a cytotoxic moiety) or radiolabel. The naked antibody may be present in a pharmaceutical composition.

[0069] “Native antibodies” refer to naturally occurring immunoglobulin molecules with varying structures. For example, native IgG antibodies are heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light chains and two identical heavy chains that are disulfide-bonded. From N- to C-terminus, each heavy chain has a variable domain (VH), also called a variable heavy domain or a heavy chain variable region, followed by three

constant heavy domains (CH1, CH2, and CH3). Similarly, from N- to C-terminus, each light chain has a variable domain (VL), also called a variable light domain or a light chain variable region, followed by a constant light (CL) domain.

[0070] The term “package insert” is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, combination therapy, contraindications and/or warnings concerning the use of such therapeutic products.

[0071] “Percent (%) amino acid sequence identity” with respect to a reference polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity for the purposes of the alignment. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, Clustal W, Megalign (DNASTAR) software or the FASTA program package. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. Alternatively, the percent identity values can be generated using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087 and is described in WO 2001/007611.

[0072] Unless otherwise indicated, for purposes herein, percent amino acid sequence identity values are generated using the ggsearch program of the FASTA package version 36.3.8c or later with a BLOSUM50 comparison matrix. The FASTA program package was authored by W. R. Pearson and D. J. Lipman (1988), “Improved Tools for Biological Sequence Analysis”, PNAS 85:2444-2448; W. R. Pearson (1996) “Effective protein sequence comparison” Meth. Enzymol. 266:227- 258; and Pearson et. al. (1997) Genomics 46:24-36 and is publicly available from www.fasta.bioch.virginia.edu/fasta_www2/fasta_down.shtml or www.ebi.ac.uk/Tools/sss/fasta. Alternatively, a public server accessible at fasta.bioch.virginia.edu/fasta_www2/index.cgi can be used to compare the sequences, using the ggsearch (global protein:protein) program and default options (BLOSUM50; open: -10; ext: -2;

Ktup = 2) to ensure a global, rather than local, alignment is performed. Percent amino acid identity is given in the output alignment header.

[0073] The term “pharmaceutical composition” or “pharmaceutical formulation” refers to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the pharmaceutical composition would be administered.

[0074] A “pharmaceutically acceptable carrier” refers to an ingredient in a pharmaceutical composition or formulation, other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative.

[0075] The terms “KLK5” and “kallikrein related peptidase 5,” as used herein, refer to any native KLK5 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length”, unprocessed KLK5 as well as any form of KLK5 that results from processing in the cell. The term also encompasses naturally occurring variants of KLK5, e.g., splice variants or allelic variants. The amino acid sequence of an exemplary human precursor KLK5 protein is shown in SEQ ID NO: 1 (UniProtKB/Swiss-Prot: Q9Y337.3). The amino acid sequence of an exemplary human mature KLK5 protein, which lacks the signal peptide (amino acids 1-22) and propeptide (amino acids 23-66) is shown in SEQ ID NO: 2. The amino acid sequence of an exemplary cynomolgus monkey precursor KLK5 protein is shown in SEQ ID NO: 100 (UniProtKB: A0A2K5W0T6). The amino acid sequence of an exemplary cynomolgus monkey mature KLK5 protein, which lacks the signal peptide (amino acids 1-22) and propeptide (amino acids 23-64) is shown in SEQ ID NO: 101.

[0076] The terms “KLK7” and “kallikrein related peptidase 7,” as used herein, refer to any native KLK7 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length”, unprocessed KLK7 as well as any form of KLK7 that results from processing in the cell. The term also encompasses naturally occurring variants of KLK7, e.g., splice variants or allelic variants. The amino acid sequence of an exemplary human precursor KLK7 protein is shown in SEQ ID NO: 3 (UniProtKB/Swiss-Prot: P49862.1). The amino acid sequence of an exemplary human mature KLK7 protein, which lacks the signal peptide (amino acids 1-22) and propeptide (amino acids 23-29) is shown in SEQ ID NO: 4. The amino acid sequence of an exemplary cynomolgus monkey precursor KLK7 protein is shown in SEQ ID NO: 5 (UniProtKB: G7PYG2). The amino acid sequence of an exemplary cynomolgus monkey mature

KLK7 protein, which lacks the signal peptide (amino acids 1-21) and propeptide (amino acids 22-29) is shown in SEQ ID NO: 6.

[0077] As used herein, “treatment” (and grammatical variations thereof such as “treat” or “treating”) refers to clinical intervention in an attempt to alter the natural course of a disease in the individual being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. In some aspects, antibodies of the invention are used to delay development of a disease or to slow the progression of a disease.

[0078] The term “variable region” or “variable domain” refers to the domain of an antibody heavy or light chain that is involved in binding the antibody to antigen. The variable domains of the heavy chain and light chain (VH and VL, respectively) of a native antibody generally have similar structures, with each domain comprising four conserved framework regions (FRs) and three complementary determining regions (CDRs). See, e.g., Kindt et al. *Kuby Immunology*, 6th ed., W.H. Freeman and Co., page 91 (2007). A variable domain may comprise heavy chain (HC) CDR1-FR2-CDR2-FR3-CDR3 with or without all or a portion of FR1 and/or FR4; and light chain (LC) CDR1-FR2-CDR2-FR3-CDR3 with or without all or a portion of FR1 and/or FR4. That is, a variable domain may lack a portion of FR1 and/or FR4 so long as it retains antigen-binding activity. A single VH or VL domain may be sufficient to confer antigen-binding specificity. Furthermore, antibodies that bind a particular antigen may be isolated using a VH or VL domain from an antibody that binds the antigen to screen a library of complementary VL or VH domains, respectively. See, e.g., Portolano et al., *J. Immunol.* 150:880-887 (1993); Clarkson et al., *Nature* 352:624-628 (1991).

[0079] The term “vector”, as used herein, refers to a nucleic acid molecule capable of propagating another nucleic acid to which it is linked. The term includes the vector as a self-replicating nucleic acid structure as well as the vector incorporated into the genome of a host cell into which it has been introduced. Certain vectors are capable of directing the expression of nucleic acids to which they are operatively linked. Such vectors are referred to herein as “expression vectors”.

II. COMPOSITIONS AND METHODS

[0080] In one aspect, the invention is based, in part, on the finding that KLK5 and KLK7 may both play a role in epithelial barrier permeability. Inhibiting both KLK5 and KLK7 may therefore show improved efficacy in treating conditions associated with excessive epithelial barrier permeability. In certain aspects, antibodies that bind to KLK5 are provided. In certain aspects, antibodies that bind to KLK7 are provided. In certain aspects, multispecific antibodies that bind to KLK5 and KLK7 are provided. Antibodies of the invention are useful, e.g., for the diagnosis or treatment of Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea.

A. Exemplary Anti-KLK7 Antibodies

[0081] In one aspect, the invention provides antibodies that bind to KLK7. In one aspect, provided are isolated antibodies that bind to KLK7. In one aspect, the invention provides antibodies that specifically bind to KLK7. In certain aspects, an anti-KLK7 antibody inhibits KLK7 protease activity. In some embodiments, an anti-KLK7 antibody inhibits human KLK7-mediated cleavage of a substrate comprising the amino acid sequence RPKPVE-Nval-WRK (SEQ ID NO: 121), wherein Nval is norvaline. In some embodiments, an anti-KLK7 antibody inhibits human KLK7-mediated cleavage of a substrate comprising the amino acid sequence RPKPVE-Nval-WRK (SEQ ID NO: 121), wherein Nval is norvaline, with an IC₅₀ of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM. In some embodiments, an anti-KLK7 antibody inhibits human KLK7-mediated cleavage of a substrate comprising the amino acid sequence RPKPVE-Nval-WRK (SEQ ID NO: 121), wherein Nval is norvaline, with an IC₅₀ of no greater than 5 nM, or no greater than 3 nM, or no greater than 2 nM, or no greater than 1 nM. In some embodiments, an anti-KLK7 antibody binds human KLK7 with a K_D of less than 20 pM, less than 10 pM, or less than 9 pM, or less than 8 pM, or less than 7 pM, or less than 6 pM, or less than 5 pM, or less than 3 pM, or less than 2 pM, or less than 1 pM, as measured by surface plasmon resonance. In some embodiments, an anti-KLK7 antibody binds human KLK7 with a K_D of no greater than 20 pM, no greater than 10 pM, or no greater than 9 pM, or no greater than 8 pM, or no greater than 7 pM, or no greater than 6 pM, or no greater than 5 pM, or no greater than 3 pM, or no greater than 2 pM, or no greater than 1 pM, as measured by surface plasmon resonance.

[0082] In some embodiments, an anti-KLK7 antibody binds an epitope within amino acids R71-N82, K152-S158, and/or Q211-K222 of KLK7, wherein the amino acids are numbered according to SEQ ID NO: 4. In some embodiments, the anti-KLK7 antibody contacts

at least one amino acid within amino acids R71-N82, contact at least one amino acid within amino acids K152-S158, and contacts at least one amino acid within amino acids Q211-K222 of KLK7, as numbered according to SEQ ID NO: 4. In some embodiments, an anti-KLK7 antibody binds an epitope comprising one or more of amino acids H72, P73, G74, S76, Q78, N82, N157, K211, and/or T213 of KLK7, as numbered according to SEQ ID NO: 4. In some embodiments, an anti-KLK7 antibody binds an epitope comprising one or more of amino acids H91, P92, G93, S95, Q97, N101, N178, K233, and/or T235 of KLK7, by chymotrypsin numbering. In some embodiments, an anti-KLK7 antibody binds an epitope comprising amino acids H72, P73, G74, S76, Q78, N82, N157, K211, and T213 of KLK7, as numbered according to SEQ ID NO: 4. In some embodiments, an anti-KLK7 antibody binds an epitope comprising amino acids H91, P92, G93, S95, Q97, N101, N178, K233, and T235 of KLK7, by chymotrypsin numbering.

[0083] In some embodiments, an anti-KLK7 antibody, when bound to KLK7, results in a conformational change of human KLK7, wherein the conformational change allosterically results in the disruption of the substrate binding site and/or the active site of human KLK7.

[0084] In some embodiments, the anti-KLK7 antibody does not bind to KLK5. In some embodiments, the anti-KLK7 antibody does not bind to KLK1, KLK4, KLK5, KLK11, and KLK14. In some embodiments, the anti-KLK7 antibody binds to human KLK7 and cynomolgus monkey KLK7.

[0085] In one aspect, the invention provides an anti-KLK7 antibody comprising at least one, at least two, at least three, at least four, at least five, or all six CDRs selected from (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12.

[0086] In one aspect, the invention provides an antibody comprising at least one, at least two, or all three VH CDR sequences selected from (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8; and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9. In one aspect, the antibody comprises CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9. In another aspect, the antibody comprises CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12. In a further aspect, the antibody comprises CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9, CDR-L3

comprising the amino acid sequence of SEQ ID NO: 12, and CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8. In a further aspect, the antibody comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8; and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9.

[0087] In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VL CDR sequences selected from (a) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10; (b) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11; and (c) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12. In one aspect, the antibody comprises (a) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10; (b) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11; and (c) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12.

[0088] In another aspect, an antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH CDR sequences selected from (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9; and (b) a VL domain comprising at least one, at least two, or all three VL CDR sequences selected from (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10, (ii) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11, and (c) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12.

[0089] In another aspect, the invention provides an antibody comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12.

[0090] In any of the aspects provided herein, an anti-KLK7 antibody is humanized. In one aspect, an anti-KLK7 antibody further comprises an acceptor human framework, e.g. a human immunoglobulin framework or a human consensus framework.

[0091] In one aspect, an anti-KLK7 antibody comprises a VH domain comprising one or more heavy chain framework sequences selected from (a) a heavy chain framework region 1 (HC-FR1) of SEQ ID NO: 123-128, (b) a heavy chain framework region 2 (HC-FR2) of SEQ ID NO: 130-133, (c) a heavy chain framework region 3 (HC-FR3) of SEQ ID NO: 135-143, and (d) a heavy chain framework region 4 (HC-FR4) of SEQ ID NO: 144-145.

[0092] In another aspect, an anti-KLK7 antibody comprises a VH domain comprising a HC-FR1 of SEQ ID NO: 123-128. In another aspect, an anti-KLK7 antibody comprises a VH domain comprising a HC-FR2 of SEQ ID NO:130-133. In another aspect, an anti-KLK7 antibody comprises a VH domain comprising a HC-FR3 of SEQ ID NO:135-143. In another aspect, an anti- KLK7 antibody comprises a VH domain comprising a HC-FR4 of SEQ ID NO:144-145.

[0093] In another aspect, an anti-KLK7 antibody comprises a VH domain comprising a HC-FR1 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity with SEQ ID NO:123-128. In one aspect, the VH domain comprises a HC-FR1 of at least 95% sequence identity with SEQ ID NO:123-128. In another aspect, the VH domain comprises a HC-FR1 of at least 98% sequence identity with SEQ ID NO:123-128.

[0094] In another aspect, an anti-KLK7 antibody comprises a VH domain comprising a HC-FR2 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO:130-133. In one aspect, the VH domain comprises a HC-FR2 of at least 95% sequence identity with SEQ ID NO:130-133. In another aspect, the VH domain comprises a HC-FR2 of at least 98% sequence identity with SEQ ID NO:130-133.

[0095] In another aspect, an anti-KLK7 antibody comprises a VH domain comprising a HC-FR3 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO:135-143. In one aspect, the VH domain comprises a HC-FR3 of at least 95% sequence identity with SEQ ID NO:135-143. In another aspect, the VH domain comprises a HC-FR3 of at least 98% sequence identity with SEQ ID NO:135-143.

[0096] In another aspect, an anti-KLK7 antibody comprises a VH domain comprising a HC-FR4 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO:144-145. In one aspect, the VH domain comprises a HC-FR4 of at least 95% sequence identity with SEQ ID NO:144-145. In another aspect, the VH domain comprises a HC-FR4 of at least 98% sequence identity with SEQ ID NO:144-145.

[0097] In one aspect, an anti-KLK7 antibody comprises a VL domain comprising one or more light chain framework sequences selected from (a) a light chain frame work region 1 (LC-FR1) of SEQ ID NO:147-150, (b) a light chain frame work region 2 (LC-FR2) of SEQ ID NO:152-154, (c) a light chain frame work region 3 (LC-FR3) of SEQ ID NO:156-158, and (d) a light chain frame work region 4 (LC-FR4) of SEQ ID NO:160.

[0098] In another aspect, an anti-KLK7 antibody comprises a VL domain comprising a LC-FR1 of SEQ ID NO:147-150. In another aspect, an anti-KLK7 antibody comprises a VL

domain comprising a LC-FR2 of SEQ ID NO:152-154. In another aspect, an anti-KLK7 antibody comprises a VL domain comprising a LC-FR3 of SEQ ID NO:156-158. In another aspect, an anti-KLK7 antibody comprises a VL domain comprising a LC-FR4 of SEQ ID NO:160.

[0099] In another aspect, an anti-KLK7 antibody comprises a VL domain comprising a LC-FR1 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO:147-150. In one aspect, the VL domain comprises a LC-FR1 of at least 95% sequence identity with SEQ ID NO:147-150. In another aspect, the VL domain comprises a LC-FR1 of at least 98% sequence identity with SEQ ID NO:147-150.

[00100] In another aspect, an anti-KLK7 antibody comprises a VL domain comprising a LC-FR2 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO:152-154. In one aspect, the VL domain comprises a LC-FR2 of at least 95% sequence identity with SEQ ID NO:152-154. In another aspect, the VL domain comprises a LC-FR2 of at least 98% sequence identity with SEQ ID NO:152-154.

[00101] In another aspect, an anti-KLK7 antibody comprises a VL domain comprising a LC-FR3 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO:156-158. In one aspect, the VL domain comprises a LC-FR3 of at least 95% sequence identity with SEQ ID NO:156-158. In another aspect, the VL domain comprises a LC-FR3 of at least 98% sequence identity with SEQ ID NO: 156-158.

[00102] In another aspect, an anti-KLK7 antibody comprises a VL domain comprising a LC-FR4 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO:160. In one aspect, the VL domain comprises a LC-FR1 of at least 95% sequence identity with SEQ ID NO: 160. In another aspect, the VL domain comprises a LC-FR1 of at least 98% sequence identity with SEQ ID NO:160.

[00103] In another aspect, an anti-KLK7 antibody comprises one or more of the CDR sequences of a VH selected from SEQ ID NOs: 13 and 15-30. In another embodiment, an anti-KLK7 antibody comprises one or more of the CDR sequences of a VL selected from SEQ ID NOs: 14 and 31-38. In another embodiment, an anti-KLK7 antibody comprises the CDR sequences of a VH selected from SEQ ID NOs: 13 and 15-30 and the CDR sequences of a VL selected from SEQ ID NOs: 14 and 31-38.

[00104] In a further aspect, an anti-KLK7 antibody comprises the CDR-H1, CDR-H2 and CDR-H3 amino acid sequences of a VH selected from SEQ ID NOs: 13 and 15-30 and

the CDR-L1, CDR-L2 and CDR-L3 amino acid sequences of a VL selected from SEQ ID NOs: 14 and 31-38.

[00105] In one aspect, an anti-KLK7 antibody comprises one or more of the heavy chain CDR amino acid sequences of a VH selected from SEQ ID NOs: 13 and 15-30 and a framework of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% sequence identity to the framework amino acid sequence of a VH selected from SEQ ID NOs: 13 and 15-30. In one aspect, the anti-KLK7 antibody comprises the three heavy chain CDR amino acid sequences of a VH selected from SEQ ID NOs: 13 and 15-30 and a framework of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% sequence identity to the framework amino acid sequence of a VH selected from SEQ ID NOs: 13 and 15-30. In one aspect, the anti-KLK7 antibody comprises the three heavy chain CDR amino acid sequences of a VH selected from SEQ ID NOs: 13 and 15-30 and a framework of at least 95% sequence identity to the framework amino acid sequence of a VH selected from SEQ ID NOs: 13 and 15-30. In another aspect, the anti-KLK7 antibody comprises the three heavy chain CDR amino acid sequences of a VH selected from SEQ ID NOs: 13 and 15-30 and a framework of at least of at least 98% sequence identity to the framework amino acid sequence of a VH selected from SEQ ID NOs: 13 and 15-30.

[00106] In one aspect, an anti-KLK7 antibody comprises one or more of the light chain CDR amino acid sequences of a VL selected from SEQ ID NOs: 14 and 31-38 and a framework of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% sequence identity to the framework amino acid sequence of a VL selected from SEQ ID NOs: 14 and 31-38. In one aspect, the anti-KLK7 antibody comprises the three light chain CDR amino acid sequences of a VL selected from SEQ ID NOs: 14 and 31-38 and a framework of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% sequence identity to the framework amino acid sequence of a VL selected from SEQ ID NOs: 14 and 31-38. In one aspect, the anti-KLK7 antibody comprises the three light chain CDR amino acid sequences of a VL selected from SEQ ID NOs: 14 and 31-38 and a framework of at least 95% sequence identity to the framework amino acid sequence of a VL selected from SEQ ID NOs: 14 and 31-38. In another aspect, the anti-KLK7 antibody comprises the three light chain CDR amino acid sequences of a VL selected from SEQ ID NOs: 14 and 31-38 and a framework of at least particularly of at least 98% sequence identity to the framework amino acid sequence of a VL selected from SEQ ID NOs: 14 and 31-38.

[00107] In one aspect, the anti-KLK7 antibody comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7; (b) CDR-H2 comprising the amino acid sequence of

SEQ ID NO: 8; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12, and a VH domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 13 and 15-30, and a VL domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 14 and 31-38. In one aspect, the VH domain has at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 13 and 15-30. In one aspect, the VL domain has at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 14 and 31-38.

[00108] In one aspect, the anti-KLK7 antibody comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12, and a VH domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 13 and 15-30, and a VL domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 14 and 31-38; wherein the antibody specifically binds to KLK7. In one aspect, the VH domain has at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 13 and 15-30. In one aspect, the VL domain has at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 14 and 31-38. In one aspect, the antibody binds to KLK7 having a dissociation constant (K_D) of less than 10 pM, or less than 9 pM, or less than 8 pM, or less than 7 pM, or less than 6 pM, or less than 5 pM as measured by surface plasmon resonance. In one aspect, the antibody binds to KLK7 having a dissociation constant (K_D) of no greater than 10 pM, or no greater than 9 pM, or no greater than 8 pM, or no greater than 7 pM, or no greater than 6 pM, or no greater than 5 pM as measured by surface plasmon resonance.

[00109] In another aspect, an anti-KLK7 antibody comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 13 and 15-30. In one aspect, an anti-KLK7 antibody comprises a heavy chain variable domain (VH) sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 13 and 15-30. In certain aspects, a VH sequence having at least 90%, 91%, 92%,

93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-KLK7 antibody comprising that sequence retains the ability to bind to KLK7. In certain aspects, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in an amino acid sequence selected from SEQ ID NOs: 13 and 15-30. In certain aspects, substitutions, insertions, or deletions occur in regions outside the CDRs (i.e., in the FRs). Optionally, the anti-KLK7 antibody comprises the VH sequence in an amino acid sequence selected from SEQ ID NOs: 13 and 15-30, including post-translational modifications of the sequence. Optionally, the anti-KLK7 antibody comprises the VH sequence in SEQ ID NO: 29 or 30, including post-translational modifications of the sequence. In a particular aspect, the VH comprises one, two or three CDRs selected from: (a) CDR-H1, comprising the amino acid sequence of SEQ ID NO: 7, (b) CDR-H2, comprising the amino acid sequence of SEQ ID NO: 8, and (c) CDR-H3, comprising the amino acid sequence of SEQ ID NO: 9. In another aspect, an anti-KLK7 antibody is provided, wherein the antibody comprises a light chain variable domain (VL) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 14 and 31-38. In one aspect, an anti-KLK7 antibody comprises a light chain variable domain (VL) sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 14 and 31-38. In certain aspects, a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-KLK7 antibody comprising that sequence retains the ability to bind to KLK7. In certain aspects, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in an amino acid sequence selected from SEQ ID NOs: 14 and 31-38. In certain aspects, the substitutions, insertions, or deletions occur in regions outside the CDRs (i.e., in the FRs). Optionally, the anti-KLK7 antibody comprises the VL sequence in an amino acid sequence selected from SEQ ID NOs: 14 and 31-38, including post-translational modifications of that sequence. Optionally, the anti-KLK7 antibody comprises the VL sequence in SEQ ID NO: 32 or 38, including post-translational modifications of that sequence. In a particular aspect, the VL comprises one, two or three CDRs selected from: (a) CDR-L1, comprising the amino acid sequence of SEQ ID NO: 10, (b) CDR-L2, comprising the amino acid sequence of SEQ ID NO: 11, and (c) CDR-L3, comprising the amino acid sequence of SEQ ID NO: 12.

[00110] In another aspect, an anti-KLK7 antibody is provided, wherein the antibody comprises a VH sequence as in any of the aspects provided above, and a VL sequence

as in any of the aspects provided above. In one aspect, the antibody comprises the VH and VL sequences in SEQ ID NO: 29 and SEQ ID NO: 32, respectively, including post-translational modifications of those sequences. In one aspect, the antibody comprises the VH and VL sequences in SEQ ID NO: 30 and SEQ ID NO: 38, respectively, including post-translational modifications of those sequences.

[00111] In a further aspect, the invention provides an antibody that binds to the same epitope as an anti-KLK7 antibody provided herein. For example, in certain aspects, an antibody is provided that binds to the same epitope as an anti-KLK7 antibody comprising a VH sequence of SEQ ID NO: 29 and a VL sequence of SEQ ID NO: 32.

[00112] In a further aspect, the invention provides an antibody that competes for binding to KLK7 with an anti-KLK7 antibody provided herein.

[00113] In a further aspect of the invention, an anti-KLK7 antibody according to any of the above aspects is a monoclonal antibody, including a chimeric, humanized or human antibody. In one aspect, an anti-KLK7 antibody is an antibody fragment, e.g., a Fv, Fab, Fab', scFv, diabody, or F(ab')₂ fragment. In another aspect, the antibody is a full-length antibody, e.g., an intact IgG1 antibody or other antibody class or isotype as defined herein.

[00114] In a further aspect, an anti-KLK7 antibody according to any of the above aspects may incorporate any of the features, singly or in combination, as described in Sections 1-8, below

B. Exemplary Anti-KLK5 Antibodies

[00115] In one aspect, the invention provides antibodies that bind to KLK5. In one aspect, provided are isolated antibodies that bind to KLK5. In one aspect, the invention provides antibodies that specifically bind to KLK5. In certain aspects, an anti-KLK5 antibody inhibits KLK5 protease activity. In some embodiments, an anti-KLK5 antibody inhibits human KLK5-mediated cleavage of the substrate Boc-Val-Pro-Arg-AMC. In some embodiments, an anti-KLK5 antibody inhibits human KLK5-mediated cleavage of the substrate Boc-Val-Pro-Arg-AMC with an IC₅₀ of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM. In some embodiments, an anti-KLK5 antibody inhibits human KLK5-mediated cleavage of the substrate Boc-Val-Pro-Arg-AMC with an IC₅₀ of no greater than 5 nM, or no greater than 3 nM, or no greater than 2 nM, or no greater than 1 nM. In some embodiments, an anti-KLK5 antibody binds KLK5 with a K_D of less than 60 pM, less than 30 pM, less than 20 pM, less than 10 pM, or less than 5 pM, as measured by surface plasmon resonance. In some embodiments, an anti-KLK5 antibody binds KLK5 with a K_D of no greater than 60 pM, no greater than 30 pM, no

greater than 20 pM, no greater than 10 pM, or no greater than 5 pM, as measured by surface plasmon resonance.

[00116] In some embodiments, an anti-KLK5 antibody, when bound to human KLK5 results in a conformational change of human KLK5, wherein the conformational change allosterically results in the disruption of the substrate binding site and/or the active site of human KLK5.

[00117] In some embodiments, an anti-KLK5 antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from Pro130, Ser131, Ala132, Gly133, Val162, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Tyr172, Pro173, Arg174, Gln174A, Ile176, Asp177, Asp178, Gly184, Asp185, Lys186, Ala186A, Arg188, Asn223, Arg224, Pro225, and Lys233 according to standard protease numbering (P113, S114, A115, G116, V145, L146, S147, Q148, K149, R150, E152, D153, A154, Y155, P156, R157, Q158, I159, D160, D161, G167, D168, K169, A170, R172, N204, R205, P206, and K214 by sequential numbering of SEQ ID NO: 2). *See, e.g.*, PCT Publication No. WO 2019/178316 A1. In some embodiments, an anti-KLK5 antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from the group consisting of Pro130, Ser131, Ala132, Val162, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Tyr172, Pro173, Arg174, Gln174A, Ile176, Asp177, Asp178, Arg224, and Lys233 according to standard protease numbering. In some embodiments, an anti-KLK5 antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from Pro130, Ser131, Ala132, Gly133, Val162, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Tyr172, Pro173, Arg174, Gln174A, Ile176, Asp177, and Lys233 according to standard protease numbering. In some embodiments, an anti-KLK5 antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from Ser131, Ala132, Gly133, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Pro173, Arg174, Gly184, Asp185, Lys186, Ala186A, Arg188, Asn223, Arg224, and Pro225 according to standard protease numbering.

[00118] In some embodiments, the anti-KLK5 antibody does not bind to KLK7. In some embodiments, the anti-KLK5 antibody does not bind to KLK1, KLK4, KLK7, KLK11, or KLK14. In some embodiments, the anti-KLK5 antibody binds to human KLK5 and cynomolgus monkey KLK5.

Antibody hu.10C5-H28L5 and variants

[00119] In one aspect, the invention provides an anti-KLK5 antibody comprising at least one, at least two, at least three, at least four, at least five, or all six CDRs selected from

(a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39 and 107; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 40 and 41; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 43 and 44; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 46-49.

[00120] In one aspect, the invention provides an antibody comprising at least one, at least two, or all three VH CDR sequences selected from (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 41; and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42. In a further aspect, the antibody comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 41; and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42.

[00121] In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VL CDR sequences selected from (a) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 43; (b) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45; and (c) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 47. In one aspect, the antibody comprises (a) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 43; (b) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45; and (c) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 47.

[00122] In one aspect, the invention provides an antibody comprising at least one, at least two, or all three VH CDR sequences selected from (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39 and 107; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 40 and 41; and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42. In another aspect, the antibody comprises CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 41, and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42.

[00123] In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VL CDR sequences selected from (a) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 43 and 44; (b) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45; and (c) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 46-49. In one aspect, the antibody comprises (a) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 43; (b) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45; and (c) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 47.

[00124] In another aspect, an antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH CDR sequences selected from (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39 and 107, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 40 and 41, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42; and (b) a VL domain comprising at least one, at least two, or all three VL CDR sequences selected from (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 43 and 44, (ii) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (c) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 46-49.

[00125] In another aspect, the invention provides an antibody comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 41; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 43; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 47.

[00126] In any of the aspects provided herein, an anti-KLK5 antibody is humanized. In one aspect, an anti-KLK5 antibody further comprises an acceptor human framework, e.g. a human immunoglobulin framework or a human consensus framework.

[00127] In one aspect, an anti-KLK5 antibody comprises a VH domain comprising one or more heavy chain framework sequences selected from (a) a heavy chain framework region 1 (HC-FR1) of SEQ ID NO:161, (b) a heavy chain framework region 2 (HC-FR2) of SEQ ID NO: 162-163, (c) a heavy chain framework region 3 (HC-FR3) of SEQ ID NO:164, and (d) a heavy chain framework region 4 (HC-FR4) of SEQ ID NO:165.

[00128] In another aspect, an anti-KLK5 antibody comprises a VH domain comprising a HC-FR1 of SEQ ID NO:161. In another aspect, an anti-KLK5 antibody comprises a VH domain comprising a HC-FR2 of SEQ ID NO: 162-163. In another aspect, an anti-KLK5 antibody comprises a VH domain comprising a HC-FR3 of SEQ ID NO: 164. In another aspect, an anti-KLK5 antibody comprises a VH domain comprising a HC-FR4 of SEQ ID NO: 165.

[00129] In another aspect, an anti-KLK5 antibody comprises a VH domain comprising a HC-FR1 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity with SEQ ID NO:161. In one aspect, the VH domain comprises a HC-FR1 of at least 95% sequence identity with SEQ ID NO: 161. In another aspect, the VH domain comprises a HC-FR1 of at least 98% sequence identity with SEQ ID NO: 161.

[00130] In another aspect, an anti-KLK5 antibody comprises a VH domain comprising a HC-FR2 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%,

96%, 97%, 98% or 99% sequence identity to SEQ ID NO:162-163. In one aspect, the VH domain comprises a HC-FR2 of at least 95% sequence identity with SEQ ID NO: 162-163. In another aspect, the VH domain comprises a HC-FR2 of at least 98% sequence identity with SEQ ID NO: 162-163.

[00131] In another aspect, an anti- KLK5 antibody comprises a VH domain comprising a HC-FR3 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO: 164. In one aspect, the VH domain comprises a HC-FR3 of at least 95% sequence identity with SEQ ID NO: 164. In another aspect, the VH domain comprises a HC-FR3 of at least 98% sequence identity with SEQ ID NO: 164.

[00132] In another aspect, an anti-KLK5 antibody comprises a VH domain comprising a HC-FR4 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO: 165. In one aspect, the VH domain comprises a HC-FR4 of at least 95% sequence identity with SEQ ID NO: 165. In another aspect, the VH domain comprises a HC-FR4 of at least 98% sequence identity with SEQ ID NO: 165.

[00133] In one aspect, an anti- KLK5 antibody comprises a VL domain comprising one or more light chain framework sequences selected from (a) a light chain framework region 1 (LC-FR1) of SEQ ID NO: 166, (b) a light chain framework region 2 (LC-FR2) of SEQ ID NO: 167-168, (c) a light chain framework region 3 (LC-FR3) of SEQ ID NO: 169, and (d) a light chain framework region 4 (LC-FR4) of SEQ ID NO: 170.

[00134] In another aspect, an anti-KLK5 antibody comprises a VL domain comprising a LC-FR1 of SEQ ID NO: 166. In another aspect, an anti-KLK5 antibody comprises a VL domain comprising a LC-FR2 of SEQ ID NO: 167-168. In another aspect, an anti-KLK5 antibody comprises a VL domain comprising a LC-FR3 of SEQ ID NO: 169. In another aspect, an anti-KLK5 antibody comprises a VL domain comprising a LC-FR4 of SEQ ID NO: 170.

[00135] In another aspect, an anti- KLK5 antibody comprises a VL domain comprising a LC-FR1 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO:166. In one aspect, the VL domain comprises a LC-FR1 of at least 95% sequence identity with SEQ ID NO: 166. In another aspect, the VL domain comprises a LC-FR1 of at least 98% sequence identity with SEQ ID NO: 166.

[00136] In another aspect, an anti-KLK5 antibody comprises a VL domain comprising a LC-FR2 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO:167-168. In one aspect, the VL domain comprises a LC-FR2 of at least 95% sequence identity with SEQ ID NO: 167-168. In

another aspect, the VL domain comprises a LC-FR2 of at least 98% sequence identity with SEQ ID NO: 167-168.

[00137] In another aspect, an anti-KLK5 antibody comprises a VL domain comprising a LC-FR3 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO: 169. In one aspect, the VL domain comprises a LC-FR3 of at least 95% sequence identity with SEQ ID NO: 169. In another aspect, the VL domain comprises a LC-FR3 of at least 98% sequence identity with SEQ ID NO: 169.

[00138] In another aspect, an anti-KLK5 antibody comprises a VL domain comprising a LC-FR4 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO: 170. In one aspect, the VL domain comprises a LC-FR4 of at least 95% sequence identity with SEQ ID NO: 170. In another aspect, the VL domain comprises a LC-FR4 of at least 98% sequence identity with SEQ ID NO: 170.

[00139] In another aspect, an anti-KLK5 antibody comprises one or more of the CDR sequences of the VH of SEQ ID NO: 50, 52, 53, 105, or 106. In another embodiment, an anti-KLK5 antibody comprises one or more of the CDR sequences of the VL of SEQ ID NO: 51 or 54-57. In another embodiment, an anti-KLK5 antibody comprises the CDR sequences of the VH of SEQ ID NO: 50, 52, 53, 105, or 106 and the CDR sequences of the VL of SEQ ID NO: 51 or 54-57.

[00140] In a further aspect, an anti-KLK5 antibody comprises the CDR-H1, CDR-H2 and CDR-H3 amino acid sequences of the VH domain of SEQ ID NO: 50, 52, 53, 105, or 106 and the CDR-L1, CDR-L2 and CDR-L3 amino acid sequences of the VL domain of SEQ ID NO: 51 or 54-57.

[00141] In one aspect, an anti-KLK5 antibody comprises one or more of the heavy chain CDR amino acid sequences of the VH domain of SEQ ID NO: 50, 52, 53, 105, or 106 and a framework of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% sequence identity to the framework amino acid sequence of the VH domain of SEQ ID NO: 50, 52, 53, 105, or 106. In one aspect, the anti-KLK5 antibody comprises the three heavy chain CDR amino acid sequences of the VH domain of SEQ ID NO: 50, 52, 53, 105, or 106 and a framework of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% sequence identity to the framework amino acid sequence of the VH domain of SEQ ID NO: 50, 52, 53, 105, or 106. In one aspect, the anti-KLK5 antibody comprises the three heavy chain CDR amino acid sequences of the VH domain of SEQ ID NO: 50, 52, 53, 105, or 106 and a framework of at least 95% sequence identity to the framework amino acid sequence of the VH domain of SEQ ID NO: 50, 52, 53, 105, or 106. In

another aspect, the anti-KLK5 antibody comprises the three heavy chain CDR amino acid sequences of the VH domain of SEQ ID NO: 50, 52, 53, 105, or 106 and a framework of at least of at least 98% sequence identity to the framework amino acid sequence of the VH domain of SEQ ID NO: 50, 52, 53, 105, or 106.

[00142] In one aspect, an anti-KLK5 antibody comprises one or more of the light chain CDR amino acid sequences of the VL domain of SEQ ID NO: 51 or 54-57 and a framework of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% sequence identity to the framework amino acid sequence of the VL domain of SEQ ID NO: 51 or 54-57. In one aspect, the anti-KLK5 antibody comprises the three light chain CDR amino acid sequences of the VL domain of SEQ ID NO: 51 or 54-57 and a framework of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% sequence identity to the framework amino acid sequence of the VL domain of SEQ ID NO: 51 or 54-57. In one aspect, the anti-KLK5 antibody comprises the three light chain CDR amino acid sequences of the VL domain of SEQ ID NO: 51 or 54-57 and a framework of at least 95% sequence identity to the framework amino acid sequence of the VL domain of SEQ ID NO: 51 or 54-57. In another aspect, the anti-KLK5 antibody comprises the three light chain CDR amino acid sequences of the VL domain of SEQ ID NO: 51 or 54-57 and a framework of at least particularly of at least 98% sequence identity to the framework amino acid sequence of the VH domain of SEQ ID NO: 50, 52, 53, 105, and 106.

[00143] In one aspect, the anti-KLK5 antibody comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:39 or 107; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 40 or 41; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 43 or 44; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 46-49, and a VH domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 50, 52, 53, 105, and 106, and a VL domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 51 and 54-67. In one aspect, the VH domain has at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 50, 52, 53, 105, and 106. In one aspect, the VL domain has at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 51 and 54-67.

[00144] In one aspect, the anti-KLK5 antibody comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:39 or 107; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:40 or 41; (c) CDR-H3 comprising the amino acid sequence of SEQ ID

NO: 42; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 43 or 44; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 46-49, and a VH domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 50, 52, 53, 105, and 106, and a VL domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 51 and 54-67; wherein the antibody specifically binds to KLK5. In one aspect, the VH domain has at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 50, 52, 53, 105, and 106. In one aspect, the VL domain has at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 51 and 54-67. In one aspect, the antibody binds to KLK5 having a dissociation constant (K_D) that is up to 10 fold reduced or up to 10 fold increase when compared to the dissociation constant (K_D) of an antibody comprising a VH sequence of SEQ ID NO: 50, 52, 53, 105, and 106 and a VL sequence of SEQ ID NO: 51 and 54-67.

[00145] In another aspect, an anti-KLK5 antibody comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 50, 52, 53, 105, and 106. In one aspect, an anti-KLK5 antibody comprises a heavy chain variable domain (VH) sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 50, 52, 53, 105, and 106. In certain aspects, a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-KLK5 antibody comprising that sequence retains the ability to bind to KLK5. In certain aspects, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 50, 52, 53, 105, and 106. In certain aspects, substitutions, insertions, or deletions occur in regions outside the CDRs (i.e., in the FRs). Optionally, the anti-KLK5 antibody comprises the VH sequence in SEQ ID NO: 50, 52, 53, 105, and 106, including post-translational modifications of that sequence. In a particular aspect, the VH comprises one, two or three CDRs selected from: (a) CDR-H1, comprising the amino acid sequence of SEQ ID NO: 39 or 107, (b) CDR-H2, comprising the amino acid sequence of SEQ ID NO: 40 or 41, and (c) CDR-H3, comprising the amino acid sequence of SEQ ID NO: 42. In another aspect, an anti-KLK5 antibody is provided, wherein the antibody comprises a light chain variable domain (VL) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 51 and 54-67. In one aspect, an anti-KLK5 antibody comprises a light chain variable domain (VL) sequence having at least 95% sequence identity to

the amino acid sequence of SEQ ID NO: 51 and 54-67. In certain aspects, a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-KLK5 antibody comprising that sequence retains the ability to bind to KLK5. In certain aspects, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 51 and 54-67. In certain aspects, the substitutions, insertions, or deletions occur in regions outside the CDRs (i.e., in the FRs). Optionally, the anti-KLK5 antibody comprises the VL sequence in SEQ ID NO: 51 and 54-67, including post-translational modifications of that sequence. In a particular aspect, the VL comprises one, two or three CDRs selected from: (a) CDR-L1, comprising the amino acid sequence of SEQ ID NO: 43 or 44, (b) CDR-L2, comprising the amino acid sequence of SEQ ID NO: 45, and (c) CDR-L3, comprising the amino acid sequence of SEQ ID NO: 46-49.

[00146] In another aspect, an anti- KLK5 antibody is provided, wherein the antibody comprises a VH sequence as in any of the aspects provided above, and a VL sequence as in any of the aspects provided above. In one aspect, the antibody comprises the VH and VL sequences in SEQ ID NO: 50, 52, 53, 105, and 106 and SEQ ID NO: 51 and 54-67, respectively, including post-translational modifications of those sequences.

[00147] In a further aspect, the invention provides an antibody that binds to the same epitope as an anti-KLK5 antibody provided herein. For example, in certain aspects, an antibody is provided that binds to the same epitope as an anti-KLK5 antibody comprising a VH sequence of SEQ ID NO: 50, 52, 53, 105, and 106 and a VL sequence of SEQ ID NO: 51 and 54-67.

[00148] In a further aspect of the invention, an anti-KLK5 antibody according to any of the above aspects is a monoclonal antibody, including a chimeric, humanized or human antibody. In one aspect, an anti-KLK5 antibody is an antibody fragment, e.g., a Fv, Fab, Fab', scFv, diabody, or F(ab')₂ fragment. In another aspect, the antibody is a full-length antibody, e.g., an intact IgG1 antibody or other antibody class or isotype as defined herein.

[00149] In a further aspect, an anti-KLK5 antibody according to any of the above aspects may incorporate any of the features, singly or in combination, as described in Sections 1-8 below.

Antibody hu.9H5-H14L4 and variants

[00150] In one aspect, the invention provides an anti-KLK5 antibody comprising at least one, at least two, at least three, at least four, at least five, or all six CDRs selected from (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:68; (b) CDR-H2 comprising

the amino acid sequence of SEQ ID NO: 69 and 70; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 71 and 72; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 75-78.

[00151] In one aspect, the invention provides an antibody comprising at least one, at least two, or all three VH CDR sequences selected from (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 70; and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 72. In a further aspect, the antibody comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 70; and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 72.

[00152] In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VL CDR sequences selected from (a) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73; (b) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74; and (c) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 76. In one aspect, the antibody comprises (a) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73; (b) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74; and (c) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 76.

[00153] In another aspect, an antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH CDR sequences selected from (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 69 and 70, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 71 and 72; and (b) a VL domain comprising at least one, at least two, or all three VL CDR sequences selected from (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (ii) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (c) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 75-78.

[00154] In another aspect, the invention provides an antibody comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 70; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 72; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 76.

[00155] In any of the aspects provided herein, an anti-KLK5 antibody is humanized. In one aspect, an anti-KLK5 antibody further comprises an acceptor human framework, e.g. a human immunoglobulin framework or a human consensus framework.

[00156] In one aspect, an anti-KLK5 antibody comprises a VH domain comprising one or more heavy chain framework sequences selected from (a) a heavy chain framework region 1 (HC-FR1) of SEQ ID NO: 171, (b) a heavy chain framework region 2 (HC-FR2) of SEQ ID NO: 172-173, (c) a heavy chain framework region 3 (HC-FR3) of SEQ ID NO: 174, and (d) a heavy chain framework region 4 (HC-FR4) of SEQ ID NO: 175.

[00157] In another aspect, an anti-KLK5 antibody comprises a VH domain comprising a HC-FR1 of SEQ ID NO: 171. In another aspect, an anti-KLK5 antibody comprises a VH domain comprising a HC-FR2 of SEQ ID NO: 172 or 173. In another aspect, an anti-KLK5 antibody comprises a VH domain comprising a HC-FR3 of SEQ ID NO: 174. In another aspect, an anti-KLK5 antibody comprises a VH domain comprising a HC-FR4 of SEQ ID NO: 175.

[00158] In another aspect, an anti-KLK5 antibody comprises a VH domain comprising a HC-FR1 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity with SEQ ID NO: 171. In one aspect, the VH domain comprises a HC-FR1 of at least 95% sequence identity with SEQ ID NO: 171. In another aspect, the VH domain comprises a HC-FR1 of at least 98% sequence identity with SEQ ID NO: 171.

[00159] In another aspect, an anti-KLK5 antibody comprises a VH domain comprising a HC-FR2 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO: 172 or 173. In one aspect, the VH domain comprises a HC-FR2 of at least 95% sequence identity with SEQ ID NO: 172 or 173. In another aspect, the VH domain comprises a HC-FR2 of at least 98% sequence identity with SEQ ID NO: 172 or 173.

[00160] In another aspect, an anti-KLK5 antibody comprises a VH domain comprising a HC-FR3 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO: 174. In one aspect, the VH domain comprises a HC-FR3 of at least 95% sequence identity with SEQ ID NO: 174. In another aspect, the VH domain comprises a HC-FR3 of at least 98% sequence identity with SEQ ID NO: 174.

[00161] In another aspect, an anti-KLK5 antibody comprises a VH domain comprising a HC-FR4 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO: 175. In one aspect, the VH domain

comprises a HC-FR4 of at least 95% sequence identity with SEQ ID NO: 175. In another aspect, the VH domain comprises a HC-FR4 of at least 98% sequence identity with SEQ ID NO: 175.

[00162] In one aspect, an anti-KLK5 antibody comprises a VL domain comprising one or more light chain framework sequences selected from (a) a light chain framework region 1 (LC-FR1) of SEQ ID NO: 176, (b) a light chain framework region 2 (LC-FR2) of SEQ ID NO: 177-178, (c) a light chain framework region 3 (LC-FR3) of SEQ ID NO: 179, and (d) a light chain framework region 4 (LC-FR4) of SEQ ID NO: 180.

[00163] In another aspect, an anti-KLK5 antibody comprises a VL domain comprising a LC-FR1 of SEQ ID NO: 176. In another aspect, an anti-KLK5 antibody comprises a VL domain comprising a LC-FR2 of SEQ ID NO: 177-178. In another aspect, an anti-KLK5 antibody comprises a VL domain comprising a LC-FR3 of SEQ ID NO: 179. In another aspect, an anti-KLK5 antibody comprises a VL domain comprising a LC-FR4 of SEQ ID NO: 180.

[00164] In another aspect, an anti-KLK5 antibody comprises a VL domain comprising a LC-FR1 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO: 176. In one aspect, the VL domain comprises a LC-FR1 of at least 95% sequence identity with SEQ ID NO: 176. In another aspect, the VL domain comprises a LC-FR1 of at least 98% sequence identity with SEQ ID NO: 176.

[00165] In another aspect, an anti-KLK5 antibody comprises a VL domain comprising a LC-FR2 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO: 177 or 178. In one aspect, the VL domain comprises a LC-FR2 of at least 95% sequence identity with SEQ ID NO: 177 or 178. In another aspect, the VL domain comprises a LC-FR2 of at least 98% sequence identity with SEQ ID NO: 177 or 178.

[00166] In another aspect, an anti-KLK5 antibody comprises a VL domain comprising a LC-FR3 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO: 179. In one aspect, the VL domain comprises a LC-FR3 of at least 95% sequence identity with SEQ ID NO: 179. In another aspect, the VL domain comprises a LC-FR3 of at least 98% sequence identity with SEQ ID NO: 179.

[00167] In another aspect, an anti-KLK5 antibody comprises a VL domain comprising a LC-FR4 of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO: 180. In one aspect, the VL domain comprises a LC-FR1 of at least 95% sequence identity with SEQ ID NO: 180. In another aspect, the VL domain comprises a LC-FR1 of at least 98% sequence identity with SEQ ID NO: 180.

[00168] In another aspect, an anti-KLK5 antibody comprises one or more of the CDR sequences of the VH of SEQ ID NO: 79 or 81-87. In another embodiment, an anti-KLK5 antibody comprises one or more of the CDR sequences of the VL of SEQ ID NO: 80 or 88-94. In another embodiment, an anti-KLK5 antibody comprises the CDR sequences of the VH of SEQ ID NO: 79 or 81-87 and the CDR sequences of the VL of SEQ ID NO: 80 or 88-94.

[00169] In a further aspect, an anti-KLK5 antibody comprises the CDR-H1, CDR-H2 and CDR-H3 amino acid sequences of the VH domain of SEQ ID NO: 79 or 81-87 and the CDR-L1, CDR-L2 and CDR-L3 amino acid sequences of the VL domain of SEQ ID NO: 80 or 88-94.

[00170] In one aspect, an anti-KLK5 antibody comprises one or more of the heavy chain CDR amino acid sequences of the VH domain of SEQ ID NO: 79 or 81-87 and a framework of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% sequence identity to the framework amino acid sequence of the VH domain of SEQ ID NO: 79 or 81-87. In one aspect, the anti-KLK5 antibody comprises the three heavy chain CDR amino acid sequences of the VH domain of SEQ ID NO: 79 or 81-87 and a framework of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% sequence identity to the framework amino acid sequence of the VH domain of SEQ ID NO: 79 or 81-87. In one aspect, the anti-KLK5 antibody comprises the three heavy chain CDR amino acid sequences of the VH domain of SEQ ID NO: 79 or 81-87 and a framework of at least 95% sequence identity to the framework amino acid sequence of the VH domain of SEQ ID NO: 79 or 81-87. In another aspect, the anti-KLK5 antibody comprises the three heavy chain CDR amino acid sequences of the VH domain of SEQ ID NO: 79 or 81-87 and a framework of at least of at least 98% sequence identity to the framework amino acid sequence of the VH domain of SEQ ID NO: 79 or 81-87.

[00171] In one aspect, an anti-KLK5 antibody comprises one or more of the light chain CDR amino acid sequences of the VL domain of SEQ ID NO: 80 or 88-94 and a framework of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% sequence identity to the framework amino acid sequence of the VL domain of SEQ ID NO: 80 or 88-94. In one aspect, the anti-KLK5 antibody comprises the three light chain CDR amino acid sequences of the VL domain of SEQ ID NO: 80 or 88-94 and a framework of at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% sequence identity to the framework amino acid sequence of the VL domain of SEQ ID NO: 80 or 88-94. In one aspect, the anti-KLK5 antibody comprises the three light chain CDR amino acid sequences of the VL domain of SEQ ID NO: 80 or 88-94 and a framework of at least 95%

sequence identity to the framework amino acid sequence of the VL domain of SEQ ID NO: 80 or 88-94. In another aspect, the anti-KLK5 antibody comprises the three light chain CDR amino acid sequences of the VL domain of SEQ ID NO: 80 or 88-94 and a framework of at least particularly of at least 98% sequence identity to the framework amino acid sequence of the VH domain of SEQ ID NO: 80 or 88-94.

[00172] In one aspect, the anti-KLK5 antibody comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 69-70; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 71-72; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 75-78, and a VH domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 79 or 81-87, and a VL domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 80 or 88-94. In one aspect, the VH domain has at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 79 or 81-87. In one aspect, the VL domain has at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 80 or 88-94.

[00173] In one aspect, the anti-KLK5 antibody comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 69-70; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 71-72; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 75-78, and a VH domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 79 or 81-87, and a VL domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 80 or 88-94; wherein the antibody specifically binds to KLK5. In one aspect, the VH domain has at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 79 or 81-87. In one aspect, the VL domain has at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 80 or 88-94. In one aspect, the antibody binds to KLK5 having a dissociation constant (K_D) that is up to 10 fold reduced or up to 10 fold increase when compared to the dissociation constant (K_D) of an antibody comprising a VH sequence of SEQ ID NO: 79 or 81-87 and a VL sequence of SEQ ID NO: 80 or 88-94.

[00174] In another aspect, an anti-KLK5 antibody comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 79 or 81-87. In one aspect, an anti-KLK5 antibody comprises a heavy chain variable domain (VH) sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 79 or 81-87. In certain aspects, a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-KLK5 antibody comprising that sequence retains the ability to bind to KLK5. In certain aspects, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 79 or 81-87. In certain aspects, substitutions, insertions, or deletions occur in regions outside the CDRs (i.e., in the FRs). Optionally, the anti-KLK5 antibody comprises the VH sequence in SEQ ID NO: 79 or 81-87, including post-translational modifications of that sequence. In a particular aspect, the VH comprises one, two or three CDRs selected from: (a) CDR-H1, comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2, comprising the amino acid sequence of SEQ ID NO: 69-70, and (c) CDR-H3, comprising the amino acid sequence of SEQ ID NO: 71-72. In another aspect, an anti-KLK5 antibody is provided, wherein the antibody comprises a light chain variable domain (VL) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 80 or 88-94. In one aspect, an anti-KLK5 antibody comprises a light chain variable domain (VL) sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 80 or 88-94. In certain aspects, a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-KLK5 antibody comprising that sequence retains the ability to bind to KLK5. In certain aspects, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 80 or 88-94. In certain aspects, the substitutions, insertions, or deletions occur in regions outside the CDRs (i.e., in the FRs). Optionally, the anti-KLK5 antibody comprises the VL sequence in SEQ ID NO: 80 or 88-94, including post-translational modifications of that sequence. In a particular aspect, the VL comprises one, two or three CDRs selected from: (a) CDR-L1, comprising the amino acid sequence of SEQ ID NO: 73, (b) CDR-L2, comprising the amino acid sequence of SEQ ID NO: 74, and (c) CDR-L3, comprising the amino acid sequence of SEQ ID NO: 75-78.

[00175] In another aspect, an anti-KLK5 antibody is provided, wherein the antibody comprises a VH sequence as in any of the aspects provided above, and a VL sequence

as in any of the aspects provided above. In one aspect, the antibody comprises the VH and VL sequences in SEQ ID NO: 79 or 81-87 and SEQ ID NO: 80 or 88-94, respectively, including post-translational modifications of those sequences.

[00176] In a further aspect, the invention provides an antibody that binds to the same epitope as an anti-KLK5 antibody provided herein. For example, in certain aspects, an antibody is provided that binds to the same epitope as an anti-KLK5 antibody comprising a VH sequence of SEQ ID NO: 79 or 81-87 and a VL sequence of SEQ ID NO: 80 or 88-94.

[00177] In a further aspect of the invention, an anti-KLK5 antibody according to any of the above aspects is a monoclonal antibody, including a chimeric, humanized or human antibody. In one aspect, an anti-KLK5 antibody is an antibody fragment, e.g., a Fv, Fab, Fab', scFv, diabody, or F(ab')₂ fragment. In another aspect, the antibody is a full-length antibody, e.g., an intact IgG1 antibody or other antibody class or isotype as defined herein.

[00178] In a further aspect, an anti-KLK5 antibody according to any of the above aspects may incorporate any of the features, singly or in combination, as described in Sections 1-8 below.

C. Exemplary Anti-KLK5/KLK7 Multispecific Antibodies

[00179] In one aspect, the invention provides multispecific antibodies that bind to both KLK5 and KLK7. In some embodiments, bispecific antibodies are provided that bind to both KLK5 and KLK7. In some embodiments, the multispecific (such as bispecific) antibodies inhibit both KLK5 protease activity and KLK7 protease activity. In some embodiments, the multispecific (such as bispecific) antibodies bind KLK5 with a K_D of less than 60 pM, less than 30 pM, less than 20 pM, less than 10 pM, or less than 5 pM, as measured by surface plasmon resonance. In some embodiments, the multispecific (such as bispecific) antibodies bind to KLK7 with a K_D of less than 20 pM, less than 10 pM, or less than 9 pM, or less than 8 pM, or less than 7 pM, or less than 6 pM, or less than 5 pM, or less than 3 pM, or less than 2 pM, or less than 1 pM, as measured by surface plasmon resonance. In some embodiments, the multispecific (such as bispecific) antibodies bind KLK5 with a K_D of no greater than 60 pM, no greater than 30 pM, no greater than 20 pM, no greater than 10 pM, or no greater than 5 pM, as measured by surface plasmon resonance. In some embodiments, the multispecific (such as bispecific) antibodies bind to KLK7 with a K_D of no greater than 20 pM, no greater than 10 pM, or no greater than 9 pM, or no greater than 8 pM, or no greater than 7 pM, or no greater than 6 pM, or no greater than 5 pM, or no greater than 3 pM, or no greater than 2 pM, or no greater than 1 pM, as measured by surface plasmon resonance.

[00180] In some embodiments, an anti-KLK5/KLK7 multispecific antibody inhibits human KLK7 protease activity and inhibits human KLK5 protease activity. In some embodiments, an anti-KLK5/KLK7 multispecific antibody inhibits human KLK7-mediated cleavage of a substrate comprising the amino acid sequence RPKPVE-Nval-WRK (SEQ ID NO: 121), wherein Nval is norvaline, with an IC₅₀ of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM. In some embodiments, an anti-KLK5/KLK7 multispecific antibody inhibits human KLK5-mediated cleavage of the substrate Boc-Val-Pro-Arg-AMC with an IC₅₀ of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM. In some embodiments, an anti-KLK5/KLK7 multispecific antibody inhibits human KLK7-mediated cleavage of a substrate comprising the amino acid sequence RPKPVE-Nval-WRK (SEQ ID NO: 121), wherein Nval is norvaline, with an IC₅₀ of no greater than 5 nM, or no greater than 3 nM, or no greater than 2 nM, or no greater than 1 nM. In some embodiments, an anti-KLK5/KLK7 multispecific antibody inhibits human KLK5-mediated cleavage of the substrate Boc-Val-Pro-Arg-AMC with an IC₅₀ of no greater than 5 nM, or no greater than 3 nM, or no greater than 2 nM, or no greater than 1 nM. In some embodiments, the K_D of the multispecific antibody for human KLK5 and the K_D of the antibody for human KLK7 are within 3-fold, or within 2.5-fold, or within 2-fold, or within 1.5-fold of one another.

[00181] In some aspects, a multispecific antibody that binds to both KLK5 and KLK7 comprises a first binding domain that binds to KLK7 and a second binding domain that binds KLK5.

[00182] In some embodiments, a multispecific antibody that binds to both KLK5 and KLK7, when bound to human KLK5, results in a conformational change of human KLK5, wherein the conformational change allosterically results in the disruption of the substrate binding site and/or the active site of human KLK5. In some embodiments, a multispecific antibody that binds to both KLK5 and KLK7, when bound to human KLK7, results in a conformational change of human KLK7, wherein the conformational change allosterically results in the disruption of the substrate binding site and/or the active site of human KLK7.

[00183] In some embodiments, the first binding domain comprises an anti-KLK7 antibody binding domain described herein. For example, in some such embodiments, the first binding domain comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12. As a further nonlimiting

example, in some embodiments, the first binding domain comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12, and a VH domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 13 and 15-30, and a VL domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 14 and 31-38. In some embodiments, the first binding domain comprises the VH and VL sequences in SEQ ID NO: 29 and SEQ ID NO: 32, respectively, including post-translational modifications of those sequences. In some embodiments, the first binding domain comprises the VH and VL sequences in SEQ ID NO: 30 and SEQ ID NO: 38, respectively, including post-translational modifications of those sequences.

[00184] In some embodiments, the second binding domain comprises an anti-KLK5 antibody binding domain described herein. For example, in some such embodiments, the second binding domain comprises (a) CDR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 39 and 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 43 and 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49. As a further nonlimiting example, in some embodiments, the second binding domain comprises (a) CDR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 39 and 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 43 and 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49, and a VH domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 50, 52, 53, 105, and 106, and a VL domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 51 and 54-67. In some embodiments, the second binding domain comprises the VH and VL

sequences in SEQ ID NO: 52 and SEQ ID NO: 55, respectively, including post-translational modifications of those sequences. In some embodiments, the second binding domain comprises the VH and VL sequences in SEQ ID NO: 53 and SEQ ID NO: 62, respectively, including post-translational modifications of those sequences.

[00185] In some embodiments, the second binding domain comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 69 and 70, and (c) CDR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 71 and 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 75-78. As a further nonlimiting example, in some embodiments, the second binding domain comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 69 and 70, and (c) CDR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 71 and 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 75-78, and a VH domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 79 and 81-87, and a VL domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 80 and 88-94. In some embodiments, the second binding domain comprises the VH and VL sequences in SEQ ID NO: 83 and SEQ ID NO: 88, respectively, including post-translational modifications of those sequences. In some embodiments, the second binding domain comprises the VH and VL sequences in SEQ ID NO: 87 and SEQ ID NO: 92, respectively, including post-translational modifications of those sequences.

[00186] In some embodiments, a multispecific antibody (such as a bispecific antibody) is provided, wherein the first binding domain binds KLK7 and the second binding domain binds KLK5, wherein the first binding domain is an anti-KLK7 antibody binding domain provided herein and the second binding domain is an anti-KLK5 binding domain provided herein. In some such embodiments, the first binding domain

[00187] In some embodiments, the first binding domain comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9;

(d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12; and the second binding domain comprises (a) CDR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 39 and 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 43 and 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49. In some embodiments, the first binding domain comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12; and the second binding domain comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 69 and 70, and (c) CDR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 71 and 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 75-78.

[00188] In some embodiments, the first binding domain comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12, and a VH domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 13 and 15-30, and a VL domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 14 and 31-38; and the second binding domain comprises (a) CDR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 39 and 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 43 and 44, (e) CDR-L2

comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49, and a VH domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 50, 52, 53, 105, and 106, and a VL domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 51 and 54-67.

[00189] In some embodiments, the first binding domain comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12, and a VH domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 13 and 15-30, and a VL domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 14 and 31-38; and the second binding domain comprises (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 69 and 70, and (c) CDR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 71 and 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 75-78, and a VH domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 79 and 81-87, and a VL domain having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from SEQ ID NOs: 80 and 88-94.

[00190] In some embodiments, a bispecific anti-KLK5/KLK7 antibody comprises a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11, and (f)

CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12; and the second binding domain comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NOs: 43, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 47.

[00191] In some embodiments, a bispecific anti-KLK5/KLK7 antibody comprises a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12; and the second binding domain comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 70, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 76.

[00192] In some embodiments, a bispecific anti-KLK5/KLK7 antibody comprises a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein (i) the first binding domain comprises a VH amino acid sequence of SEQ ID NO: 29 and a VL amino acid sequence of SEQ ID NO: 32, or a VH amino acid sequence of SEQ ID NO: 30 and a VL amino acid sequence of SEQ ID NO: 38; and (ii) the second binding domain comprises a VH sequence of SEQ ID NO: 52 and a VL amino acid sequence of SEQ ID NO: 55; or a VH sequence of SEQ ID NO: 53 and a VL amino acid sequence of SEQ ID NO: 62. In some embodiments, the first binding domain comprises a VH sequence of SEQ ID NO: 30 and a VL sequence of SEQ ID NO: 38, and the second binding domain comprises a VH sequence of SEQ ID NO: 53 and a VL sequence of SEQ ID NO: 62.

[00193] In some embodiments, a bispecific anti-KLK5/KLK7 antibody comprises a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein (i) the first binding domain comprises a VH amino acid sequence of SEQ ID NO: 29 and a VL amino acid sequence of SEQ ID NO: 32, or a VH amino acid sequence of SEQ ID NO: 30 and a VL amino acid sequence of SEQ ID NO: 38; and (ii) the second binding domain comprises a VH sequence of SEQ ID NO: 83 and a VL amino acid sequence of SEQ ID NO: 88; or a VH sequence of SEQ ID NO: 87 and a VL amino acid sequence of SEQ ID NO: 92. In some embodiments, the first binding domain comprises a VH sequence of SEQ ID NO: 30 and a VL sequence of SEQ ID NO: 38, and the second binding domain comprises a VH sequence of SEQ ID NO: 87 and a VL sequence of SEQ ID NO: 92.

[00194] In some embodiments, a bispecific anti-KLK5/KLK7 antibody comprises a first binding domain that binds KLK7 and a second binding domain that binds KLK5, wherein the first binding domain comprises a first heavy chain variable region and a first light chain variable region, and the second binding domain comprises a second heavy chain variable region and a second light chain variable region. In some such embodiments, the first heavy chain variable region comprises a Q39E substitution (Kabat numbering) and the first light chain variable region comprises a Q38K substitution (Kabat numbering); and the second heavy chain variable region comprises a Q39K substitution (Kabat numbering) and the second light chain variable region comprises a Q38E substitution (Kabat numbering). In some embodiments, the first heavy chain variable region comprises a Q39K substitution (Kabat numbering) and the first light chain variable region comprises a Q38E substitution (Kabat numbering); and the second heavy chain variable region comprises a Q39E substitution (Kabat numbering) and the second light chain variable region comprises a Q38K substitution (Kabat numbering). In some embodiments, the Q39E/Q38K and Q39K/Q38E substitutions reduce mispairing of the heavy and light chains of the bispecific antibody.

[00195] In some embodiments, the first binding domain comprises a first heavy chain variable domain linked to a first heavy chain constant region and a first light chain variable domain linked to a first light chain constant region; and the second binding domain comprises a second heavy chain variable domain linked to a second heavy chain constant region and a second light chain variable domain linked to a second light chain constant region. In some such embodiments, the first heavy chain constant region comprises a S183K substitution (EU numbering) and the first light chain constant region comprises a V133E substitution (EU numbering), and the second heavy chain constant region comprises a S183E substitution (EU

numbering) and the second light chain constant region comprises a V133K substitution (EU numbering). In some embodiments, the first heavy chain constant region comprises a S183E substitution (EU numbering) and the first light chain constant region comprises a V133K substitution (EU numbering), and the second heavy chain constant region comprises a S183K substitution (EU numbering) and the second light chain constant region comprises a V133E substitution (EU numbering). In some embodiments, the S183K/V133E and S183E/V133K substitutions reduce mispairing of the heavy and light chains of the bispecific antibody.

[00196] In some embodiments, a bispecific anti-KLK5/KLK7 antibody comprises Q39E/Q38K and Q39K/Q38E substitutions in the binding domains and S183K/V133E and S183E/V133K substitutions in the constant regions. *See, e.g.*, WO 2016/172485, which is incorporated by reference here in its entirety for any purpose. A nonlimiting exemplary schematic of a bispecific antibody is shown in Figure 15.

[00197] In some embodiments, a bispecific anti-KLK5/KLK7 antibody is provided, wherein the bispecific antibody comprises a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 108 or 192, and a light chain amino acid sequence of SEQ ID NO: 109, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 110 or 193 and a light chain amino acid sequence of SEQ ID NO: 111. In some embodiments, a bispecific anti-KLK5/KLK7 antibody is provided, wherein the bispecific antibody comprises a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 112 or 194, and a light chain amino acid sequence of SEQ ID NO: 113, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 114 or 195 and a light chain amino acid sequence of SEQ ID NO: 115.

[00198] In some embodiments, a bispecific anti-KLK5/KLK7 antibody is provided, wherein the bispecific antibody comprises a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 108 or 192, and a light chain amino acid sequence of SEQ ID NO: 109, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 114 or 195 and a light chain amino acid sequence of SEQ ID NO: 111. In some embodiments, a bispecific anti-KLK5/KLK7 antibody is provided, wherein the bispecific

antibody comprises a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 112 or 194, and a light chain amino acid sequence of SEQ ID NO: 113, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 110 or 193 and a light chain amino acid sequence of SEQ ID NO: 115.

[00199] In some embodiments, a bispecific anti-KLK5/KLK7 antibody is provided, wherein the bispecific antibody comprises a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 194, and a light chain amino acid sequence of SEQ ID NO: 113, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 195, and a light chain amino acid sequence of SEQ ID NO: 115.

[00200] In some embodiments, a bispecific anti-KLK5/KLK7 antibody is provided, wherein the bispecific antibody comprises a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 112, and a light chain amino acid sequence of SEQ ID NO: 113, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 195, and a light chain amino acid sequence of SEQ ID NO: 115.

[00201] In some embodiments, a bispecific anti-KLK5/KLK7 antibody is provided, wherein the bispecific antibody comprises a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 194, and a light chain amino acid sequence of SEQ ID NO: 113, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 114, and a light chain amino acid sequence of SEQ ID NO: 115.

[00202] In a further aspect, a multispecific antibody according to any of the above aspects may incorporate any of the features, singly or in combination, as described in Sections 1-8 below.

1. Antibody Affinity

[00203] In certain aspects, an antibody provided herein has a dissociation constant (K_D) of $\leq 1 \mu\text{M}$, $\leq 100 \text{ nM}$, $\leq 10 \text{ nM}$, $\leq 1 \text{ nM}$, $\leq 0.1 \text{ nM}$, $\leq 0.01 \text{ nM}$, or $\leq 0.001 \text{ nM}$ (e.g., 10^{-8} M or less, e.g., from 10^{-8} M to 10^{-13} M , e.g., from 10^{-9} M to 10^{-13} M).

[00204] In one aspect, K_D is measured using surface plasmon resonance. In one aspect, K_D is measured using a BIAcore® surface plasmon resonance assay, such as a BIAcore™ T200 or BIAcore™ 8K assay. For example, an assay using a BIAcore™ 8K (BIAcore, Inc., Piscataway, NJ) is performed at 25°C or 37°C with immobilized antibody on a protein A chip at ~300 response units (RU). Ten-fold serial dilutions of antigen (such as human KLK7 or human KLK5) are injected in HBS-P buffer at 37°C with a flow rate of 100 $\mu\text{L}/\text{min}$. Alternatively, ten-fold serial dilutions of antigen are injected in HBS-P buffer at 25°C with a flow rate of 30 $\mu\text{L}/\text{min}$. Association rates (k_a) and dissociation rates (k_d) are calculated using a 1:1 Langmuir binding model (for example, using BIAcore Insight Evaluation Software version 2.0). The equilibrium dissociation constant (K_D) are calculated as the ratio k_d/k_a .

[00205] In an alternative method, K_D is measured by a radiolabeled antigen binding assay (RIA). In one aspect, an RIA is performed with the Fab version of an antibody of interest and its antigen. For example, solution binding affinity of Fabs for antigen is measured by equilibrating Fab with a minimal concentration of (^{125}I)-labeled antigen in the presence of a titration series of unlabeled antigen, then capturing bound antigen with an anti-Fab antibody-coated plate (see, e.g., Chen et al., *J. Mol. Biol.* 293:865-881(1999)). To establish conditions for the assay, MICROTITER® multi-well plates (Thermo Scientific) are coated overnight with 5 $\mu\text{g}/\text{ml}$ of a capturing anti-Fab antibody (Cappel Labs) in 50 mM sodium carbonate (pH 9.6), and subsequently blocked with 2% (w/v) bovine serum albumin in PBS for two to five hours at room temperature (approximately 23°C). In a non-adsorbent plate (Nunc #269620), 100 pM or 26 pM [^{125}I]-antigen are mixed with serial dilutions of a Fab of interest (e.g., consistent with assessment of the anti-VEGF antibody, Fab-12, in Presta et al., *Cancer Res.* 57:4593-4599 (1997)). The Fab of interest is then incubated overnight; however, the incubation may continue for a longer period (e.g., about 65 hours) to ensure that equilibrium is reached. Thereafter, the mixtures are transferred to the capture plate for incubation at room temperature (e.g., for one hour). The solution is then removed, and the plate washed eight times with 0.1% polysorbate 20 (TWEEN-20®) in PBS. When the plates have dried, 150 $\mu\text{L}/\text{well}$ of scintillant (MICROSCINT-20™, Packard) is added, and the plates are counted on a TOPCOUNT™ gamma counter (Packard) for ten minutes. Concentrations of each Fab that give less than or equal to 20% of maximal binding are chosen for use in competitive binding assays.

2. Antibody Fragments

[00206] In certain aspects, an antibody provided herein is an antibody fragment.

[00207] In one aspect, the antibody fragment is a Fab, Fab', Fab'-SH, or F(ab')₂ fragment, in particular a Fab fragment. Papain digestion of intact antibodies produces two identical antigen-binding fragments, called "Fab" fragments containing each the heavy- and light-chain variable domains (VH and VL, respectively) and also the constant domain of the light chain (CL) and the first constant domain of the heavy chain (CH1). The term "Fab fragment" thus refers to an antibody fragment comprising a light chain comprising a VL domain and a CL domain, and a heavy chain fragment comprising a VH domain and a CH1 domain. "Fab' fragments" differ from Fab fragments by the addition of residues at the carboxy terminus of the CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH are Fab' fragments in which the cysteine residue(s) of the constant domains bear a free thiol group. Pepsin treatment yields an F(ab')₂ fragment that has two antigen-binding sites (two Fab fragments) and a part of the Fc region. For discussion of Fab and F(ab')₂ fragments comprising salvage receptor binding epitope residues and having increased *in vivo* half-life, see U.S. Patent No. 5,869,046.

[00208] In another aspect, the antibody fragment is a diabody, a triabody or a tetrabody. "Diabodies" are antibody fragments with two antigen-binding sites that may be bivalent or bispecific. See, for example, EP 404,097; WO 1993/01161; Hudson et al., Nat. Med. 9:129-134 (2003); and Hollinger et al., Proc. Natl. Acad. Sci. USA 90: 6444-6448 (1993). Triabodies and tetrabodies are also described in Hudson et al., Nat. Med. 9:129-134 (2003).

[00209] In a further aspect, the antibody fragment is a single chain Fab fragment. A "single chain Fab fragment" or "scFab" is a polypeptide consisting of an antibody heavy chain variable domain (VH), an antibody heavy chain constant domain 1 (CH1), an antibody light chain variable domain (VL), an antibody light chain constant domain (CL) and a linker, wherein said antibody domains and said linker have one of the following orders in N-terminal to C-terminal direction: a) VH-CH1-linker-VL-CL, b) VL-CL-linker-VH-CH1, c) VH-CL-linker-VL-CH1 or d) VL-CH1-linker-VH-CL. In particular, said linker is a polypeptide of at least 30 amino acids, preferably between 32 and 50 amino acids. Said single chain Fab fragments are stabilized via the natural disulfide bond between the CL domain and the CH1 domain. In addition, these single chain Fab fragments might be further stabilized by generation of interchain disulfide bonds via insertion of cysteine residues (e.g., position 44 in the variable heavy chain and position 100 in the variable light chain according to Kabat numbering).

[00210] In another aspect, the antibody fragment is single-chain variable fragment (scFv). A “single-chain variable fragment” or “scFv” is a fusion protein of the variable domains of the heavy (VH) and light chains (VL) of an antibody, connected by a linker. In particular, the linker is a short polypeptide of 10 to 25 amino acids and is usually rich in glycine for flexibility, as well as serine or threonine for solubility, and can either connect the N-terminus of the VH with the C-terminus of the VL, or *vice versa*. This protein retains the specificity of the original antibody, despite removal of the constant regions and the introduction of the linker. For a review of scFv fragments, see, e.g., Plückthun, in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenberg and Moore eds., (Springer-Verlag, New York), pp. 269-315 (1994); see also WO 93/16185; and U.S. Patent Nos. 5,571,894 and 5,587,458.

[00211] In another aspect, the antibody fragment is a single-domain antibody. “Single-domain antibodies” are antibody fragments comprising all or a portion of the heavy chain variable domain or all or a portion of the light chain variable domain of an antibody. In certain aspects, a single-domain antibody is a human single-domain antibody (Domantis, Inc., Waltham, MA; see, e.g., U.S. Patent No. 6,248,516 B1).

[00212] Antibody fragments can be made by various techniques, including but not limited to proteolytic digestion of an intact antibody as well as recombinant production by recombinant host cells (e.g., *E. coli*), as described herein.

3. *Chimeric and Humanized Antibodies*

[00213] In certain aspects, an antibody provided herein is a chimeric antibody. Certain chimeric antibodies are described, e.g., in U.S. Patent No. 4,816,567; and Morrison et al., *Proc. Natl. Acad. Sci. USA*, 81:6851-6855 (1984)). In one example, a chimeric antibody comprises a non-human variable region (e.g., a variable region derived from a mouse, rat, hamster, rabbit, or non-human primate, such as a monkey) and a human constant region. In a further example, a chimeric antibody is a “class switched” antibody in which the class or subclass has been changed from that of the parent antibody. Chimeric antibodies include antigen-binding fragments thereof.

[00214] In certain aspects, a chimeric antibody is a humanized antibody. Typically, a non-human antibody is humanized to reduce immunogenicity to humans, while retaining the specificity and affinity of the parental non-human antibody. Generally, a humanized antibody comprises one or more variable domains in which the CDRs (or portions thereof) are derived from a non-human antibody, and FRs (or portions thereof) are derived from human antibody sequences. A humanized antibody optionally will also comprise at least a

portion of a human constant region. In some aspects, some FR residues in a humanized antibody are substituted with corresponding residues from a non-human antibody (e.g., the antibody from which the CDR residues are derived), e.g., to restore or improve antibody specificity or affinity.

[00215] Humanized antibodies and methods of making them are reviewed, e.g., in Almagro and Fransson, *Front. Biosci.* 13:1619-1633 (2008), and are further described, e.g., in Riechmann et al., *Nature* 332:323-329 (1988); Queen et al., *Proc. Nat'l Acad. Sci. USA* 86:10029-10033 (1989); US Patent Nos. 5, 821,337, 7,527,791, 6,982,321, and 7,087,409; Kashmiri et al., *Methods* 36:25-34 (2005) (describing specificity determining region (SDR) grafting); Padlan, *Mol. Immunol.* 28:489-498 (1991) (describing “resurfacing”); Dall’Acqua et al., *Methods* 36:43-60 (2005) (describing “FR shuffling”); and Osbourn et al., *Methods* 36:61-68 (2005) and Klimka et al., *Br. J. Cancer*, 83:252-260 (2000) (describing the “guided selection” approach to FR shuffling).

[00216] Human framework regions that may be used for humanization include but are not limited to: framework regions selected using the “best-fit” method (see, e.g., Sims et al. *J. Immunol.* 151:2296 (1993)); framework regions derived from the consensus sequence of human antibodies of a particular subgroup of light or heavy chain variable regions (see, e.g., Carter et al. *Proc. Natl. Acad. Sci. USA*, 89:4285 (1992); and Presta et al. *J. Immunol.*, 151:2623 (1993)); human mature (somatically mutated) framework regions or human germline framework regions (see, e.g., Almagro and Fransson, *Front. Biosci.* 13:1619-1633 (2008)); and framework regions derived from screening FR libraries (see, e.g., Baca et al., *J. Biol. Chem.* 272:10678-10684 (1997) and Rosok et al., *J. Biol. Chem.* 271:22611-22618 (1996)).

4. Human Antibodies

[00217] In certain aspects, an antibody provided herein is a human antibody. Human antibodies can be produced using various techniques known in the art. Human antibodies are described generally in van Dijk and van de Winkel, *Curr. Opin. Pharmacol.* 5: 368-74 (2001) and Lonberg, *Curr. Opin. Immunol.* 20:450-459 (2008).

[00218] Human antibodies may be prepared by administering an immunogen to a transgenic animal that has been modified to produce intact human antibodies or intact antibodies with human variable regions in response to antigenic challenge. Such animals typically contain all or a portion of the human immunoglobulin loci, which replace the endogenous immunoglobulin loci, or which are present extrachromosomally or integrated randomly into the animal’s chromosomes. In such transgenic mice, the endogenous immunoglobulin loci have

generally been inactivated. For review of methods for obtaining human antibodies from transgenic animals, see Lonberg, *Nat. Biotech.* 23:1117-1125 (2005). See also, e.g., U.S. Patent Nos. 6,075,181 and 6,150,584 describing XENOMOUSE™ technology; U.S. Patent No. 5,770,429 describing HUMAB® technology; U.S. Patent No. 7,041,870 describing K-M MOUSE® technology, and U.S. Patent Application Publication No. US 2007/0061900, describing VELOCIMOUSE® technology). Human variable regions from intact antibodies generated by such animals may be further modified, e.g., by combining with a different human constant region.

[00219] Human antibodies can also be made by hybridoma-based methods. Human myeloma and mouse-human heteromyeloma cell lines for the production of human monoclonal antibodies have been described. (See, e.g., Kozbor *J. Immunol.*, 133: 3001 (1984); Brodeur et al., *Monoclonal Antibody Production Techniques and Applications*, pp. 51-63 (Marcel Dekker, Inc., New York, 1987); and Boerner et al., *J. Immunol.*, 147: 86 (1991).) Human antibodies generated via human B-cell hybridoma technology are also described in Li et al., *Proc. Natl. Acad. Sci. USA*, 103:3557-3562 (2006). Additional methods include those described, for example, in U.S. Patent No. 7,189,826 (describing production of monoclonal human IgM antibodies from hybridoma cell lines) and Ni, *Xiandai Mianyixue*, 26(4):265-268 (2006) (describing human-human hybridomas). Human hybridoma technology (Trioma technology) is also described in Vollmers and Brandlein, *Histology and Histopathology*, 20(3):927-937 (2005) and Vollmers and Brandlein, *Methods and Findings in Experimental and Clinical Pharmacology*, 27(3):185-91 (2005).

[00220] Human antibodies may also be generated by isolating variable domain sequences selected from human-derived phage display libraries. Such variable domain sequences may then be combined with a desired human constant domain. Techniques for selecting human antibodies from antibody libraries are described below.

5. Library-Derived Antibodies

[00221] In certain aspects, an antibody provided herein is derived from a library. Antibodies of the invention may be isolated by screening combinatorial libraries for antibodies with the desired activity or activities. Methods for screening combinatorial libraries are reviewed, e.g., in Lerner et al. in *Nature Reviews* 16:498-508 (2016). For example, a variety of methods are known in the art for generating phage display libraries and screening such libraries for antibodies possessing the desired binding characteristics. Such methods are reviewed, e.g., in Frenzel et al. in *mAbs* 8:1177-1194 (2016); Bazan et al. in *Human Vaccines and*

Immunotherapeutics 8:1817-1828 (2012) and Zhao et al. in *Critical Reviews in Biotechnology* 36:276-289 (2016) as well as in Hoogenboom et al. in *Methods in Molecular Biology* 178:1-37 (O'Brien et al., ed., Human Press, Totowa, NJ, 2001) and in Marks and Bradbury in *Methods in Molecular Biology* 248:161-175 (Lo, ed., Human Press, Totowa, NJ, 2003).

[00222] In certain phage display methods, repertoires of VH and VL genes are separately cloned by polymerase chain reaction (PCR) and recombined randomly in phage libraries, which can then be screened for antigen-binding phage as described in Winter et al. in *Annual Review of Immunology* 12: 433-455 (1994). Phage typically display antibody fragments, either as single-chain Fv (scFv) fragments or as Fab fragments. Libraries from immunized sources provide high-affinity antibodies to the immunogen without the requirement of constructing hybridomas. Alternatively, the naive repertoire can be cloned (e.g., from human) to provide a single source of antibodies to a wide range of non-self and also self antigens without any immunization as described by Griffiths et al. in *EMBO Journal* 12: 725-734 (1993). Furthermore, naive libraries can also be made synthetically by cloning unrearranged V-gene segments from stem cells, and using PCR primers containing random sequence to encode the highly variable CDR3 regions and to accomplish rearrangement *in vitro*, as described by Hoogenboom and Winter in *Journal of Molecular Biology* 227: 381-388 (1992). Patent publications describing human antibody phage libraries include, for example: US Patent Nos. 5,750,373; 7,985,840; 7,785,903 and 8,679,490 as well as US Patent Publication Nos. 2005/0079574, 2007/0117126, 2007/0237764 and 2007/0292936.

[00223] Further examples of methods known in the art for screening combinatorial libraries for antibodies with a desired activity or activities include ribosome and mRNA display, as well as methods for antibody display and selection on bacteria, mammalian cells, insect cells or yeast cells. Methods for yeast surface display are reviewed, e.g., in Scholler et al. in *Methods in Molecular Biology* 503:135-56 (2012) and in Cherf et al. in *Methods in Molecular biology* 1319:155-175 (2015) as well as in Zhao et al. in *Methods in Molecular Biology* 889:73-84 (2012). Methods for ribosome display are described, e.g., in He et al. in *Nucleic Acids Research* 25:5132-5134 (1997) and in Hanes et al. in *PNAS* 94:4937-4942 (1997).

[00224] Antibodies or antibody fragments isolated from human antibody libraries are considered human antibodies or human antibody fragments herein.

6. Multispecific Antibodies

[00225] In certain aspects, an antibody provided herein is a multispecific antibody, e.g., a bispecific antibody. "Multispecific antibodies" are monoclonal antibodies that have

binding specificities for at least two different sites, i.e., different epitopes on different antigens or different epitopes on the same antigen. In certain aspects, the multispecific antibody has three or more binding specificities. In certain aspects, one of the binding specificities is for KLK7 and the other specificity is for any other antigen. In certain aspects, one of the binding specificities is for KLK7 and the other specificity is for KLK5. In certain aspects, bispecific antibodies may bind to two (or more) different epitopes of an antigen. Multispecific antibodies may be prepared as full-length antibodies or antibody fragments.

[00226] Techniques for making multispecific antibodies include, but are not limited to, recombinant co-expression of two immunoglobulin heavy chain-light chain pairs having different specificities (see Milstein and Cuello, *Nature* 305: 537 (1983)) and “knob-in-hole” engineering (see, e.g., U.S. Patent No. 5,731,168, and Atwell et al., *J. Mol. Biol.* 270:26 (1997)). Nonlimiting exemplary knob-in-hole substitutions include T366W (knob) and T366S/L368A/Y407V (hole). In some embodiments, the knob-in-hole substitutions are in IgG1 constant domains.

[00227] Multi-specific antibodies may also be made by engineering electrostatic steering effects for making antibody Fc-heterodimeric molecules. See, e.g., WO 2009/089004; Dillon et al., *Mabs* 9(2): 213-230 (2017). As a nonlimiting example, in a bispecific antibody comprising two heavy chain variable regions and two light chain variable regions, a first heavy chain variable region may comprise a Q39E substitution (Kabat numbering) and a first light chain variable region may comprise a Q38K substitution (Kabat numbering); and a second heavy chain variable region may comprise a Q39K substitution (Kabat numbering) and a second light chain variable region may comprise a Q38E substitution (Kabat numbering). In some embodiments, the Q39E/Q38K and Q39K/Q38E substitutions reduce mispairing of the heavy and light chains of the bispecific antibody. Similarly, a first heavy chain constant region may comprise a S183K substitution (EU numbering) and a first light chain constant region may comprise a V133E substitution (EU numbering), and the a second heavy chain constant region may comprise a S183E substitution (EU numbering) and a second light chain constant region may comprise a V133K substitution (EU numbering). In some embodiments, the S183K/V133E and S183E/V133K substitutions reduce mispairing of the heavy and light chains of the bispecific antibody.

[00228] In some embodiments, a bispecific antibody comprises Q39E/Q38K and Q39K/Q38E substitutions in the binding domains and S183K/V133E and S183E/V133K substitutions in the constant regions. In some embodiments, a bispecific antibody comprises both knob-in-hole substitutions and electrostatic substitutions. See, e.g., WO 2016/172485,

which is incorporated by reference here in its entirety for any purpose. A nonlimiting exemplary schematic of a bispecific antibody is shown in Figure 15.

[00229] Accordingly, in some embodiments, a multispecific antibody is provided, which comprises a) a first heavy chain/light chain pair binding to a first antigen which comprises a first heavy chain polypeptide (H1) and a first light chain polypeptide (L1), and b) a second heavy chain/light chain pair binding to a second antigen which comprises a second heavy chain polypeptide (H2) and a second light chain polypeptide (L2), wherein each H1 and H2 comprises a heavy chain variable domain (VH) and a heavy chain constant domain (CH1), and each L1 and L2 comprises a light chain variable domain (VL) and a light chain constant domain (CL); wherein the CH1 domain of H1 comprises an amino acid substitution at S183 (EU numbering) and the CL domain of L1 comprises an amino acid substitution at V133 (EU numbering); and wherein the VH domain of H1 comprises an amino acid substitution at position Q39 and the VL domain of L1 comprises an amino acid substitutions at position Q38 and/or the VH domain of H2 comprises an amino acid substitutions at position Q39 and the VL domain of L2 comprises an amino acid substitution at position Q38 (all Kabat numbering). In some embodiments, the VH domain of H1 comprises an amino acid substitution at Q39 (Kabat numbering) and the VL domain of L1 comprises an amino acid substitution at Q38 (Kabat numbering). In some embodiments, the CH1 domain of H2 comprises an amino acid substitution at S183 (EU numbering) and the CL domain of L2 comprises an amino acid substitution at V133 (EU numbering). In some embodiments, the VH domain of H2 further comprises an amino acid substitution at position Q39 and the VL domain of L2 further comprises an amino acid substitution at position Q38 (Kabat numbering). In some embodiments, the CH1 domain of H1 comprises a S183K mutation and CL of L1 comprises a V133E mutation, and CH1 of H2 comprises a S183E mutation and the CL domain of L2 comprises the V133K mutation. In some embodiments, the VH domain of H1 comprises a Q39E mutation, the VL domain of L1 comprises a Q38K mutation, the VH domain of H2 comprises a Q39K mutation and the VL domain of L2 comprises a Q38E mutation (all Kabat numbering).

[00230] Multi-specific antibodies may also be made by cross-linking two or more antibodies or fragments (see, e.g., US Patent No. 4,676,980, and Brennan et al., *Science*, 229: 81 (1985)); using leucine zippers to produce bi-specific antibodies (see, e.g., Kostelny et al., *J. Immunol.*, 148(5):1547-1553 (1992) and WO 2011/034605); using the common light chain technology for circumventing the light chain mis-pairing problem (see, e.g., WO 98/50431); using “diabody” technology for making bispecific antibody fragments (see, e.g., Hollinger et al., *Proc. Natl. Acad. Sci. USA*, 90:6444-6448 (1993)); and using single-chain Fv (sFv) dimers (see,

e.g., Gruber et al., *J. Immunol.*, 152:5368 (1994)); and preparing trispecific antibodies as described, e.g., in Tutt et al. *J. Immunol.* 147: 60 (1991).

[00231] Engineered antibodies with three or more antigen binding sites, including for example, “Octopus antibodies”, or DVD-Ig are also included herein (see, e.g., WO 2001/77342 and WO 2008/024715). Other examples of multispecific antibodies with three or more antigen binding sites can be found in WO 2010/115589, WO 2010/112193, WO 2010/136172, WO 2010/145792, and WO 2013/026831. The bispecific antibody or antigen binding fragment thereof also includes a “Dual Acting FAb” or “DAF” comprising an antigen binding site that binds to KLK7 as well as another different antigen, such as KLK5 (see, e.g., US 2008/0069820 and WO 2015/095539).

[00232] Multi-specific antibodies may also be provided in an asymmetric form with a domain crossover in one or more binding arms of the same antigen specificity, i.e. by exchanging the VH/VL domains (see e.g., WO 2009/080252 and WO 2015/150447), the CH1/CL domains (see e.g., WO 2009/080253) or the complete Fab arms (see e.g., WO 2009/080251, WO 2016/016299, also see Schaefer et al, PNAS, 108 (2011) 1187-1191, and Klein et al., MAbs 8 (2016) 1010-20). In one aspect, the multispecific antibody comprises a cross-Fab fragment. The term “cross-Fab fragment” or “xFab fragment” or “crossover Fab fragment” refers to a Fab fragment, wherein either the variable regions or the constant regions of the heavy and light chain are exchanged. A cross-Fab fragment comprises a polypeptide chain composed of the light chain variable region (VL) and the heavy chain constant region 1 (CH1), and a polypeptide chain composed of the heavy chain variable region (VH) and the light chain constant region (CL). Asymmetrical Fab arms can also be engineered by introducing charged or non-charged amino acid mutations into domain interfaces to direct correct Fab pairing. See e.g., WO 2016/172485.

[00233] Various further molecular formats for multispecific antibodies are known in the art and are included herein (see e.g., Spiess et al., Mol Immunol 67 (2015) 95-106).

[00234] Examples of bispecific antibody formats that may be useful for this purpose include, but are not limited to, the so-called “BiTE” (bispecific T cell engager) molecules wherein two scFv molecules are fused by a flexible linker (see, e.g., WO 2004/106381, WO 2005/061547, WO 2007/042261, and WO 2008/119567, Nagorsen and Bäuerle, Exp Cell Res 317, 1255-1260 (2011)); diabodies (Holliger et al., Prot Eng 9, 299-305 (1996)) and derivatives thereof, such as tandem diabodies (“TandAb”; Kipriyanov et al., J Mol Biol 293, 41-56 (1999)); “DART” (dual affinity retargeting) molecules which are based on the diabody format but feature a C-terminal disulfide bridge for additional stabilization (Johnson et

al., J Mol Biol 399, 436-449 (2010)), and so-called triomabs, which are whole hybrid mouse/rat IgG molecules (reviewed in Seimetz et al., Cancer Treat Rev 36, 458-467 (2010)). Particular T cell bispecific antibody formats included herein are described in WO 2013/026833, WO 2013/026839, WO 2016/020309; Bacac et al., Oncoimmunology 5(8) (2016) e1203498.

7. *Antibody Variants*

[00235] In certain aspects, amino acid sequence variants of the antibodies provided herein are contemplated. For example, it may be desirable to alter the binding affinity and/or other biological properties of the antibody. Amino acid sequence variants of an antibody may be prepared by introducing appropriate modifications into the nucleotide sequence encoding the antibody, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution can be made to arrive at the final construct, provided that the final construct possesses the desired characteristics, e.g., antigen-binding.

a) Substitution, Insertion, and Deletion Variants

[00236] In certain aspects, antibody variants having one or more amino acid substitutions are provided. Sites of interest for substitutional mutagenesis include the CDRs and FRs. Conservative substitutions are shown in Table 1 under the heading of “preferred substitutions”. More substantial changes are provided in Table 1 under the heading of “exemplary substitutions”, and as further described below in reference to amino acid side chain classes. Amino acid substitutions may be introduced into an antibody of interest and the products screened for a desired activity, e.g., retained/improved antigen binding, decreased immunogenicity, or improved ADCC or CDC.

TABLE 1

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	Val; Leu; Ile	Val
Arg (R)	Lys; Gln; Asn	Lys
Asn (N)	Gln; His; Asp, Lys; Arg	Gln
Asp (D)	Glu; Asn	Glu
Cys (C)	Ser; Ala	Ser
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp; Gln	Asp

Original Residue	Exemplary Substitutions	Preferred Substitutions
Gly (G)	Ala	Ala
His (H)	Asn; Gln; Lys; Arg	Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Norleucine	Leu
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe	Ile
Lys (K)	Arg; Gln; Asn	Arg
Met (M)	Leu; Phe; Ile	Leu
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Val; Ser	Ser
Trp (W)	Tyr; Phe	Tyr
Tyr (Y)	Trp; Phe; Thr; Ser	Phe
Val (V)	Ile; Leu; Met; Phe; Ala; Norleucine	Leu

[00237] Amino acids may be grouped according to common side-chain properties:

- (1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile;
- (2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;
- (3) acidic: Asp, Glu;
- (4) basic: His, Lys, Arg;
- (5) residues that influence chain orientation: Gly, Pro;
- (6) aromatic: Trp, Tyr, Phe.

[00238] Non-conservative substitutions will entail exchanging a member of one of these classes for a member of another class.

[00239] One type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (e.g., a humanized or human antibody). Generally, the resulting variant(s) selected for further study will have modifications (e.g., improvements) in certain biological properties (e.g., increased affinity, reduced immunogenicity) relative to the parent antibody and/or will have substantially retained certain biological properties of the parent antibody. An exemplary substitutional variant is an affinity matured antibody, which may be conveniently generated, e.g., using phage display-based affinity maturation techniques such as those described herein. Briefly, one or more CDR residues are mutated and the variant antibodies displayed on phage and screened for a particular biological activity (e.g., binding affinity).

[00240] Alterations (e.g., substitutions) may be made in CDRs, e.g., to improve antibody affinity. Such alterations may be made in CDR “hotspots”, i.e., residues encoded by codons that undergo mutation at high frequency during the somatic maturation process (see, e.g., Chowdhury, *Methods Mol. Biol.* 207:179-196 (2008)), and/or residues that contact antigen, with the resulting variant VH or VL being tested for binding affinity. Affinity maturation by constructing and reselecting from secondary libraries has been described, e.g., in Hoogenboom et al. in *Methods in Molecular Biology* 178:1-37 (O’Brien et al., ed., Human Press, Totowa, NJ, (2001).) In some aspects of affinity maturation, diversity is introduced into the variable genes chosen for maturation by any of a variety of methods (e.g., error-prone PCR, chain shuffling, or oligonucleotide-directed mutagenesis). A secondary library is then created. The library is then screened to identify any antibody variants with the desired affinity. Another method to introduce diversity involves CDR-directed approaches, in which several CDR residues (e.g., 4-6 residues at a time) are randomized. CDR residues involved in antigen binding may be specifically identified, e.g., using alanine scanning mutagenesis or modeling. CDR-H3 and CDR-L3 in particular are often targeted.

[00241] In certain aspects, substitutions, insertions, or deletions may occur within one or more CDRs so long as such alterations do not substantially reduce the ability of the antibody to bind antigen. For example, conservative alterations (e.g., conservative substitutions as provided herein) that do not substantially reduce binding affinity may be made in the CDRs. Such alterations may, for example, be outside of antigen contacting residues in the CDRs. In certain variant VH and VL sequences provided above, each CDR either is unaltered, or contains no more than one, two or three amino acid substitutions.

[00242] A useful method for identification of residues or regions of an antibody that may be targeted for mutagenesis is called “alanine scanning mutagenesis” as described by Cunningham and Wells (1989) *Science*, 244:1081-1085. In this method, a residue or group of target residues (e.g., charged residues such as arg, asp, his, lys, and glu) are identified and replaced by a neutral or negatively charged amino acid (e.g., alanine or polyalanine) to determine whether the interaction of the antibody with antigen is affected. Further substitutions may be introduced at the amino acid locations demonstrating functional sensitivity to the initial substitutions. Alternatively, or additionally, a crystal structure of an antigen-antibody complex may be used to identify contact points between the antibody and antigen. Such contact residues and neighboring residues may be targeted or eliminated as candidates for substitution. Variants may be screened to determine whether they contain the desired properties.

[00243] Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody to an enzyme (e.g., for ADEPT (antibody directed enzyme prodrug therapy)) or a polypeptide which increases the serum half-life of the antibody.

b) Glycosylation variants

[00244] In certain aspects, an antibody provided herein is altered to increase or decrease the extent to which the antibody is glycosylated. Addition or deletion of glycosylation sites to an antibody may be conveniently accomplished by altering the amino acid sequence such that one or more glycosylation sites is created or removed.

[00245] Where the antibody comprises an Fc region, the oligosaccharide attached thereto may be altered. Native antibodies produced by mammalian cells typically comprise a branched, biantennary oligosaccharide that is generally attached by an N-linkage to Asn297 of the CH2 domain of the Fc region. See, e.g., Wright et al. *TIBTECH* 15:26-32 (1997). The oligosaccharide may include various carbohydrates, e.g., mannose, N-acetyl glucosamine (GlcNAc), galactose, and sialic acid, as well as a fucose attached to a GlcNAc in the “stem” of the biantennary oligosaccharide structure. In some aspects, modifications of the oligosaccharide in an antibody of the invention may be made in order to create antibody variants with certain improved properties.

[00246] In one aspect, antibody variants are provided having a non-fucosylated oligosaccharide, i.e. an oligosaccharide structure that lacks fucose attached (directly or indirectly) to an Fc region. Such non-fucosylated oligosaccharide (also referred to as “afucosylated” oligosaccharide) particularly is an N-linked oligosaccharide which lacks a fucose residue attached to the first GlcNAc in the stem of the biantennary oligosaccharide structure. In one aspect, antibody variants are provided having an increased proportion of non-fucosylated oligosaccharides in the Fc region as compared to a native or parent antibody. For example, the proportion of non-fucosylated oligosaccharides may be at least about 20%, at least about 40%, at least about 60%, at least about 80%, or even about 100% (i.e. no fucosylated oligosaccharides are present). The percentage of non-fucosylated oligosaccharides is the (average) amount of oligosaccharides lacking fucose residues, relative to the sum of all oligosaccharides attached to Asn 297 (e. g. complex, hybrid and high mannose structures) as measured by MALDI-TOF mass spectrometry, as described in WO 2006/082515, for example. Asn297 refers to the

asparagine residue located at about position 297 in the Fc region (EU numbering of Fc region residues); however, Asn297 may also be located about ± 3 amino acids upstream or downstream of position 297, i.e., between positions 294 and 300, due to minor sequence variations in antibodies. Such antibodies having an increased proportion of non-fucosylated oligosaccharides in the Fc region may have improved Fc γ RIIIa receptor binding and/or improved effector function, in particular improved ADCC function. See, e.g., US 2003/0157108; US 2004/0093621.

[00247] Examples of cell lines capable of producing antibodies with reduced fucosylation include Lec13 CHO cells deficient in protein fucosylation (Ripka et al. *Arch. Biochem. Biophys.* 249:533-545 (1986); US 2003/0157108; and WO 2004/056312, especially at Example 11), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene, *FUT8*, knockout CHO cells (see, e.g., Yamane-Ohnuki et al. *Biotech. Bioeng.* 87:614-622 (2004); Kanda, Y. et al., *Biotechnol. Bioeng.*, 94(4):680-688 (2006); and WO 2003/085107), or cells with reduced or abolished activity of a GDP-fucose synthesis or transporter protein (see, e.g., US2004259150, US2005031613, US2004132140, US2004110282).

[00248] In a further aspect, antibody variants are provided with bisected oligosaccharides, e.g., in which a biantennary oligosaccharide attached to the Fc region of the antibody is bisected by GlcNAc. Such antibody variants may have reduced fucosylation and/or improved ADCC function as described above. Examples of such antibody variants are described, e.g., in Umana et al., *Nat Biotechnol* 17, 176-180 (1999); Ferrara et al., *Biotechnol Bioeng* 93, 851-861 (2006); WO 99/54342; WO 2004/065540, WO 2003/011878.

[00249] Antibody variants with at least one galactose residue in the oligosaccharide attached to the Fc region are also provided. Such antibody variants may have improved CDC function. Such antibody variants are described, e.g., in WO 1997/30087; WO 1998/58964; and WO 1999/22764.

c) **Fc region variants**

[00250] In certain aspects, one or more amino acid modifications may be introduced into the Fc region of an antibody provided herein, thereby generating an Fc region variant. The Fc region variant may comprise a human Fc region sequence (e.g., a human IgG₁, IgG₂, IgG₃ or IgG₄ Fc region) comprising an amino acid modification (e.g., a substitution) at one or more amino acid positions.

[00251] In certain aspects, the invention contemplates an antibody variant that possesses some but not all effector functions, which make it a desirable candidate for applications in which the half-life of the antibody *in vivo* is important yet certain effector

functions (such as complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC)) are unnecessary or deleterious. *In vitro* and/or *in vivo* cytotoxicity assays can be conducted to confirm the reduction/depletion of CDC and/or ADCC activities. For example, Fc receptor (FcR) binding assays can be conducted to ensure that the antibody lacks FcγR binding (hence likely lacking ADCC activity), but retains FcRn binding ability. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FcγRIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-492 (1991). Non-limiting examples of *in vitro* assays to assess ADCC activity of a molecule of interest is described in U.S. Patent No. 5,500,362 (see, e.g., Hellstrom, I. et al. *Proc. Nat'l Acad. Sci. USA* 83:7059-7063 (1986)) and Hellstrom, I et al., *Proc. Nat'l Acad. Sci. USA* 82:1499-1502 (1985); 5,821,337 (see Bruggemann, M. et al., *J. Exp. Med.* 166:1351-1361 (1987)). Alternatively, non-radioactive assays methods may be employed (see, for example, ACTITM non-radioactive cytotoxicity assay for flow cytometry (CellTechnology, Inc. Mountain View, CA; and CytoTox 96® non-radioactive cytotoxicity assay (Promega, Madison, WI). Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, e.g., in a animal model such as that disclosed in Clynes et al. *Proc. Nat'l Acad. Sci. USA* 95:652-656 (1998). C1q binding assays may also be carried out to confirm that the antibody is unable to bind C1q and hence lacks CDC activity. See, e.g., C1q and C3c binding ELISA in WO 2006/029879 and WO 2005/100402. To assess complement activation, a CDC assay may be performed (see, for example, Gazzano-Santoro *et al.*, *J. Immunol. Methods* 202:163 (1996); Cragg, M.S. et al., *Blood* 101:1045-1052 (2003); and Cragg, M.S. and M.J. Glennie, *Blood* 103:2738-2743 (2004)). FcRn binding and *in vivo* clearance/half life determinations can also be performed using methods known in the art (see, e.g., Petkova, S.B. et al., *Int'l. Immunol.* 18(12):1759-1769 (2006); WO 2013/120929 A1).

[00252] Antibodies with reduced effector function include those with substitution of one or more of Fc region residues 238, 265, 269, 270, 297, 327 and 329 (U.S. Patent No. 6,737,056). Such Fc mutants include Fc mutants with substitutions at two or more of amino acid positions 265, 269, 270, 297 and 327, including the so-called "DANA" Fc mutant with substitution of residues 265 and 297 to alanine (US Patent No. 7,332,581).

[00253] Certain antibody variants with improved or diminished binding to FcRs are described. (See, e.g., U.S. Patent No. 6,737,056; WO 2004/056312, and Shields et al., *J. Biol. Chem.* 9(2): 6591-6604 (2001).)

[00254] In certain aspects, an antibody variant comprises an Fc region with one or more amino acid substitutions which improve ADCC, e.g., substitutions at positions 298, 333, and/or 334 of the Fc region (EU numbering of residues).

[00255] In certain aspects, an antibody variant comprises an Fc region with one or more amino acid substitutions which diminish FcγR binding, e.g., substitutions at positions 234 and 235 of the Fc region (EU numbering of residues). In one aspect, the substitutions are L234A and L235A (LALA). In certain aspects, the antibody variant further comprises D265A and/or P329G in an Fc region derived from a human IgG₁ Fc region. In one aspect, the substitutions are L234A, L235A and P329G (LALA-PG) in an Fc region derived from a human IgG₁ Fc region. (See, e.g., WO 2012/130831). In another aspect, the substitutions are L234A, L235A and D265A (LALA-DA) in an Fc region derived from a human IgG₁ Fc region.

[00256] In some aspects, alterations are made in the Fc region that result in altered (*i.e.*, either improved or diminished) C1q binding and/or Complement Dependent Cytotoxicity (CDC), e.g., as described in US Patent No. 6,194,551, WO 99/51642, and Idusogie et al. *J. Immunol.* 164: 4178-4184 (2000).

[00257] Antibodies with increased half-lives and improved binding to the neonatal Fc receptor (FcRn), which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., *J. Immunol.* 117:587 (1976) and Kim et al., *J. Immunol.* 24:249 (1994)), are described in US2005/0014934 (Hinton et al.). Those antibodies comprise an Fc region with one or more substitutions therein which improve binding of the Fc region to FcRn. Such Fc variants include those with substitutions at one or more of Fc region residues: 238, 252, 254, 256, 265, 272, 286, 303, 305, 307, 311, 312, 317, 340, 356, 360, 362, 376, 378, 380, 382, 413, 424, 428 or 434, e.g., substitution of Fc region residue 434 (See, e.g., US Patent No. 7,371,826; Dall'Acqua, W.F., et al. *J. Biol. Chem.* 281 (2006) 23514-23524). In some embodiments, an antibody provided herein comprises substitutions M428L and/or N434S, such as M428L and N434S ("LS").

[00258] Fc region residues critical to the mouse Fc-mouse FcRn interaction have been identified by site-directed mutagenesis (see e.g. Dall'Acqua, W.F., et al. *J. Immunol* 169 (2002) 5171-5180). Residues I253, H310, H433, N434, and H435 (EU index numbering) are involved in the interaction (Medesan, C., et al., *Eur. J. Immunol.* 26 (1996) 2533; Firan, M., et al., *Int. Immunol.* 13 (2001) 993; Kim, J.K., et al., *Eur. J. Immunol.* 24 (1994) 542). Residues I253, H310, and H435 were found to be critical for the interaction of human Fc with murine FcRn (Kim, J.K., et al., *Eur. J. Immunol.* 29 (1999) 2819). Studies of the human Fc-human FcRn complex have shown that residues I253, S254, H435, and Y436 are crucial for the interaction (Firan, M., et al., *Int. Immunol.* 13 (2001) 993; Shields, R.L., et al., *J. Biol. Chem.* 276 (2001)

6591-6604). In Yeung, Y.A., et al. (J. Immunol. 182 (2009) 7667-7671) various mutants of residues 248 to 259 and 301 to 317 and 376 to 382 and 424 to 437 have been reported and examined.

[00259] In certain aspects, an antibody variant comprises an Fc region with one or more amino acid substitutions, which reduce FcRn binding, e.g., substitutions at positions 253, and/or 310, and/or 435 of the Fc-region (EU numbering of residues). In certain aspects, the antibody variant comprises an Fc region with the amino acid substitutions at positions 253, 310 and 435. In one aspect, the substitutions are I253A, H310A and H435A in an Fc region derived from a human IgG1 Fc-region. See, e.g., Grevys, A., et al., J. Immunol. 194 (2015) 5497-5508.

[00260] In certain aspects, an antibody variant comprises an Fc region with one or more amino acid substitutions, which reduce FcRn binding, e.g., substitutions at positions 310, and/or 433, and/or 436 of the Fc region (EU numbering of residues). In certain aspects, the antibody variant comprises an Fc region with the amino acid substitutions at positions 310, 433 and 436. In one aspect, the substitutions are H310A, H433A and Y436A in an Fc region derived from a human IgG1 Fc-region. (See, e.g., WO 2014/177460 A1).

[00261] In certain aspects, an antibody variant comprises an Fc region with one or more amino acid substitutions which increase FcRn binding, e.g., substitutions at positions 252, and/or 254, and/or 256 of the Fc region (EU numbering of residues). In certain aspects, the antibody variant comprises an Fc region with amino acid substitutions at positions 252, 254, and 256. In one aspect, the substitutions are M252Y, S254T and T256E in an Fc region derived from a human IgG1 Fc-region. See also Duncan & Winter, *Nature* 322:738-40 (1988); U.S. Patent No. 5,648,260; U.S. Patent No. 5,624,821; and WO 94/29351 concerning other examples of Fc region variants.

[00262] The C-terminus of the heavy chain of the antibody as reported herein can be a complete C-terminus ending with the amino acid residues PGK. The C-terminus of the heavy chain can be a shortened C-terminus in which one or two of the C terminal amino acid residues have been removed. In one preferred aspect, the C-terminus of the heavy chain is a shortened C-terminus ending PG. In one aspect of all aspects as reported herein, an antibody comprising a heavy chain including a C-terminal CH3 domain as specified herein, comprises the C-terminal glycine-lysine dipeptide (G446 and K447, EU index numbering of amino acid positions). In one aspect of all aspects as reported herein, an antibody comprising a heavy chain including a C-terminal CH3 domain, as specified herein, comprises a C-terminal glycine residue (G446, EU index numbering of amino acid positions).

d) Cysteine engineered antibody variants

[00263] In certain aspects, it may be desirable to create cysteine engineered antibodies, e.g., THIOMAB™ antibodies, in which one or more residues of an antibody are substituted with cysteine residues. In particular aspects, the substituted residues occur at accessible sites of the antibody. By substituting those residues with cysteine, reactive thiol groups are thereby positioned at accessible sites of the antibody and may be used to conjugate the antibody to other moieties, such as drug moieties or linker-drug moieties, to create an immunoconjugate, as described further herein. Cysteine engineered antibodies may be generated as described, e.g., in U.S. Patent No. 7,521,541, 8,30,930, 7,855,275, 9,000,130, or WO 2016040856.

e) Antibody Derivatives

[00264] In certain aspects, an antibody provided herein may be further modified to contain additional nonproteinaceous moieties that are known in the art and readily available. The moieties suitable for derivatization of the antibody include but are not limited to water soluble polymers. Non-limiting examples of water soluble polymers include, but are not limited to, polyethylene glycol (PEG), copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1, 3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random copolymers), and dextran or poly(n-vinyl pyrrolidone)polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols (e.g., glycerol), polyvinyl alcohol, and mixtures thereof. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water. The polymer may be of any molecular weight, and may be branched or unbranched. The number of polymers attached to the antibody may vary, and if more than one polymer is attached, they can be the same or different molecules. In general, the number and/or type of polymers used for derivatization can be determined based on considerations including, but not limited to, the particular properties or functions of the antibody to be improved, whether the antibody derivative will be used in a therapy under defined conditions, etc.

8. Immunoconjugates

[00265] The invention also provides immunoconjugates comprising an antibody herein conjugated (chemically bonded) to one or more therapeutic agents such as cytotoxic agents, chemotherapeutic agents, drugs, growth inhibitory agents, toxins (e.g., protein toxins,

enzymatically active toxins of bacterial, fungal, plant, or animal origin, or fragments thereof), or radioactive isotopes.

[00266] In one aspect, an immunoconjugate is an antibody-drug conjugate (ADC) in which an antibody is conjugated to one or more of the therapeutic agents mentioned above. The antibody is typically connected to one or more of the therapeutic agents using linkers. An overview of ADC technology including examples of therapeutic agents and drugs and linkers is set forth in *Pharmacol Review* 68:3-19 (2016).

[00267] In another aspect, an immunoconjugate comprises an antibody as described herein conjugated to an enzymatically active toxin or fragment thereof, including but not limited to diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes.

[00268] In another aspect, an immunoconjugate comprises an antibody as described herein conjugated to a radioactive atom to form a radioconjugate. A variety of radioactive isotopes are available for the production of radioconjugates. Examples include At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³², Pb²¹² and radioactive isotopes of Lu. When the radioconjugate is used for detection, it may comprise a radioactive atom for scintigraphic studies, for example tc99m or I123, or a spin label for nuclear magnetic resonance (NMR) imaging (also known as magnetic resonance imaging, mri), such as iodine-123 again, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese or iron.

[00269] Conjugates of an antibody and cytotoxic agent may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCl), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., *Science* 238:1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See

WO 94/11026. The linker may be a “cleavable linker” facilitating release of a cytotoxic drug in the cell. For example, an acid-labile linker, peptidase-sensitive linker, photolabile linker, dimethyl linker or disulfide-containing linker (Chari et al., *Cancer Res.* 52:127-131 (1992); U.S. Patent No. 5,208,020) may be used.

[00270] The immunoconjugates or ADCs herein expressly contemplate, but are not limited to such conjugates prepared with cross-linker reagents including, but not limited to, BMPS, EMCS, GMBS, HBVS, LC-SMCC, MBS, MPBH, SBAP, SIA, SIAB, SMCC, SMPB, SMPH, sulfo-EMCS, sulfo-GMBS, sulfo-KMUS, sulfo-MBS, sulfo-SIAB, sulfo-SMCC, and sulfo-SMPB, and SVSB (succinimidyl-(4-vinylsulfone)benzoate) which are commercially available (e.g., from Pierce Biotechnology, Inc., Rockford, IL., U.S.A).

D. Recombinant Methods and Compositions

[00271] Antibodies may be produced using recombinant methods and compositions, e.g., as described in US 4,816,567. For these methods one or more isolated nucleic acid(s) encoding an antibody are provided.

[00272] In case of a native antibody or native antibody fragment two nucleic acids are required, one for the light chain or a fragment thereof and one for the heavy chain or a fragment thereof. Such nucleic acid(s) encode an amino acid sequence comprising the VL and/or an amino acid sequence comprising the VH of the antibody (e.g., the light and/or heavy chain(s) of the antibody). These nucleic acids can be on the same expression vector or on different expression vectors.

[00273] In case of a bispecific antibody with heterodimeric heavy chains four nucleic acids are required, one for the first light chain, one for the first heavy chain comprising the first heteromonomeric Fc-region polypeptide, one for the second light chain, and one for the second heavy chain comprising the second heteromonomeric Fc-region polypeptide. The four nucleic acids can be comprised in one or more nucleic acid molecules or expression vectors. Such nucleic acid(s) encode an amino acid sequence comprising the first VL and/or an amino acid sequence comprising the first VH including the first heteromonomeric Fc-region and/or an amino acid sequence comprising the second VL and/or an amino acid sequence comprising the second VH including the second heteromonomeric Fc-region of the antibody (e.g., the first and/or second light and/or the first and/or second heavy chains of the antibody). These nucleic acids can be on the same expression vector or on different expression vectors, normally these nucleic acids are located on two or three expression vectors, i.e. one vector can comprise more than one of these nucleic acids. Examples of these bispecific antibodies are CrossMabs (see,

e.g., Schaefer, W. et al, PNAS, 108 (2011) 11187-1191). For example, one of the heteromonomeric heavy chain comprises the so-called “knob mutations” (T366W and optionally one of S354C or Y349C) and the other comprises the so-called “hole mutations” (T366S, L368A and Y407V and optionally Y349C or S354C) (see, e.g., Carter, P. et al., Immunotechnol. 2 (1996) 73) according to EU index numbering.

[00274] In one aspect, isolated nucleic acids encoding an antibody as used in the methods as reported herein are provided.

[00275] In one aspect, a method of making an antibody is provided, wherein the method comprises culturing a host cell comprising nucleic acid(s) encoding the antibody, as provided above, under conditions suitable for expression of the antibody, and optionally recovering the antibody from the host cell (or host cell culture medium).

[00276] For recombinant production of an antibody, nucleic acids encoding the antibody, e.g., as described above, are isolated and inserted into one or more vectors for further cloning and/or expression in a host cell. Such nucleic acids may be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody) or produced by recombinant methods or obtained by chemical synthesis.

[00277] Suitable host cells for cloning or expression of antibody-encoding vectors include prokaryotic or eukaryotic cells described herein. For example, antibodies may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed. For expression of antibody fragments and polypeptides in bacteria, see, e.g., US 5,648,237, US 5,789,199, and US 5,840,523. (See also Charlton, K.A., In: Methods in Molecular Biology, Vol. 248, Lo, B.K.C. (ed.), Humana Press, Totowa, NJ (2003), pp. 245-254, describing expression of antibody fragments in *E. coli*.) After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

[00278] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for antibody-encoding vectors, including fungi and yeast strains whose glycosylation pathways have been “humanized”, resulting in the production of an antibody with a partially or fully human glycosylation pattern. See Gerngross, T.U., Nat. Biotech. 22 (2004) 1409-1414; and Li, H. et al., Nat. Biotech. 24 (2006) 210-215.

[00279] Suitable host cells for the expression of (glycosylated) antibody are also derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which

may be used in conjunction with insect cells, particularly for transfection of *Spodoptera frugiperda* cells.

[00280] Plant cell cultures can also be utilized as hosts. See, e.g., US 5,959,177, US 6,040,498, US 6,420,548, US 7,125,978, and US 6,417,429 (describing PLANTIBODIESTM technology for producing antibodies in transgenic plants).

[00281] Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293T cells as described, e.g., in Graham, F.L. et al., *J. Gen Virol.* 36 (1977) 59-74); baby hamster kidney cells (BHK); mouse sertoli cells (TM4 cells as described, e.g., in Mather, J.P., *Biol. Reprod.* 23 (1980) 243-252); monkey kidney cells (CV1); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK); buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TRI cells (as described, e.g., in Mather, J.P. et al., *Annals N.Y. Acad. Sci.* 383 (1982) 44-68); MRC 5 cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR-CHO cells (Urlaub, G. et al., *Proc. Natl. Acad. Sci. USA* 77 (1980) 4216-4220); and myeloma cell lines such as Y0, NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production, see, e.g., Yazaki, P. and Wu, A.M., *Methods in Molecular Biology*, Vol. 248, Lo, B.K.C. (ed.), Humana Press, Totowa, NJ (2004), pp. 255-268.

[00282] In one aspect, the host cell is eukaryotic, e.g., a Chinese Hamster Ovary (CHO) cell or lymphoid cell (e.g., Y0, NS0, Sp20 cell).

E. Assays

[00283] Anti-KLK7 antibodies and anti-KLK5 provided herein may be identified, screened for, or characterized for their physical/chemical properties and/or biological activities by various assays known in the art.

1. Binding assays and other assays

[00284] In one aspect, an antibody of the invention is tested for its antigen binding activity, e.g., by known methods such as ELISA, Western blot, etc.

[00285] In another aspect, competition assays may be used to identify an antibody that competes with an antibody provided herein, such as hu.1411c-H11L2, for binding to KLK7. In certain aspects, such a competing antibody binds to the same epitope (e.g., a linear or a

conformational epitope) that is bound by hu.1411c-H11L2. In certain aspects, such a competing antibody binds to the same epitope (e.g., a linear or a conformational epitope) that is bound by hu.1411c-H11L2. In some embodiments, competition assays may be used to identify an antibody that competes with an antibody provided herein, such as hu.10C5-H28L5 or hu.9H5-H14L4, for binding to KLK5. In certain aspects, such a competing antibody binds to the same epitope (e.g., a linear or a conformational epitope) that is bound by hu.10C5-H28L5 or hu.9H5-H14L4. Detailed exemplary methods for mapping an epitope to which an antibody binds are provided in Morris (1996) "Epitope Mapping Protocols", in *Methods in Molecular Biology* vol. 66 (Humana Press, Totowa, NJ).

[00286] In an exemplary competition assay, immobilized antigen (such as KLK5 or KLK7) is incubated in a solution comprising a first labeled antibody that binds to the antigen (e.g., hu.1411c-H11L2, hu.10C5-H28L5 or hu.9H5-H14L4) and a second unlabeled antibody that is being tested for its ability to compete with the first antibody for binding to the antigen. The second antibody may be present in a hybridoma supernatant. As a control, immobilized antigen is incubated in a solution comprising the first labeled antibody but not the second unlabeled antibody. After incubation under conditions permissive for binding of the first antibody to antigen, excess unbound antibody is removed, and the amount of label associated with immobilized antigen is measured. If the amount of label associated with immobilized antigen is substantially reduced in the test sample relative to the control sample, then that indicates that the second antibody is competing with the first antibody for binding to antigen. See Harlow and Lane (1988) *Antibodies: A Laboratory Manual* ch.14 (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY).

2. Activity assays

[00287] KLK7 is a chymotrypsin-like serine protease. In some embodiments, KLK7 cleaves polypeptides after aromatic and/or hydrophobic amino acids, such as after tyrosine, phenylalanine, and/or leucine. In one aspect, assays are provided for identifying anti-KLK7 antibodies that inhibit human KLK7 activity. Biological activity may include, e.g., KLK7 protease activity. Antibodies having such biological activity *in vivo* and/or *in vitro* are also provided.

[00288] In certain aspects, an antibody of the invention is tested for such biological activity. Assays for determining KLK7 protease activity are known in the art, and typically include incubating KLK7 in the presence of substrate and a test molecule (such as an anti-KLK7 antibody). A nonlimiting assay for testing whether an anti-KLK7 antibody (or a

multispecific antibody comprising an anti-KLK7 binding arm) inhibits KLK7 protease activity follows: A KLK7 direct functional assay may be performed at room temperature in a 384-well plate at a final reaction volume of 15 μ L. Inhibitor samples are diluted to 3x final concentration in assay buffer (75 mM Tris, pH 8.0, 150 mM NaCl, 0.01% Tween 20). Inhibitor (e.g., anti-KLK7 antibody) or control samples (5 μ L) are added to the plate, followed by 5 μ L human KLK7 (SEQ ID NO: 4) in assay buffer at a final concentration of 0.5 nM. After 40 min, 5 μ L Mca-RPKPVE-Nval-WRK(Dnp) (SEQ ID NO: 121; Bachem M-2110, 4.3 mM stock solution in DMSO) at a final concentration of 10 μ M in assay buffer is added. After addition of substrate, the plate is read in PHERAstar® microplate reader (BMG Labtech) using optic module FI 320 405 with the gain set to 0%. Measurements are taken every 100 s for ~1.5 h. Reaction rates (expressed as RFU/s) are calculated by linear regression in the linear range. Reaction rates may be normalized to the values of 0% and 100% activity controls, and fit with a 4-parameter equation to calculate IC₅₀ values. For bivalent inhibitors, the raw IC₅₀ may be multiplied by two.

[00289] KLK5 is a trypsin-like serine protease. In one aspect, assays are provided for identifying anti-KLK5 antibodies that inhibit human KLK5 activity. Biological activity may include, e.g., KLK5 protease activity. In one embodiment, the anti-KLK5 antibodies inhibit the serine protease activity of KLK5. Antibodies having such biological activity *in vivo* and/or *in vitro* are also provided.

[00290] In certain aspects, an antibody of the invention is tested for such biological activity. Assays for determining KLK5 protease activity are known in the art, and may include, for example, incubating KLK5 in the presence of substrate and a test molecule (such as an anti-KLK5 antibody). In some embodiments, the biological activity of an anti-KLK5 antibody is tested by one or more methods selected from a direct activity assay, fluorescent peptide assay, an LC/MS assay, and a Ki(app) assay. In some embodiments, the biological activity is measured by one or more methods selected from a recombinant KLK5 direct activity assay, coupled pro-KLK1 fluorescent peptide assay, a coupled pro-KLK7 fluorescent peptide assay, a pro-KLK1 LC/MS assay, a pro-KLK7 LC/MS assay, and a Ki(app) assay. In some embodiments, the IC₅₀ values are measured by the assays described herein. In some embodiments, an anti-KLK5 antibody of the invention inhibits the biological activity of KLK5 by at least 50% as measured by one or more methods selected from a recombinant KLK5 direct activity assay, coupled pro-KLK1 fluorescent peptide assay, a coupled pro-KLK7 fluorescent peptide assay, a pro-KLK1 LC/MS assay, a pro-KLK7 LC/MS assay, and a Ki(app)

assay. In some embodiments, the biological activity is the serine protease activity of KLK5. In some embodiments, the IC₅₀ values are measured by the assays described herein.

[00291] A nonlimiting assay for testing whether an anti-KLK5 antibody (or a multispecific antibody comprising an anti-KLK5 binding arm) inhibits KLK5 protease activity follows: A KLK5 direct functional assay may be performed at room temperature in a 384-well plate at a final reaction volume of 15 μ L. Inhibitor samples are diluted to 3x final concentration in assay buffer (75 mM Tris, pH 8.0, 150 mM NaCl, 0.01% Tween 20). Inhibitor (e.g., anti-KLK5 antibody) or control samples (5 μ L) are added to the plate, followed by 5 μ L human KLK5 (SEQ ID NO: 2) in assay buffer at a final concentration of 0.5 nM. After 40 min, 5 μ L Boc-Val-Pro-Arg-AMC (Bachem I-1120, 31.3 mM stock solution in water) at a final concentration of 50 μ M in assay buffer is added. After addition of substrate, the plate is read in PHERAstar[®] microplate reader (BMG Labtech) using optic module FI 320 405 with the gain set to 0%. Measurements are taken every 100 s for ~1.5 h. Reaction rates (expressed as RFU/s) are calculated by linear regression in the linear range. Reaction rates may be normalized to the values of 0% and 100% activity controls, and fit with a 4-parameter equation to calculate IC₅₀ values. For bivalent inhibitors, the raw IC₅₀ may be multiplied by two.

F. Methods and Compositions for Diagnostics and Detection

[00292] In certain aspects, any of the antibodies provided herein is useful for detecting the presence of antigen in a biological sample. The term “detecting” as used herein encompasses quantitative or qualitative detection. In certain aspects, a biological sample comprises a cell or tissue, such as a skin sample.

[00293] In one aspect, an antibody for use in a method of diagnosis or detection is provided. In a further aspect, a method of detecting the presence of KLK5 and/or KLK7 in a biological sample is provided. In certain aspects, the method comprises contacting the biological sample with an anti-KLK5 antibody or anti-KLK7 antibody as described herein under conditions permissive for binding of the antibody to its antigen, and detecting whether a complex is formed between the antibody and the antigen. Such method may be an *in vitro* or *in vivo* method. In some embodiments, methods of selecting patients for treatment with an antibody provided herein comprise determining KLK5 and/or KLK7 expression in a sample from the patient.

[00294] In certain aspects, labeled anti-KLK7 antibodies are provided. In certain aspects, labeled anti-KLK5 antibodies are provided. In certain aspects, labeled multispecific anti-KLK5/KLK7 antibodies are provided. Labels include, but are not limited to, labels or

moieties that are detected directly (such as fluorescent, chromophoric, electron-dense, chemiluminescent, and radioactive labels), as well as moieties, such as enzymes or ligands, that are detected indirectly, e.g., through an enzymatic reaction or molecular interaction. Exemplary labels include, but are not limited to, the radioisotopes ^{32}P , ^{14}C , ^{125}I , ^3H , and ^{131}I , fluorophores such as rare earth chelates or fluorescein and its derivatives, rhodamine and its derivatives, dansyl, umbelliferone, luciferases, e.g., firefly luciferase and bacterial luciferase (U.S. Patent No. 4,737,456), luciferin, 2,3-dihydrophthalazinediones, horseradish peroxidase (HRP), alkaline phosphatase, β -galactosidase, glucoamylase, lysozyme, saccharide oxidases, e.g., glucose oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase, heterocyclic oxidases such as uricase and xanthine oxidase, coupled with an enzyme that employs hydrogen peroxide to oxidize a dye precursor such as HRP, lactoperoxidase, or microperoxidase, biotin/avidin, spin labels, bacteriophage labels, stable free radicals, and the like.

G. Pharmaceutical Compositions

[00295] In a further aspect, provided are pharmaceutical compositions comprising any of the antibodies provided herein, e.g., for use in any of the below therapeutic methods. In one aspect, a pharmaceutical composition comprises any of the antibodies provided herein and a pharmaceutically acceptable carrier. In another aspect, a pharmaceutical composition comprises any of the antibodies provided herein and at least one additional therapeutic agent, e.g., as described below.

[00296] Pharmaceutical compositions of an anti-KLK7 antibody and/or anti-KLK5 antibody and/or anti-KLK5/KLK7 antibody as described herein are prepared by mixing such antibody or antibodies having the desired degree of purity with one or more optional pharmaceutically acceptable carriers (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized compositions or aqueous solutions. Pharmaceutically acceptable carriers are generally nontoxic to recipients at the dosages and concentrations employed, and include, but are not limited to: buffers such as histidine, phosphate, citrate, acetate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride; benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine;

monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as polyethylene glycol (PEG). Exemplary pharmaceutically acceptable carriers herein further include interstitial drug dispersion agents such as soluble neutral-active hyaluronidase glycoproteins (sHASEGP), for example, human soluble PH-20 hyaluronidase glycoproteins, such as rHuPH20 (HYLENEX[®], Halozyme, Inc.). Certain exemplary sHASEGPs and methods of use, including rHuPH20, are described in US Patent Publication Nos. 2005/0260186 and 2006/0104968. In one aspect, a sHASEGP is combined with one or more additional glycosaminoglycanases such as chondroitinases.

[00297] In some embodiments, an antibody or antibodies provided herein are formulated for subcutaneous administration. In some embodiments, an antibody or antibodies provided herein are formulated for intravenous administration. In some embodiments, an antibody or antibodies provided herein are formulated for topical administration.

[00298] Exemplary lyophilized antibody compositions are described in US Patent No. 6,267,958. Aqueous antibody compositions include those described in US Patent No. 6,171,586 and WO 2006/044908, the latter compositions including a histidine-acetate buffer.

[00299] The pharmaceutical composition herein may also contain more than one active ingredients as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. For example, in some embodiments, a pharmaceutical composition comprises an anti-KLK7 antibody in combination with an anti-KLK5 antibody. Such active ingredients are suitably present in combination in amounts that are effective for the purpose intended.

[00300] Active ingredients may be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980).

[00301] Pharmaceutical compositions for sustained release may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, or microcapsules.

[00302] The pharmaceutical compositions to be used for *in vivo* administration are generally sterile. Sterility may be readily accomplished, e.g., by filtration through sterile filtration membranes.

H. Therapeutic Methods and Routes of Administration

[00303] Any of the antibodies provided herein may be used in therapeutic methods, alone or in combination.

[00304] In one aspect, an anti-KLK7 antibody for use as a medicament is provided. In one aspect, an anti-KLK5 antibody for use as a medicament is provided. In one aspect, a multispecific anti-KLK5/KLK7 antibody for use as a medicament is provided. In one aspect, a combination of an anti-KLK7 antibody and an anti-KLK5 antibody for use as a medicament is provided. In further aspects, such antibodies for use in treating Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and/or rosacea are provided. In certain aspects, an anti-KLK7 antibody for use in a method of treatment is provided. In certain aspects, an anti-KLK5 antibody for use in a method of treatment is provided. In certain aspects, a multispecific anti-KLK5/KLK7 antibody for use in a method of treatment is provided. In certain aspects, a combination of an anti-KLK7 antibody and anti-KLK5 antibody for use in a method of treatment is provided. In certain aspects, the invention provides such antibodies for use in a method of treating an individual having Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and/or rosacea comprising administering to the individual an effective amount of the antibody or antibodies. In one such aspect, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent (e.g., one, two, three, four, five, or six additional therapeutic agents), e.g., as described below.

[00305] In further aspects, the invention provides an anti-KLK7 antibody and/or an anti-KLK5 antibody and/or a multispecific anti-KLK5/KLK5 antibody for use in reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines. In certain aspects, the invention provides an anti-KLK7 antibody and/or an anti-KLK5 antibody and/or a multispecific anti-KLK5/KLK5 antibody for use in a method of reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines in an individual comprising administering to the individual an effective amount of the antibody or antibodies to reduce

epithelium inflammation, reduce epithelium permeability, reduce transepidermal water loss, reduce dermal infiltrates, reduce parakeratosis, and/or restore the epithelial barrier. An “individual” according to any of the above aspects is preferably a human.

[00306] In a further aspect, the invention provides for the use of an anti-KLK7 antibody and/or an anti-KLK5 antibody and/or a multispecific anti-KLK5/KLK5 antibody in the manufacture or preparation of a medicament. In one aspect, the medicament is for treatment of Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and/or rosacea. In a further aspect, the medicament is for use in a method of treating Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and/or rosacea comprising administering to an individual having Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and/or rosacea an effective amount of the medicament. In one such aspect, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, e.g., as described below. In a further aspect, the medicament is for reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines. In a further aspect, the medicament is for use in a method of reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines in an individual comprising administering to the individual an effective amount of the medicament to reduce epithelium inflammation, reduce epithelium permeability, reduce transepidermal water loss, reduce dermal infiltrates, reduce parakeratosis, and/or restore the epithelial barrier. An “individual” according to any of the above aspects may be a human.

[00307] In a further aspect, the invention provides a method for treating Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and/or rosacea. In one aspect, the method comprises administering to an individual having Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and/or rosacea an effective amount of an anti-KLK7 antibody and/or an anti-KLK5 antibody and/or a multispecific anti-KLK5/KLK5 antibody. In one such aspect, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, as described below.

[00308] In some embodiments, methods of ameliorating skin rash and/or scaling in an individual with Netherton Syndrome are provided, comprising administering to the individual an effective amount of an anti-KLK7 antibody and/or an anti-KLK5 antibody and/or a multispecific anti-KLK5/KLK5 antibody.

[00309] An “individual” according to any of the above aspects may be a human.

[00310] In a further aspect, the invention provides a method for reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines in an individual. In one aspect, the method comprises administering to the individual an effective amount of an anti-KLK7 antibody and/or an anti-KLK5 antibody and/or a multispecific anti-KLK5/KLK5 antibody to reduce epithelium inflammation, reduce epithelium permeability, reduce transepidermal water loss, reduce dermal infiltrates, reduce parakeratosis, restore the epithelial barrier, and/or reduce skin inflammatory cytokines. Nonlimiting exemplary skin inflammatory cytokines include IL-8, TNF α , IL-6, IL-4, and G-CSF. In one aspect, an “individual” is a human.

[00311] In a further aspect, the invention provides pharmaceutical compositions comprising any of the antibodies provided herein, e.g., for use in any of the above therapeutic methods. In one aspect, a pharmaceutical composition comprises any of the antibodies provided herein and a pharmaceutically acceptable carrier. In another aspect, a pharmaceutical composition comprises any of the antibodies provided herein and at least one additional therapeutic agent, e.g., as described below.

[00312] Antibodies of the invention can be administered alone or used in a combination therapy. For instance, the combination therapy includes administering an antibody of the invention and administering at least one additional therapeutic agent (e.g. one, two, three, four, five, or six additional therapeutic agents). In certain aspects, the combination therapy comprises administering an antibody of the invention and administering at least one additional therapeutic agent, such as an anti-inflammatory agent. In some embodiments, the anti-inflammatory agent is administered orally. In some embodiments, the anti-inflammatory agent is administered topically. Anti-inflammatory agents include, but are not limited to, low-dose antibiotics, steroids, corticosteroids, tacrolimus, anti-IL4R antibodies, TNF inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, and IL-4 receptor inhibitors. Nonlimiting exemplary anti-inflammatory agents include doxycycline, methotrexate, prednisone, cyclosporine, mycophenolate mofetil, dupilumab, certolizumab pegol, etanercept, adalimumab, infliximab, golimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, abatacept, tidrakizumab-asmn, risankisumab-rzaa, and guselkumab.

[00313] In some embodiments, for example, in the treatment of rosacea, the additional therapeutic is doxycycline administered orally. In some embodiments, for example in the treatment of atopic dermatitis, the additional therapeutic is dupilumab administered

subcutaneously; and/or a steroid administered topically. In some embodiments, for example, in the treatment of rosacea, the additional therapeutic is selected from a steroid administered topically; methotrexate administered orally; cyclosporine administered orally; and a TNF inhibitor, typically administered subcutaneously.

[00314] Such combination therapies noted above encompass combined administration (where two or more therapeutic agents are included in the same or separate pharmaceutical compositions), and separate administration, in which case, administration of the antibody of the invention can occur prior to, simultaneously, and/or following, administration of the additional therapeutic agent or agents. In one aspect, administration of the antibody or antibodies of the invention and administration of an additional therapeutic agent occur within about one month, or within about one, two or three weeks, or within about one, two, three, four, five, or six days, of each other. In one aspect, the antibody and additional therapeutic agent are administered to the patient on Day 1 of the treatment.

[00315] An antibody of the invention (and any additional therapeutic agent) can be administered by any suitable means, including parenteral, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. Dosing can be by any suitable route, e.g., by injections, such as intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic. Various dosing schedules including but not limited to single or multiple administrations over various time-points, bolus administration, and pulse infusion are contemplated herein.

[00316] In some embodiments, an antibody of the invention is administered subcutaneously. In some embodiments, the antibody is administered every four weeks or every month. In some embodiments, an antibody of the invention is administered intravenously. In some embodiments, the antibody is administered every four weeks or every month. In some embodiments, for example, when the antibody comprises half-life extending substitutions such as M428L (EU numbering) and N434S (EU numbering), the antibody is administered every eight weeks.

[00317] Antibodies of the invention would be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The antibody need not be, but is optionally formulated with one or more agents

currently used to prevent or treat the disorder in question. The effective amount of such other agents depends on the amount of antibody present in the pharmaceutical composition, the type of disorder or treatment, and other factors discussed above. These are generally used in the same dosages and with administration routes as described herein, or about from 1 to 99% of the dosages described herein, or in any dosage and by any route that is empirically/clinically determined to be appropriate.

[00318] For the prevention or treatment of disease, the appropriate dosage of an antibody of the invention (when used alone or in combination with one or more other additional therapeutic agents) will depend on the type of disease to be treated, the type of antibody, the severity and course of the disease, whether the antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, and the discretion of the attending physician. The antibody is suitably administered to the patient at one time or over a series of treatments. Depending on the type and severity of the disease, about 1 µg/kg to 15 mg/kg (e.g., 0.1mg/kg-10mg/kg) of antibody can be an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. One typical daily dosage might range from about 1 µg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment would generally be sustained until a desired suppression of disease symptoms occurs. One exemplary dosage of the antibody would be in the range from about 0.05 mg/kg to about 10 mg/kg. Thus, one or more doses of about 0.5 mg/kg, 2.0 mg/kg, 4.0 mg/kg or 10 mg/kg (or any combination thereof) may be administered to the patient. Such doses may be administered intermittently, e.g., every week or every three weeks (e.g., such that the patient receives from about two to about twenty, or, e.g., about six doses of the antibody). An initial higher loading dose, followed by one or more lower doses may be administered. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

[00319] In various embodiments, an anti-KLK5 antibody used in a method herein may be replaced with a KLK5 antagonist, wherein the KLK5 antagonist inhibits KLK5 protease activity. In various embodiments, an anti-KLK7 antibody used in a method herein may be replaced with a KLK7 antagonist, wherein the KLK7 antagonist inhibits KLK5 protease activity. In various embodiments, a bispecific anti-KLK5.KLK7 antibody used in a method herein may be replaced with a KLK5/KLK7 antagonist, wherein the KLK5/KLK7 antagonist inhibits KLK5 protease activity and KLK7 protease activity.

I. Articles of Manufacture

[00320] In another aspect of the invention, an article of manufacture containing materials useful for the treatment, prevention and/or diagnosis of the disorders described above is provided. The article of manufacture comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, IV solution bags, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is by itself or combined with another composition effective for treating, preventing and/or diagnosing the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an antibody of the invention. The label or package insert indicates that the composition is used for treating the condition of choice. Moreover, the article of manufacture may comprise (a) a first container with a composition contained therein, wherein the composition comprises an antibody of the invention; and (b) a second container with a composition contained therein, wherein the composition comprises a further cytotoxic or otherwise therapeutic agent. The article of manufacture in this aspect of the invention may further comprise a package insert indicating that the compositions can be used to treat a particular condition. Alternatively, or additionally, the article of manufacture may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

III. EXAMPLES

[00321] The following are examples of methods and compositions of the invention. It is understood that various other embodiments may be practiced, given the general description provided above.

Example 1: Generation of anti-KLK7 Antibodies

[00322] New Zealand White rabbits were immunized with human KLK7 (SEQ ID NO: 4) and single B cells were isolated using a modified protocol related to published literature. *See, e.g.,* Offner et al., *PLoS ONE* 9(2), 2014. This modified workflow included direct FACS sorting of IgG⁺ huKLK7⁺ B cells into single wells. The B cell culture supernatants were assayed by ELISA for binding to human KLK7 and an irrelevant control protein. KLK7 specific B cells were lysed and immediately frozen in -80°C for storage until molecular cloning. Variable

regions (VH and VL) of each monoclonal antibody from rabbit B cells were cloned into expression vectors from extracted mRNA as previously described. *See id.* Individual recombinant rabbit antibodies were expressed in Expi293 cells and subsequently purified with protein A. ~244 anti-KLK7 antibodies were obtained that bound to both human and cyno KLK7. 171 antibodies were cloned and expressed for further characterization. Purified anti-KLK7 antibodies were screened for binding affinity to huKLK7, selectivity to huKLK7, and functional activity.

[00323] The binding affinity of the antibodies was determined by BIAcore™ T200 machine. Rabbit antibodies were recombinantly expressed. For kinetics measurements, antibodies were captured on research grade protein A chip (GE Healthcare, USA) to achieve approximately 300 RU. Ten-fold serial dilutions of human and cyno KLK7 were injected in HBS-P buffer at 25°C with a flow rate of 30 µL/min. Association rates (k_a) and dissociation rates (k_d) were calculated using a 1:1 Langmuir binding model (BIAcore™ T200 Evaluation Software version 2.0). The equilibrium dissociation constant (KD) was calculated as the ratio k_d/k_a .

[00324] The results of the off-rates against human KLK7 and cynomolgus monkey KLK7 for a subset of the most potent antibodies are shown in Table 1. No binding was observed to huKLK1, huKLK4, huKLK5, or huKLK11, confirming that these antibodies are specific.

Table 1

Clone ID	hu KLK7 k_d (1/s)	Cy KLK7 k_d (1/s)
5D10	<1E-6	<1E-6
7C7(14D10)	<1E-6	2.08E-5
9C7	<1E-6	3.66E-5
11D11	<1E-6	1.06E-4
15A2	<1E-6	3.90E-4
14H11	<1E-6	<1E-6
12F11	2.84E-5	4.95E-4
13A4	<1E-6	<1E-6
13C10	<1E-6	1.78E-4
15E6	<1E-6	7.65E-5
10C8	<1E-6	1.97E-4
11H7	3.51E-4	1.53E-4
27E9	4.02E-3	3.06E-4
17B9	1.25E-3	6.96E-4
25B8	2.87E-5	4.01E-4
27D10	4.34E-4	9.75E-4
2-18D4	1e-5	1e-5

[00325] A KLK7 direct functional assay was performed at room temperature in a 384-well plate (black, low-volume round bottom, Corning # 4514) with a final reaction volume

of 15 μ L. Inhibitor samples were diluted to 3x final concentration in assay buffer (75 mM Tris, pH 8.0, 150 mM NaCl, 0.01% Tween 20). Reactions lacking inhibitor and reactions with 200 nM final SFTI 21705 (Genentech, 10 mM stock in DMSO; also referred to as SFTI-KLK7; sequence GKCLFSNPPICFPN (SEQ ID NO: 196); *see, e.g.*, de Veer et al., 2017, *J. Invest. Dermatol.*, 137: 430-439) were used as 100% and 0% activity controls, respectively. Inhibitor or control samples (5 μ L) were added to the plate, followed by 5 μ L human KLK7 (SEQ ID NO: 4 plus a C-terminal FLAG tag; Genentech) or 5 μ L cyno KLK7 (SEQ ID NO: 6 plus a C-terminal FLAG tag; Genentech) in assay buffer at a final concentration of 0.5 nM (Mca substrate assay). After 40 min, 5 μ L Mca-RPKPVE-Nval-WRK(Dnp) (SEQ ID NO: 121; Bachem M-2110, 4.3 mM stock solution in DMSO) at a final concentration of 10 μ M substrate in assay buffer were added. After addition of substrate, the plate was read in PHERAstar[®] microplate reader (BMG Labtech) using optic module FI 320 405 with the gain set to 0%. Measurements were taken every 100 s for ~1.5 h. Reaction rates (expressed as RFU/s) were calculated by linear regression in the linear range. Reaction rates were normalized to the values of the 0% and 100% activity controls and fit with a 4-parameter equation to calculate IC₅₀ values. For certain data relating to bivalent inhibitors, the raw IC₅₀ was multiplied by two, as noted below.

[00326] Initial rates were calculated for each assay well by linear regression of the relative fluorescence units (RFU) measured at each time point. The first two time points were typically ignored. Percent control activities were calculated relative to the average of the No Inhibition and Full Inhibition controls. These percent control activities were plotted versus inhibitor concentration and fit using a 4-parameter equation to determine IC₅₀ values. Table 2 shows the results of the human KLK7 and cynomolgus monkey KLK7 inhibition assays for certain antibody clones. In Table 2, the IC₅₀s are not corrected for bivalency because all clones are bivalent.

Table 2: IC₅₀ for anti-KLK7 antibodies using MCA peptide substrate, bivalency not accounted for in IC₅₀ (Fig. 1a and b)

Clone ID	Hu KLK7 (0.5 nM) IC ₅₀ (nM)	Cy KLK7 (0.3125 nM) IC ₅₀ (nM)
5D10	0.15±0.01	0.18±0.009
7C7(14D10)	0.11±0.004	0.07±0.006
9C7	1.19±0.04	0.47±0.016
11D11	0.12±0.004	0.09±0.004
15A2	0.2±0.01	0.90±0.088
14H11	0.11±0.004	0.15±0.004
12F11	0.31±0.013	1.58±0.18
13A4	0.79±0.02	0.51±0.046
13C10	0.12±0.005	0.51±0.023
15E6	0.1±0.01	0.25±0.008

10C8	0.28±0.02	0.21±0.009
11H7	0.12±0.01	0.13±0.005
27E9	0.28±0.02	0.18±0.006
17B9	1.59±0.18	3.37±1.26
25B8	0.24±0.01	0.17±0.011
27D10	0.43±0.05	2.98±0.565

Example 2: Humanization of anti-KLK7 Antibodies

[00327] After screening as described in Example 1, 17 antibodies with the best inhibitory activities were chosen for further characterization. The antibody with the strongest binding affinity, inhibitory activity, and fewest manufacturing issues (14H11) was selected for humanization. Antibody 14H11 heavy chain variable region (SEQ ID NO: 116) was first modified by substituting C35a with S to eliminate an unpaired cysteine, resulting in antibody 14H11c (VH, SEQ ID NO: 13; VL SEQ ID NO: 14).

[00328] Rabbit monoclonal antibody 14H11c was humanized as follows. Residue numbers are according to Kabat et al., Sequences of proteins of immunological interest, 5th Ed., Public Health Service, National Institutes of Health, Bethesda, Md. (1991).

[00329] Variants constructed during the humanization of 14H11c were assessed in the form of human IgG1. Hypervariable regions from the rabbit antibody, positions 24-34 (L1; SEQ ID NO: 10), 50-56 (L2; SEQ ID NO: 11) and 89-97 (L3; SEQ ID NO: 12) in VL domain were grafted into human KV1D-39*01 framework; and 31-35b (H1; SEQ ID NO: 7), 50-65 (H2; SEQ ID NO: 8) and 95-102 (H3; SEQ ID NO: 9) in VH domain were grafted into human HV3-53*01 framework. All VL and VH Vernier positions from rabbit antibodies were also grafted into their respective human germline frameworks. The grafts with all rabbit amino acids in Vernier positions are referred to as L1H1 (hu.14H11c.L1H1; SEQ ID NOs: 15 (VH) and 31 (VL)).

[00330] The binding affinity of the humanized antibodies was determined by BIAcore™ 8K SPR system. For kinetics measurements, antibodies were captured on research grade protein A chip (GE Healthcare) to achieve approximately 300 RU. Ten-fold serial dilutions of human KLK7 were injected in HBS-P buffer at 37°C with a flow rate of 100 µL/min. Association rates (ka) and dissociation rates (kd) were calculated using a 1:1 Langmuir binding model (BIAcore Insight Evaluation Software version 2.0). The equilibrium dissociation constant (KD) was calculated as the ratio kd/ka.

[00331] The binding affinity of hu.14H11c.L1H1 antibody was compared to its chimeric parental clone. Rabbit Vernier positions of hu.14H11c.L1H1 antibodies were converted back to human residues to evaluate the contribution of each rabbit Vernier positions to binding

affinity to hKLK7. Three additional light chains (L2: L1+Ala43 (SEQ ID NO: 32), L3: L1+Phe71 (SEQ ID NO: 33), and L4: L1+Ala43+Phe71 (SEQ ID NO: 34)) and nine additional heavy chains (H2: H1+Val2 (SEQ ID NO: 16), H3: H1+Val48 (SEQ ID NO: 17), H4: H1+Ser49 (SEQ ID NO: 18), H5: H1+Arg71 (SEQ ID NO: 19), H6: H1+Asn73 (SEQ ID NO: 20), H7: H1+Leu78 (SEQ ID NO: 21), H8: H1+Tyr91 (SEQ ID NO: 22), H9: H1+Gln105 (SEQ ID NO: 23), H10: no rabbit residues in Vernier positions (SEQ ID NO: 24)) were made. *See Figures 1A-1B.* Tyr71 on light chain (L2; SEQ ID NO: 32), and Gln2 and Pro105 on the heavy chain (H11; SEQ ID NO: 29) were determined to be important rabbit Vernier residues based on binding affinity evaluation of the variant antibodies described above (data not shown). Chimeric 14H11c bound with a K_D of $< 1\text{pM}$, while hu.14H11c.L2H11, bound with a K_D of 0.4pM .

Table 3. Affinities of humanized anti-KLK7 antibody

Ligand	Sample	k_a (1/Ms)	k_d (1/s)	K_D (M)
human KLK7	chimeric rb.14H11c-hlgG1	2.16E+07	$<1\text{E-}06$	$<1\text{E-}12$
	hu.14H11c.L2H11-hlgG1 (VH/VL; SEQ ID NOs: 29,32)	3.43E+07	1.22E-05	3.56E-13
	One-armed hu.14H11c.L2H11-hlgG1 knob-in-hole (VH/VL; SEQ ID NOs: 30,38; IgG1 knob SEQ ID NOs: 96 linked to VH; paired with "dummy" IgG1 hole SEQ ID NO: 182)	2.82E+07	2.52E-05	8.94E-13

Example 3: Affinity optimization of anti-KLK5 antibodies

[00332] To increase the affinity of anti-KLK5 antibodies hu.9H5.L4H14 and hu.10C5.L5H28, 544 and 576 single point mutation variants were generated, respectively. The resulting antibodies were screened by surface plasmon resonance and ranked according to off-rates. *See Figure 4* (hu.10C5.L5H28 variants) and *Figure 5* (hu.9H5.L4H14 variants). There were only five mutations in hu.10C5.L5H28 that resulted in a significantly slower off-rate. These were LC.S34K (SEQ ID NO: 54), LC.F92Y (SEQ ID NO: 55), LC.S95F (SEQ ID NO: 56), HC.G33P (SEQ ID NO: 105), and HC.N53V (SEQ ID NO: 52). *See Figures 2A-2B.* For hu.9H5.L4H14, there were only four mutations with slower off-rates than the parental antibody: LC.H89V (SEQ ID NO: 88), LC.S95Y (SEQ ID NO: 89), HC.G54A (SEQ ID NO: 81), and HC.G98Q (SEQ ID NO: 82). *See Figures 3A-3B.*

[00333] To identify good combinations of variants, we generated one-armed (OA) monovalent antibodies with a human IgG1 Fc with both individual and combined sets of mutations. Good combinations were identified by surface plasmon resonance characterization. Tables 4-7 show the kinetic properties of the one-armed (OA) monovalent antibodies.

Table 4. Affinities of hu.9H5.L4H14 variants for human KLK5

antibody variant (all with Q38E/Q39K)	ka (1/Ms)	kd (1/s)	KD (M)	VH/VL SEQ IDs
OA.hu.9H5.H14L4	1.07E+06	2.72E-04	2.54E-10	84/91
OA.hu.9H5.H14L4.G54A.H89V	3.79E+06	3.85E-05	1.02E-11	85/92
OA.hu.9H5.H14L4.G54A.S95Y	9.92E+05	1.60E-05	1.62E-11	85/93
OA.hu.9H5.H14L4.G54A.H89V.S95Y	6.99E+05	1.37E-05	1.96E-11	85/94
OA.hu.9H5.H14L4.G98Q.H89V	2.40E+06	4.46E-05	1.86E-11	86/92
OA.hu.9H5.H14L4.G98Q.S95Y	7.85E+05	3.94E-05	5.02E-11	86/93
OA.hu.9H5.H14L4.G98Q.H89V.S95Y	2.47E+06	4.91E-05	1.99E-11	86/94
OA.hu.9H5.H14L4.G54A.G98Q.H89V	8.54E+06	2.97E-06	3.48E-13	87/92
OA.hu.9H5.H14L4.G54A.G98Q.S95Y	2.73E+06	2.71E-05	9.94E-12	87/93
OA.hu.9H5.H14L4.G54A.G98Q.H89V.S95Y	1.98E+06	2.39E-05	1.21E-11	87/94

Table 5. Affinities of hu9H5.L4H14 variants for cyno KLK5

antibody variant (all with Q38E/Q39K)	ka (1/Ms)	kd (1/s)	KD (M)	VH/VL SEQ IDs
OA.hu.9H5.H14L4	1.12E+07	6.97E-04	6.23E-11	84/91
OA.hu.9H5.H14L4.G54A.H89V	1.24E+07	1.10E-04	8.93E-12	85/92
OA.hu.9H5.H14L4.G54A.S95Y	4.82E+06	8.44E-05	1.75E-11	85/93
OA.hu.9H5.H14L4.G54A.H89V.S95Y	4.28E+06	7.36E-05	1.72E-11	85/94
OA.hu.9H5.H14L4.G98Q.H89V	1.48E+07	1.45E-04	9.78E-12	86/92
OA.hu.9H5.H14L4.G98Q.S95Y	4.02E+06	1.45E-04	3.61E-11	86/93
OA.hu.9H5.H14L4.G98Q.H89V.S95Y	4.02E+06	1.33E-04	3.30E-11	86/94
OA.hu.9H5.H14L4.G54A.G98Q.H89V	2.19E+07	6.52E-05	2.98E-12	87/92
OA.hu.9H5.H14L4.G54A.G98Q.S95Y	5.97E+06	9.18E-05	1.54E-11	87/93

OA.hu.9H5.H14L4.G54A.G98Q.H89V.S95Y	3.95E+06	5.75E-05	1.46E-11	87/94
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Table 6. Affinities of hu10C5.L5H28 variants for human KLK5

antibody variant (all except OA.hu.10C5.L5H28.WT and OA.hu.10C5.N53V with Q38E/Q39K)	ka (1/Ms)	kd (1/s)	KD (pM)	VH/VL SEQ IDs
OA.hu.10C5.L5H28.WT	1.25E+07	1.28E-03	102.417	50/51
OA.hu.10C5.N53V	6.84E+06	9.23E-05	13.497	52/51
OA.hu.10C5.N53V.S34K	3.42E+06	9.88E-06	2.887	53/61
OA.hu.10C5.N53V.F92Y	6.41E+06	2.45E-05	3.817	53/62
OA.hu.10C5.N53V.S95F	5.82E+06	1.51E-05	2.587	53/63
OA.hu.10C5.N53V.S34K.F92Y	3.00E+06	< 1E-06 *	< 0.334	53/64
OA.hu.10C5.N53V.S34K.S95F	4.25E+06	< 1E-06 *	< 0.235	53/65
OA.hu.10C5.N53V.F92Y.S95F	1.01E+07	8.65E-06	0.853	53/66
OA.hu.10C5.N53V.S34K.F92Y.S95F	5.13E+06	1.88E-06	0.367	53/67

Table 7. Affinities of hu10C5.L5H28 variants for cyno KLK5

antibody variant (all except OA.hu.10C5.L5H28.WT and OA.hu.10C5.N53V with Q38E/Q39K)	ka (1/Ms)	kd (1/s)	KD (pM)	VH/VL SEQ IDs
OA.hu.10C5.L5H28.WT	1.14E+07	4.24E-03	371.354	50/51
OA.hu.10C5.N53V	1.46E+07	5.20E-04	35.520	52/51
OA.hu.10C5.N53V.S34K	5.48E+06	8.88E-05	16.218	53/61
OA.hu.10C5.N53V.F92Y	1.82E+07	1.61E-04	8.846	53/62
OA.hu.10C5.N53V.S95F	1.35E+07	1.00E-04	7.444	53/63
OA.hu.10C5.N53V.S34K.F92Y	5.90E+06	3.08E-05	5.220	53/64
OA.hu.10C5.N53V.S34K.S95F	9.41E+06	2.86E-05	3.034	53/65
OA.hu.10C5.N53V.F92Y.S95F	1.52E+07	5.72E-05	3.764	53/66
OA.hu.10C5.N53V.S34K.F92Y.S95F	1.06E+07	2.81E-05	2.646	53/67

[00334] Figure 6 shows surface plasmon resonance traces for the indicated hu.10C5.L5H28 variants for human KLK5 (Figure 6A) and cynomolgus monkey KLK5 (Figure

6B). Figure 7 shows surface plasmon resonance traces for the indicated hu.9H5.L4H14 variants for human KLK5 (Figure 7A) and cynomolgus monkey KLK5 (Figure 7B).

Example 4: Generation and characterization of anti-KLK5/KLK7 bispecific antibodies

[00335] To choose good combinations of 10C5.L5H28 variants to pair with the anti-KLK7 arm in a bispecific antibody, we evaluated each variant for KLK5 inhibitory activity, non-specific binding in a baculovirus binding assay, and correct bispecific generation upon co-expression with the anti-KLK7 arm in a single cell. Each variant was constructed with mutations previously described to enhance correct chain pairing for single cell bispecific assembly. *See* Dillon et al., *Mabs* 9(2): 213-230 (2017). The anti-KLK5 LC contained Q38E and V133K and the HC contained Q39K and S183E. The anti-KLK7 LC contained Q38K and V133E and the HC contained Q39E and S183K.

[00336] All one-armed anti-KLK5 antibody variants exhibited similar potencies in the KLK5 inhibition assay, with IC50s ranging from 1.14 nM to 2.30 nM (data not shown.).

[00337] Non-specific binding of each anti-KLK5 antibody variant was measured in an ELISA using baculovirus particles, substantially as described in Hotzel et al., *Mabs* 4(6): 753-760 (2012).

[00338] Two variants (N53V/S34K and N53V/S34K/F92Y/S95F) were eliminated following the baculovirus binding assay because of higher nonspecific binding, which can lead to poor pharmacokinetic properties. *See* Tables 8 and 9.

Table 8: Baculovirus binding ELISA for hu10C5.L5H28 variants

Sample	BV ELISA	VH/VL SEQ IDs
hu.10C5.L5H28.WT	0.22	50/51
hu.10C5.N53V	0.38	52/51
hu.10C5.N53V.S34K	1.81	52/54
hu.10C5.N53V.F92Y	0.19	52/55
hu.10C5.N53V.S95F	0.28	52/56
hu.10C5.N53V.S34K.F92Y	0.29	52/57
hu.10C5.N53V.S34K.S95F	0.29	52/58
hu.10C5.N53V.F92Y.S95F	n.d.	52/59
hu.10C5.N53V.S34K.F92Y.S95F	0.46	52/60

Table 9: Baculovirus binding ELISA for hu.9H5.L4H14 variants

xKLK5 variant (all with Q38E/Q39K)	BV ELISA	VH/VL SEQ IDs
OA.hu.9H5.H14L4	0.02	84/91
OA.hu.9H5.H14L4.G54A.H89V	0.30	85/92
OA.hu.9H5.H14L4.G54A.S95Y	0.17	85/93
OA.hu.9H5.H14L4.G54A.H89V.S95Y	0.34	85/94
OA.hu.9H5.H14L4.G98Q.H89V	0.32	86/92
OA.hu.9H5.H14L4.G98Q.S95Y	0.12	86/93
OA.hu.9H5.H14L4.G98Q.H89V.S95Y	0.33	86/94
OA.hu.9H5.H14L4.G54A.G98Q.H89V	0.27	87/92
OA.hu.9H5.H14L4.G54A.G98Q.S95Y	0.12	87/93
OA.hu.9H5.H14L4.G54A.G98Q.H89V.S95Y	0.20	87/94

[00339] The ability of each variant to pair correctly with the anti-KLK7 arm upon co-expression in HEK293 cells was evaluated. As shown in Table 10, all variants with LC.S34K exhibited poor assembly properties.

Table 10. Mass spectrometry measurement of % correct bispecific upon single cell production.

Clone (hu.10C5 VH/VL; hu.14H11 VH/VL)	Correct (%)	2xHoleLC (%)	2xKnobLC (%)
hu.10C5VKYF.hu14H11c.L2H11 1:1 (53/67; 30/38)	58.5	0.0	41.5
hu.10C5VK.hu14H11c.L2H11 1:1 (53/61; 30/38)	67.9	1.5	30.6
hu.10C5VY.hu14H11c.L2H11 1:1 (53/62; 30/38)	89.0	0.0	11.0
hu.10C5VF.hu14H11c.L2H11 1:1 (53/63; 30/38)	84.9	1.3	13.8
hu.10C5VKY.hu14H11c.L2H11 1:1 (53/64; 30/38)	63.4	1.9	34.7
hu.10C5VKF.hu14H11c.L2H11 1:1 (53/65; 30/38)	55.3	0.0	44.7

[00340] Based on the combined properties, hu.10C5.L5H28.N53V.F92Y with Q39K/Q38E mutations (VH, SEQ ID NO: 53; VL, SEQ ID NO: 62) was chosen as the anti-KLK5 arm to pair with the hu14H11c.L2H11 with Q39E/Q38K mutations (VH, SEQ ID NO: 30; VL, SEQ ID NO: 38) anti-KLK7 arm. Two versions of the bispecific antibody were generated with hIgG1 N297G, which has attenuated effector function. One of the versions contained two mutations (M428L/N434S) that have been shown to enhance antibody half-life *in vivo*. See Zalevsky et al. Nature Biotech, 2010, 28: 157-9; Ko et al. Nature, 2014, 514: 642-5; Gaudinski et al. PLOS Medicine, 2018, 15:e1002493.

[00341] The affinities of the anti-KLK5/KLK7 bispecific antibodies, with and without the M428L/N434S ("LS") mutations, was determined for human and cynomolgus monkey KLK5 and KLK7.

Table 11. Affinities of bispecific antibodies for human and cyno KLK5

	Human KLK5			Cyno KLK5		
	ka (1/Ms)	kd (1/s)	KD (pM)	ka (1/Ms)	kd (1/s)	KD (pM)
hu.10C5VY.hu14H11c.L2H11 WT (SEQ ID NOs: 108/109 and 110/111)	(2.1±0.9)E+7	(1.5±0.6)E-5	0.8±0.2	(1.0±0.2) E+7	(1.9±0.1)E-4	19±1
hu.10C5VY.hu14H11c.L2H11 LS (SEQ ID NOs: 112/113 and 114/115)	(1.5±0.7) E+7	(1.97±0.09)E-5	1.5±0.6	(1.11±0.03) E+7	(1.8±0.5)E-4	16±4

Table 12. Affinities of bispecific antibodies for human and cyno KLK7

	Human KLK7			Cyno KLK7		
	ka (1/Ms)	kd (1/s)	KD (pM)	ka (1/Ms)	kd (1/s)	KD (pM)
hu.10C5VY.hu14H11c.L2H11 WT (SEQ ID NOs: 108/109 and 110/111)	(5.8±0.1) E+7	< 1E-6	<1	(4±1) E+7	(9±5)E-5	2.3±0.6
hu.10C5VY.hu14H11c.L2H11 LS (SEQ ID NOs: 112/113 and 114/115)	(5.7±0.5) E+7	(1.4±0.1)E-5	0.24±0.9	(3±1)E+7	(7±3)E-5	3±2

[00342] Activity of the bispecific antibodies was assayed using KLK7 and KLK5 direct functional assays, substantially as described in Example 1. For KLK5 functional assays,

the assay in Example 1 was modified to use human or cynomolgus monkey KLK5 (SEQ ID NOs: 2 and 101, respectively) in place of KLK7, and substrate Boc-Val-Pro-Arg-AMC (Bachem I-1120, 31.3 mM stock solution in water) at a final concentration of 50 μ M. 200 nM SPINK9.SRE.Fc (SEQ ID NO: 197; Genentech; *see, e.g.*, Brannstrom et al., 2012, *Biol. Chem.* 393: 369-377) was used as a 0% activity control. The results are shown in Tables 13 and 14.

Table 13: IC₅₀ for the anti-KLK5/KLK7 bispecific antibodies and parental monospecific antibodies against human KLK5 and KLK7, bivalency corrected in IC₅₀s (AMC = Boc-Val-Pro-Arg-AMC; MCA = Mca-RPKPVE-Nval-WRK(Dnp))

Antibody	IC ₅₀ (nM)		
	KLK5 AMC	KLK7 MCA	
hu.10C5VY.hu14H11c.L2H11 WT (SEQ ID NOs: 108/109 and 110/111)	0.67 $\pm$ 0.06	0.37 $\pm$ 0.08	
hu.10C5VY.hu14H11c.L2H11 LS (SEQ ID NOs: 112/113 and 114/115)	0.54 $\pm$ 0.04	0.34 $\pm$ 0.07	
hu14H11c.L2H11 (SEQ ID NOs: 29/32)	>10	0.29 $\pm$ 0.06	
hu10C5VY (SEQ ID NOs: 52/55)	0.46 $\pm$ 0.04	>10	

Table 14: IC₅₀ for the anti-KLK5/KLK7 bispecific antibodies and parental monospecific antibodies against cynomolgus monkey KLK5 and KLK7, bivalency corrected in IC₅₀s (AMC = Boc-Val-Pro-Arg-AMC; MCA = Mca-RPKPVE-Nval-WRK(Dnp))

Antibody	IC ₅₀ (nM)		
	KLK5 AMC	KLK7 MCA	
hu.10C5VY.hu14H11c.L2H11 WT (SEQ ID NOs: 108/109 and 110/111)	0.73 $\pm$ 0.04	0.37 $\pm$ 0.05	
hu.10C5VY.hu14H11c.L2H11 LS (SEQ ID NOs: 112/113 and 114/115)	0.58 $\pm$ 0.02	0.36 $\pm$ 0.05	
hu14H11c.L2H11 (SEQ ID NOs: 29/32)	>10	0.29 $\pm$ 0.06	
hu10C5VY (SEQ ID NOs: 52/55)	0.56 $\pm$ 0.03	>10	

Example 5: Expression of KLK5 and KLK7 in atopic dermatitis, rosacea, and psoriasis

[00343] Immunochemistry was used to determine the expression of KLK5 in human rosacea and atopic dermatitis samples. As shown in Figure 8, KLK5 protein is elevated in human rosacea and atopic dermatitis, compared to normal skin.

[00344] To determine whether KLK7 is also expressed in human dermatitis conditions, an antisense RNA probe was used for *in situ* hybridization to visualize KLK5 and

KLK7 expression. Figure 9 show representative KLK7 mRNA staining in atopic dermatitis, rosacea, and psoriasis, compared to normal skin. Figure 10 shows that KLK5 (10A) and KLK7 (10B) mRNA show similar anatomic expression in human skin and are both upregulated in atopic dermatitis, rosacea, and psoriasis. The increase in SPINK5 expression was not significant in atopic dermatitis or rosacea, but was significant in psoriasis. The data in Figure 10 shows double-blinded quantification by a pathologist.

Example 6: Intradermal injection of KLK5 or KLK7 increases transepidermal water loss

[00345] To test whether KLK5 or KLK7 directly promotes epithelial barrier dysregulation and increases transepidermal water loss, 2µg recombinant KLK5 or KLK7 was intradermally injected into dorsal skin of Balb/c mice.

[00346] As shown in Figure 11, 6 hours after injection, both KLK5 and KLK7 injected animals have increased transepidermal water loss, as measured by a portable skin Vapometer (Delfin technologies). These data suggested that KLK5 and KLK7 may each promote increased epithelial permeability.

Example 7: Inhibition of KLK5 and KLK7 ameliorates murine inflammatory dermatitis

[00347] Surrogate anti-murine KLK5 and anti-murine KLK7 inhibitory antibodies were generated to test the therapeutic efficacy of inhibiting KLK5 and KLK7 in murine atopic dermatitis. Murine atopic dermatitis was induced by topical treatment with SDS and staphylococcus aureus protein A. Mice with inflammatory dermatitis then received an intraperitoneal injection of 250 µg isotype control (anti-gp120), anti-murine KLK5 antibody, anti-murine KLK7 antibody, or a combination of anti-KLK5 and anti-KLK7 antibodies. Murine SPINK5-Fc fusion protein was used here as a non-specific inhibitor for multiple KLKs (including KLK5, KLK7, and KLK14).

[00348] As shown in Figure 12, while inhibition of KLK5 or KLK7 alone provides moderate protection in daily dermatitis clinical score (12A), total terminal atopic dermatitis score (12B), and AUC skin score (12C), co-inhibition of KLK5 and KLK7 provides a superior therapeutic efficacy, similar to SPINK5-Fc. Since SPINK5 inhibits other KLKs in addition to KLK5 and KLK7, this data suggests that inhibition of KLK5 and KLK7 is sufficient for therapeutic efficacy.

[00349] Inflammatory atopic dermatitis is associated with T cell infiltration and IL-13 production. Neutralizing IL-13 improves atopic dermatitis in murine animal models and human atopic dermatitis patients. In a second experiment, an anti-IL-13 antibody was used as a

positive control in the SDS/S. aureus protein A atopic dermatitis model. As shown in Figure 13, the combination of anti-KLK5 and anti-KLK7 antibodies reduced total terminal AD scores, reduced transepidermal water loss (TEWL), and reduced histologic disease severity scores, to a similar extent as anti-IL-13 antibody. Figure 14 shows representative hematoxylin and eosin staining, demonstrating that combined anti-KLK5 and KLK7 antibodies reduced dermal inflammation and parakeratosis to a similar extent as anti-IL-13 antibody.

[00350] Taken together, these results suggest a redundant role for KLK5 and KLK7 in promoting epithelial barrier permeability. Combined inhibition of KLK5 and KLK7 is therefore expected to result in improved dermatitis clinical scores, skin barrier function, and histopathology manifestation, compared to inhibition of KLK5 or KLK7 alone.

Example 8: Skin rash and scaling in Spink5 deficient mice improves with anti-mKLK5/mKLK7 bispecific antibody treatment or anti-mKLK5 antibody / anti-mKLK7 antibody combination treatment

[00351] Spink5 f/f Cre-ERT2+ mice were intraperitoneally injected with 16 mg/kg, 8 mg/kg, or 4 mg/kg tamoxifen to delete the Spink5 gene. One day before tamoxifen treatment, anti-murine KLK5 antibody (2.5 mg per mouse) and anti-murine KLK7 antibody (0.5 mg per mouse) or an isotype control antibody (2.5 mg per mouse). An excess of anti-mKLK5 antibody compared to anti-mKLK7 antibody was used because the anti-mKLK5 antibody was determined to be 100-fold less potent than the anti-mKLK7 antibody, with an IC₅₀ of 4.78 nM compared to an IC₅₀ of 0.48 nM for the anti-mKLK7 antibody. Back skin was analyzed 6 days post injection of tamoxifen. Spink5 f/f Cre-ERT2-negative mice were also treated with 16 mg/kg tamoxifen as a control.

[00352] The back skin of the mice 6 days post infection is shown in Figures 16A-16D. Skins of the Spink5 deficient mice treated with an isotype control became dry, scaly, inflamed, and reddened. These exterior Netherton Syndrome-like symptoms were significantly improved by combined injection of anti-mKLK5 antibody and anti-mKLK7 antibody across different tamoxifen dose.

[00353] Back skin of the mice were homogenized in phosphate-buffered saline to produce skin lysates. The lysates were analyzed for cytokine levels using Bio-Plex Multiplex Immunoassays (BioRad).

[00354] The results of the cytokine assays are shown in Figure 17A-17E. Levels of cytokines IL-8 (17A), TNF- α (17B), IL-6 (17C), IL-4 (17D), and G-CSF (17E) were reduced

by anti- mKLK5/mKLK7 bispecific antibody treatment compared to isotype control antibody treatment.

[00355] Figure 18 shows representative cross-sections of hematoxylin and eosin stained skin from Spink5 deficient mice treated with 16 mg/kg tamoxifen and isotype control antibody or combined anti-mKLK5 antibody/anti-mKLK7 antibody. While the skin from Spink5 deficient mice treated with isotype control antibody shows significant leukocyte infiltration, thickening of epidermis layers, and epidermis desquamation, a combined blockade of mKLK5 and mKLK7 significantly reduced the pathological manifestation.

Example 9: Anti-KLK5/KLK7 bispecific antibody inhibits KLK5- and KLK7-induced epithelial permeability

[00356] Human epidermal keratinocytes were seeded into a tissue culture trans-well plate coated with collagen and differentiated with 1.5mM CaCl₂ for 2 days. After differentiation, CaCl₂ was reduced to 0.1mM. The top apical side of the monolayer was treated with KLK5 (5µg/ml), KLK7 (5µg/ml), KLK5+KLK7 (5µg/ml each), or KLK5+KLK7 (5µg/ml each) + 100µg/ml anti-KLK5/KLK7 bispecific antibody (hu.10C5VY.hu14H11c.L2H11 LS) for 72h or 96h. Trans-epithelial electrical resistance (TEER) was measured with a volt/ohm meter at each time point.

[00357] The results are shown in Figures 22A-22B. Addition of recombinant KLK5, KLK7, or KLK5/KLK7 together induced epithelial permeability as quantified by trans-epithelial electrical resistance. Anti-KLK5/KLK7 bispecific antibody significantly reduced the KLK5- and KLK7- induced epithelial permeability.

Example 10: Structural determination of anti-KLK7 antibody 14H11c bound to KLK7

[00358] Recombinant KLK7 residues I30-R253 (SEQ ID NO: 4) was expressed in a mammalian expression system (CHO cells), with a His-tag at the N-terminus, followed by an enterokinase cleavage site engineered between the His-tag and KLK7. The CHO cells were co-expressed with EndoH with 1 mg/mL of Kifunensine. The expression media was harvested and purified with Ni-NTA as the first step. Protein eluted from the Ni-NTA column was further purified on a Superdex 200 (S200) size-exclusion column. The His tag on KLK7 was removed by treating with enterokinase overnight, and KLK7 was further purified on a SP HP cation exchange column with 25 mM Hepes pH7.8 and a gradient of 0-800 mM NaCl.

[00359] Fab fragments including heavy and light chains of anti-KLK7 antibody rb.14H11c were expressed in HEK293 cells. A His-tag was added at the C-terminus of the heavy

chain for ease of purification using a Ni-NTA resin, followed by size exclusion chromatography in PBS. The sequences of the heavy and light chain are shown in SEQ ID NOs: 198 and 199, respectively. For the purposes of this example, the sequences were numbered beginning with the signal sequence. The numbering of the Fab heavy chain shown in SEQ ID NO: 198 therefore begins with 20 (amino acids 20-256) and the numbering of the Fab light chain shown in SEQ ID NO: 199 therefore begins with 23 (amino acids 23-237).

[00360] KLK7 was mixed with the 14H11c Fab, at a molar ratio of 1:1.5 KLK7:Fab and the complex was purified by size-exclusion chromatography in 25 mM HEPES pH 7.8, 150 mM NaCl. The peak containing the KLK7:Fab complex was methylated on the lysines (*Methods in Structure*, 2006, 14, 1617-1622) and further purified on an S200 column using 25 mM TRIS pH 7.8 and 150 mM NaCl. The complex was concentrated to 10 mg/mL and crystals were grown by hanging drop with 1 μ L protein and 1 μ L of 10% PEG 4K and 0.2M ammonium sulfate. Crystals appeared after 3 days and matured over an additional 2-3 days. Crystals were then harvested for data collection.

[00361] X-ray diffraction data was collected under cryocooled conditions at 100 Kelvin using various synchrotron X-ray radiation at the Advanced Light Source (Berkeley, CA) according to standard methods. Diffraction images were processed and reduced using the data processing software XDS (Kabsch, W. *XDS. Acta Cryst. D66*, 125-132 (2010)). Models were generated using the molecular replacement technique with the program PHASER. The structure of human KLK7 (*Proc Natl Acad Sci U S A* **104**: 16086-16091 (2007)) and Fab antibody model were used as search models. The structures underwent iterative rounds of model adjustment using the program COOT and refinement using the PHENIX. Models were refined to acceptable R and R free values and Ramachandran statistics (calculated by Molprobit). Amino acid residue numbering for KLK7 was based on the chymotrypsin numbering system (*Proc Natl Acad Sci U S A* **104**: 16086-16091 (2007) for KLK7, PDB code 2QXI for reference; also referred to as "standard protease numbering").

[00362] The structure of the 14H11c Fab bound to human KLK7 is shown in Figures 20A-20B. The complete Fab bound to KLK7 is shown in Figure 20A, with an overlay of KLK7 alone. Figure 20B shows the KLK7-Fab interface.

[00363] Table 15 lists the 14H11c heavy chain amino acids and KLK7 amino acids involved in the Fab-KLK7 interface.

Table 15: Interface residues between 14H11c heavy chain and KLK7

Interface residues in 14H11c Heavy Chain	Interface residues in KLK7 (Chymotrypsin numbering system)	Interface residues in KLK7 (sequential numbering of SEQ ID NO: 4)
Ser 49	His 91	His72
Ser 50	Ser 95	Ser76
Tyr 51	Thr 96	Thr77
Tyr 52	Gln 97	Gln78
Tyr 71	Thr 98	Thr79
Ser 74	Val 100	Val81
Ser 75	Asn 101	Asn82
Ala 77	Lys 173	Lys152
Tyr 79	Leu 175	Leu154
Phe 120	Leu 176	Leu155
Glu 122	Glu 177	Glu156
Thr 123	Asn 178	Asn157
Gly 124	Ser 179	Ser158
Gly 125	Gln 230	Gln209
Tyr 126	Cys 232	Cys210
Gly 127	Lys 233	Lys211
Tyr 128	Phe 234	Phe212
	Thr 235	Thr213
	Lys 236	Lys214
	Trp 237	Trp215
	Asp 240	Asp218

[00364] Table 16 lists the 14H11c light chain amino acids and KLK7 amino acids involved in the Fab-KLK7 interface.

Table 16: Interface residues between 14H11c light chain and KLK7

Interface residues in 14H11c Light Chain	Interface residues in KLK7 (Chymotrypsin numbering system)	Interface residues in KLK7 (sequential numbering of SEQ ID NO: 4)
Glu 49	Arg 90	Arg71
Asp 50	His 91	His72
Ile 51	Pro 92	Pro73
Ala 52	Gly 93	Gly74
Tyr 114	Tyr 94	Tyr75
Tyr 116	Ser 95	Ser76
Ser 117	Thr 96	Thr77
Ser 118	Gln 97	Gln78
Thr 119	Val 100	Val81
	Asn 101	Asn82
	Trp 237	Trp215
	Thr 241	Thr219
	Lys 244	Lys222

[00365] Table 17 lists the 14H11c heavy chain amino acids and KLK7 amino acids that form hydrogen bonds in the structure, and Table 18 lists the 14H11c heavy chain amino acids and KLK7 amino acids that form salt bridges.

Table 17: Hydrogen bonds between 14H11c heavy chain and KLK7

Heavy Chain Residue	Bond Length (Angstrom)	KLK7 residue (Chymotrypsin numbering system)	KLK7 residue (sequential numbering of SEQ ID NO: 4)
Tyr 52 [OH]	2.8	Ser 95 [OG]	Ser76 [OG]
Ser 95 [O]	3.8	Gln 97 [NE2]	Gln78 [NE2]
Gly 125 [O]	3.1	Thr 235 [N]	Thr213 [N]
Gly 125 [O]	3.9	Thr 235 [OG1]	Thr213 [OG1]
Tyr 128 [O]	3.7	Asn 101 [ND2]	Asn82 [ND2]
Tyr 52 [OH]	3.0	Gln 97 [OE1]	Gln78 [OE1]
Ala 77 [N]	3.7	Gln 97 [OE1]	Gln78 [OE1]

Tyr 79 [OH]	2.8	Gln 97 [OE1]	Gln78 [OE1]
Tyr 126 [N]	3.2	Lys 233 [O]	Lys211 [O]
Gly 127 [N]	2.9	Lys 233 [O]	Lys211 [O]
Tyr 128 [N]	2.9	Asn 101 [OD1]	Asn82 [OD1]
Tyr 128 [OH]	2.9	Asn 178 [OD1]	Asn157 [OD1]

Table 18: Salt bridges between 14H11c heavy chain and KLK7

Heavy Chain Residue	Bond Length (Angstrom)	KLK7 residue (Chymotrypsin numbering system)	KLK7 residue (sequential numbering of SEQ ID NO: 4)
Glu 122 [OE1]	3.2	Lys 233 [NZ]	Lys211 [NZ]
Glu 122 [OE2]	3.8	Lys 233 [NZ]	Lys211 [NZ]

[00366] Table 19 lists the 14H11c heavy chain amino acids and KLK7 amino acids that form hydrogen bonds in the structure.

Table 19: Hydrogen bonds between 14H11c light chain and KLK7

Light Chain Residue	Bond Length (Angstrom)	KLK7 residue (Chymotrypsin numbering system)	KLK7 residue (sequential numbering of SEQ ID NO: 4)
Tyr 114 [OH]	2.9	His 91 [NE2]	His72 [NE2]
Tyr 116 [OH]	3.1	Gly 93 [O]	Gly74 [O]
Ser 117 [OG]	2.9	Pro 92 [O]	Pro73 [O]
Thr 119 [OG1]	2.7	Pro 92 [O]	Pro73 [O]

[00367] Based on the crystal structure, anti-KLK7 antibody rb.14H11c binds a discontinuous epitope of KLK7, with an interface comprising regions R71-N82, K152-S158, and Q211-K222 of KLK7 (SEQ ID NO: 4). rb.14H11c forms hydrogen bonds and/or salt bridges with amino acids H72, P73, G74, S76, Q78, N82, N157, K211, and T213 of KLK7, as numbered according to SEQ ID NO: 4 (H91, P92, G93, S95, Q97, N101, N178, K233, and T235, by chymotrypsin numbering).

[00368] As shown in Figure 20C, 14H11c Fab binding to the 170s loop of KLK7 (chymotrypsin numbering) results in concerted conformational changes in 170s loop, with most significant changes in the conformations of L176 (L155 in SEQ ID NO: 4) and D174 (D153 in SEQ ID NO: 4). L176, which is in a hydrophobic core of KLK7 in the native state, is facing the

Fab (and is stabilized by interactions with Fab). Due to steric clash with the Fab, D174 moves into the region closer to substrate binding region, resulting in movement of Y172 (Y151 in SEQ ID NO: 4) and W215 (W192 in SEQ ID NO: 4), clashing with the 180s loop, resulting in unfolding of both 180s and 220s loops and a constriction of the substrate binding site. It is believed that these conformational changes results in inactivation of the KLK7 enzyme.

[00369] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the invention. The disclosures of all patent and scientific literature cited herein are expressly incorporated in their entirety by reference.

IV. Table of Certain Sequences

SEQ ID NO	Description	Sequence
1	Human KLK5 amino acid sequence (UniProtKB/Swiss-Prot: Q9Y337.3)	MATARPPWMW VLCAITALL LGVTEHVLAN NDVSCDHPSN TVPSGSNQDL GAGAGEDARS DDSSSRIING SDCDMHTQPW QAALLLRPNQ LYCGAVLVHP QWLLTAAHCR KKVFRVRLGH YSLSPVYESG QQMFQGVKSI PHPGYSHPGH SNDMLIKLN RRIRPTKDVR PINVSSHCP S AGTKCLVSGW GTTKSPQVHF PKVLQCLNIS VLSQKRCEDA YPRQIDDTMF CAGDKAGRDS CQGDSSGGPVV CNGSLQGLVS WGDYPCARP N RPGVYTNLCK FTKWIQETIQ ANS
2	Human mature KLK5 amino acid sequence (amino acids 67-293 of UniProtKB/Swiss-Prot: Q9Y337.3; signal is 1-22, propeptide is 23-66)	IINGSD CDMHTQPWQA ALLLRPNQLY CGAVLVHPQW LLTAAHCRKK VFRVRLGHYS LSPVYESGQQ MFQGVKSIPH PGYSHPGHSN DLMLIKLNRR IRPTKDVRPI NVSSHCP SAG TKCLVSGWGT TKSPQVHFPK VLQCLNISVL SQRCEADAYP RQIDDTMFCA GDKAGRDSQ GDSSGGPVVCN GSLQGLVSWG DYPCARP NRP GVTNLCKFT KWIQETIQAN S
100	Cynomolgus monkey KLK5 amino acid sequence (UniProtKB: A0A2K5W0T6)	MATARTPWMW VLCAITALL LGVTEHVLAN DDVSCDNPSN TVPSGSNRDV GAGDDARSDD SSSRIINGSD CDEHTQPWQA ALLLGNQLY CGGVLVHPQW LLTAAHCRKK VFRVRLGHYS LSPVYESGQQ MFQGIKSIPH PGYSHPGHSN DLMLIKLNRR IHSTKDVRPI NVSSHCP SAG TKCLVSGWGT TRSPQVHFPK VLQCLNISVL SQRCEADAYP RQIDDTMFCA GDEAGRDSQ GDSSGGPVVCN GSLQGLVSWG DYPCAKPNRP GVTNLCKFT KWIQETIQAN S
101	Cynomolgus monkey mature KLK5 amino acid sequence (amino acids 1-22 of UniProtKB: A0A2K5W0T6; signal is , propeptide is 23-64)	IINGSDCDEH TQPWQAALLL GPNQLYCGGV LVHPQWLLTA AHCRRKQVFRV RLGHYSLSVP YESGQQMFQG IKSIPHPGYS HPGHSNDLML IKLNRRIHST KDVRPINVSS HCPSAGTKCL VSGWGTTRSP QVHFPKVLQC LNISVLSQKR CEDAYPRQID DTMFCAGDEA GRDSCQGD SG GPVVCNGLQ GLVSWG DYPC AKPNRPGVYT NLCKFTKWIQ ETIQANS
3	Human KLK7 amino acid sequence (UniProtKB/Swiss-Prot: P49862.1)	MARSLLLPLQ ILLLSLALET AGEEAQGDKI IDGAPCARGS HPWQVALLSG NQLHCGGVLV NERWVLTA AH CKMNEYTVHL GSDTLGDRRA QRIKASKSFR HPGYSTQTHV NDLMLVKLNS QARLSSMVKK VRLPSRCEPP GTTCTVSGWG TTTSPDVTFP SDLMCVDVKL ISPQDCTKVY KDLLNSMLC AGIPDSKKNA CNGDSSGGPLV CRGTLQGLVS WGTFFCGQPN DPGVYTQVCK FTKWINDTMK KHR
4	Human mature KLK7 amino acid sequence (amino acids 30-253 of UniProtKB/Swiss-Prot: P49862.1; signal is 1-22, propeptide is 23-29)	IDGAPCARG SHPWQVALLS GNQLHCGGVV VNERWVLTA AH HCKMNEYTVH LGSDTLGDRR AQRIKASKSF RHPGYSTQTH VNDLMLVKLN SQARLSSMVK KVR LPSRCEP PGTTCTVSGW GTTTSPDVTF PSDLMCVDVK LISPDCTKV YKDLLENSML CAGIPDSKKN ACNGDSSGGL VCRGTLQGLV SWGTFFCGQP NDPGVYTQVC KFTKWINDTM KHR
5	Cynomolgus monkey KLK7 amino acid sequence (UniProtKB: G7PYG2)	MAGSLLLPLQ ILLLSLALGT AGEEAQGDKI IDGAPCTRGS HPWQVALLSG NQLHCGGVLV NERWVLTA AH CKMNDYTVHL GSDTLGDRKA QRIKASRSFR HPGYSTQTHV NDLMLVKLNS PARLSSTVKK VRLPSRCEPP GTTCTVSGWG TTTSPDVTFP SDLMCVDVKL ISSQDCTKVY KDMLGNSMLC AGIPNSKKNA CNGDSSGGPLV CRGTLQGLVS WGTFFCGQPN DPGVYTQVCK FTKWINDTIK KHR
6	Cynomolgus monkey mature KLK7 amino acid sequence (amino acids 30-253 of UniProtKB: G7PYG2; signal is 1-21, propeptide is 22-29)	IDGAPCTRGS HPWQVALLSG NQLHCGGVLV NERWVLTA AH CKMNDYTVHL GSDTLGDRKA QRIKASRSFR HPGYSTQTHV NDLMLVKLNS PARLSSTVKK VRLPSRCEPP GTTCTVSGWG TTTSPDVTFP SDLMCVDVKL ISSQDCTKVY KDMLGNSMLC AGIPNSKKNA CNGDSSGGPLV CRGTLQGLVS WGTFFCGQPN DPGVYTQVCK FTKWINDTIK KHR
7	rb.14H11c CDRH1 hu.14H11c.V3-53*1.H1 CDRH1	SSYYMS

	hu.14H11c.V3-53*1.H2 CDRH1 hu.14H11c.V3-53*1.H3 CDRH1 hu.14H11c.V3-53*1.H4 CDRH1 hu.14H11c.V3-53*1.H5 CDRH1 hu.14H11c.V3-53*1.H6 CDRH1 hu.14H11c.V3-53*1.H7 CDRH1 hu.14H11c.V3-53*1.H8 CDRH1 hu.14H11c.V3-53*1.H9 CDRH1 hu.14H11c.V3-53*1.H10 CDRH1 hu.14H11c.V3-53*4.H1 CDRH1 hu.14H11c.V3-23.H1 CDRH1 hu.14H11c.V3-33*2.H1 CDRH1 hu.14H11c.V3-21.H1 CDRH1 hu.14H11c-H11 CDRH1 hu.14H11c-H11.Q39E CDRH1	
8	rb.14H11c CDRH2 hu.14H11c.V3-53*1.H1 CDRH2 hu.14H11c.V3-53*1.H2 CDRH2 hu.14H11c.V3-53*1.H3 CDRH2 hu.14H11c.V3-53*1.H4 CDRH2 hu.14H11c.V3-53*1.H5 CDRH2 hu.14H11c.V3-53*1.H6 CDRH2 hu.14H11c.V3-53*1.H7 CDRH2 hu.14H11c.V3-53*1.H8 CDRH2 hu.14H11c.V3-53*1.H9 CDRH2 hu.14H11c.V3-53*1.H10 CDRH2 hu.14H11c.V3-53*4.H1 CDRH2 hu.14H11c.V3-23.H1 CDRH2 hu.14H11c.V3-33*2.H1 CDRH2 hu.14H11c.V3-21.H1 CDRH2 hu.14H11c-H11 CDRH2 hu.14H11c-H11.Q39E CDRH2	SIYAGSSGAPYYAGWAKG
9	rb.14H11c CDRH3	EGFAETGGYGYAAYFNL

	hu.14H11c.V3-53*1.H1 CDRH3 hu.14H11c.V3-53*1.H2 CDRH3 hu.14H11c.V3-53*1.H3 CDRH3 hu.14H11c.V3-53*1.H4 CDRH3 hu.14H11c.V3-53*1.H5 CDRH3 hu.14H11c.V3-53*1.H6 CDRH3 hu.14H11c.V3-53*1.H7 CDRH3 hu.14H11c.V3-53*1.H8 CDRH3 hu.14H11c.V3-53*1.H9 CDRH3 hu.14H11c.V3-53*1.H10 CDRH3 hu.14H11c.V3-53*4.H1 CDRH3 hu.14H11c.V3-23.H1 CDRH3 hu.14H11c.V3-33*2.H1 CDRH3 hu.14H11c.V3-21.H1 CDRH3 hu.14H11c-H11 CDRH3 hu.14H11c-H11.Q39E CDRH3	
10	rb.14H11c CDRL1 hu.14H11c.K1-39.L1 CDRL1 hu.14H11c.K1-39.L2 CDRL1 hu.14H11c.K1-39.L3 CDRL1 hu.14H11c.K1-39.L4 CDRL1 hu.14H11c.K1-5.L1 CDRL1 hu.14H11c.K1-8.L1 CDRL1 hu.14H11c.K1-6.L1 CDRL1 hu.14H11c-L2.Q38K CDRL1	IASEDIASSVS
11	rb.14H11c CDRL2 hu.14H11c.K1-39.L1 CDRL2 hu.14H11c.K1-39.L2 CDRL2 hu.14H11c.K1-39.L3 CDRL2 hu.14H11c.K1-39.L4 CDRL2 hu.14H11c.K1-5.L1 CDRL2 hu.14H11c.K1-8.L1 CDRL2 hu.14H11c.K1-6.L1 CDRL2 hu.14H11c-L2.Q38K CDRL2	GASNLES
12	rb.14H11c CDRL3 hu.14H11c.K1-39.L1 CDRL3 hu.14H11c.K1-39.L2 CDRL3 hu.14H11c.K1-39.L3 CDRL3 hu.14H11c.K1-39.L4 CDRL3 hu.14H11c.K1-5.L1 CDRL3 hu.14H11c.K1-8.L1 CDRL3 hu.14H11c.K1-6.L1 CDRL3 hu.14H11c-L2.Q38K CDRL3	LGGYSYSTGTA
122	rb.14H11c VH FR1	QSLEESGGDLVKPGASLTLTCTASGFSS

123	hu.14H11c.V3-53*1.H1 VH FR1 hu.14H11c.V3-53*1.H3 VH FR1 hu.14H11c.V3-53*1.H4 VH FR1 hu.14H11c.V3-53*1.H5 VH FR1 hu.14H11c.V3-53*1.H6 VH FR1 hu.14H11c.V3-53*1.H7 VH FR1 hu.14H11c.V3-53*1.H8 VH FR1 hu.14H11c.V3-53*1.H9 VH FR1 hu.14H11c-H11 VH FR1 hu.14H11c-H11.Q39E VH FR1	EQQLVESGGGLIQPGGSLRLSCAASGFSFS
124	hu.14H11c.V3-53*1.H2 VH FR1 hu.14H11c.V3-53*1.H10 VH FR1	EVQLVESGGGLIQPGGSLRLSCAASGFSFS
125	hu.14H11c.V3-53*4.H1 VH FR1	EQQLVESGGGLVQPGGSLRLSCAASGFSFS
126	hu.14H11c.V3-23.H1 VH FR1	EQQLLESGGGLVQPGGSLRLSCAASGFSFS
127	hu.14H11c.V3-33*2.H1 VH FR1	EQQLVESGGGVVQPGGSLRLSCAASGFSFS
128	hu.14H11c.V3-21.H1 VH FR1	EQQLVESGGGLVKPGGSLRLSCAASGFSFS
129	rb.14H11c VH FR2 hu.14H11c.V3-53*1.H1 VH FR2 hu.14H11c.V3-53*1.H2 VH FR2 hu.14H11c.V3-53*1.H5 VH FR2 hu.14H11c.V3-53*1.H6 VH FR2 hu.14H11c.V3-53*1.H7 VH FR2 hu.14H11c.V3-53*1.H8 VH FR2 hu.14H11c.V3-53*1.H9 VH FR2 hu.14H11c.V3-53*4.H1 VH FR2 hu.14H11c.V3-23.H1 VH FR2 hu.14H11c.V3-33*2.H1 VH FR2 hu.14H11c.V3-21.H1 VH FR2	WVRQAPGKGLEWIA
130	hu.14H11c.V3-53*1.H3 VH FR2	WVRQAPGKGLEWVA
131	hu.14H11c.V3-53*1.H4 VH FR2	WVRQAPGKGLEWIS
132	hu.14H11c.V3-53*1.H10 VH FR2 hu.14H11c-H11 VH FR2	WVRQAPGKGLEWVS
133	hu.14H11c-H11.Q39E VH FR2	WVREAPGKGLEWVS
134	rb.14H11c VH FR3	RFTISKTSSTAVTLQMSSLTAADTATYFCAR
135	hu.14H11c.V3-53*1.H1 VH FR3 hu.14H11c.V3-53*1.H2 VH FR3 hu.14H11c.V3-53*1.H3 VH FR3 hu.14H11c.V3-53*1.H4 VH FR3 hu.14H11c.V3-53*1.H9 VH FR3 hu.14H11c.V3-23.H1 VH FR3	RFTISKDSSKNTVYLQMNSLRAEDTAVYFCAR
136	hu.14H11c.V3-53*1.H5 VH FR3	RFTISRDSKNTVYLQMNSLRAEDTAVYFCAR
137	hu.14H11c.V3-53*1.H6 VH FR3	RFTISKDSSKNTVYLQMNSLRAEDTAVYFCAR
138	hu.14H11c.V3-53*1.H7 VH FR3	RFTISKDSSKNTLYLQMNSLRAEDTAVYFCAR
139	hu.14H11c.V3-53*1.H8 VH FR3	RFTISKDSSKNTVYLQMNSLRAEDTAVYYCAR
140	hu.14H11c.V3-53*1.H10 VH FR3 hu.14H11c-H11 VH FR3	RFTISRDSKNTLYLQMNSLRAEDTAVYYCAR

	hu.14H11c-H11.Q39E VH FR3	
141	hu.14H11c.V3-53*4.H1 VH FR3	RFTISKHSSKNTVYLQMNSLRAEDTAVYFCAR
142	hu.14H11c.V3-33*2.H1 VH FR3	RFTISKDSSSTNTVFLQMNSLRAEDTAVYFCAR
143	hu.14H11c.V3-21.H1 VH FR3	RFTISKDTASTSVYLQMNSLRAEDTAVYFCAR
144	rb.14H11c VH FR4 hu.14H11c.V3-53*1.H1 VH FR4 hu.14H11c.V3-53*1.H2 VH FR4 hu.14H11c.V3-53*1.H3 VH FR4 hu.14H11c.V3-53*1.H4 VH FR4 hu.14H11c.V3-53*1.H5 VH FR4 hu.14H11c.V3-53*1.H6 VH FR4 hu.14H11c.V3-53*1.H7 VH FR4 hu.14H11c.V3-53*1.H8 VH FR4 hu.14H11c.V3-53*4.H1 VH FR4 hu.14H11c.V3-23.H1 VH FR4 hu.14H11c.V3-33*2.H1 VH FR4 hu.14H11c.V3-21.H1 VH FR4 hu.14H11c-H11 VH FR4 hu.14H11c-H11.Q39E VH FR4	WGPGTLVTVSS
145	hu.14H11c.V3-53*1.H9 VH FR4 hu.14H11c.V3-53*1.H10 VH FR4	WGQGTLVTVSS
146	rb.14H11c VL FR1	AIEMTQSPPSLSASVGETVRI RC
147	hu.14H11c.K1-39.L1 VL FR1 hu.14H11c.K1-39.L2 VL FR1 hu.14H11c.K1-39.L3 VL FR1 hu.14H11c.K1-39.L4 VL FR1 hu.14H11c-L2.Q38K VL FR1	DIQMTQSPSSLSASVGDRVTTTC
148	hu.14H11c.K1-5.L1 VL FR1	DIQMTQSPSTLSASVGDRVTTTC
149	hu.14H11c.K1-8.L1 VL FR1	AIEMTQSPSSFSASTGDRVTTTC
150	hu.14H11c.K1-6.L1 VL FR1	AIQMTQSPSSLSASVGDRVTTTC
151	rb.14H11c VL FR2	WYQQKPGKPPPTLLIY
152	hu.14H11c.K1-39.L1 VL FR2 hu.14H11c.K1-39.L3 VL FR2 hu.14H11c.K1-5.L1 VL FR2 hu.14H11c.K1-8.L1 VL FR2 hu.14H11c.K1-6.L1 VL FR2	WYQQKPGKPPKLLIY
153	hu.14H11c.K1-39.L2 VL FR2 hu.14H11c.K1-39.L4 VL FR2	WYQQKPGKAPKLLIY
154	hu.14H11c-L2.Q38K VL FR2	WYQKKPGKAPKLLIY
155	rb.14H11c VL FR3	GVPPRFSGSGSGTDYTLTIGGVQAEDAATYYC
156	hu.14H11c.K1-39.L1 VL FR3 hu.14H11c.K1-39.L2 VL FR3 hu.14H11c.K1-8.L1 VL FR3 hu.14H11c.K1-6.L1 VL FR3 hu.14H11c-L2.Q38K VL FR3	GVPSRFSGSGSGTDYTLTISSLQPEDFATYYC
157	hu.14H11c.K1-39.L3 VL FR3 hu.14H11c.K1-39.L4 VL FR3	GVPSRFSGSGSGTDFTLTISLQPEDFATYYC
158	hu.14H11c.K1-5.L1 VL FR3	GVPSRFSGSGSGTEYTLTISSLQPDDEFATYYC
159	rb.14H11c VL FR4	FGAGTKVEIK
160	hu.14H11c.K1-39.L1 VL FR4 hu.14H11c.K1-39.L2 VL FR4 hu.14H11c.K1-39.L3 VL FR4 hu.14H11c.K1-39.L4 VL FR4 hu.14H11c.K1-5.L1 VL FR4 hu.14H11c.K1-8.L1 VL FR4 hu.14H11c.K1-6.L1 VL FR4 hu.14H11c-L2.Q38K VL FR4	FGGGTKVEIK
116	rb.14H11 Heavy Chain Variable Region (VH)	QSLEESGGDL VKPGASLTLT CTASGFSFSS SYMCMWVRQA PGKLEWIAS IYAGSSGAPY YAGWAKGRFT ISKTSSTAVT

		LQMSSLTAAD TATYFCAREG FAETGGYGYA AYFNLWGPPT LVTVSS
13	rb.14H11c Heavy Chain Variable Region (VH)	QSLEESGGDL VKPGASLTLT CTASGFSFSS SYMSWVRQA PGKGLEWIAS IYAGSSGAPY YAGWAKGRFT ISKTSSTAVT LQMSSLTAAD TATYFCAREG FAETGGYGYA AYFNLWGPPT LVTVSS
14	rb.14H11c Light Chain Variable Region (VL) rb.14H11 VL	AIEMTQSPPS LSASVGETVR IRCLASEDIA SSVSWYQQKP GKPPTLLIYG ASNLESGVPP RFTGSGSGTD YTLTIGGVQA EDAATYYCLG GYSYSTGTA FGAGTKVEIK
198	rb.14H11c Heavy Chain Fab (amino acids 20-256, when numbered beginning with signal sequence)	QSLEESGGDL VKPGASLTLT CTASGFSFSS SYMSWVRQA PGKGLEWIAS IYAGSSGAPY YAGWAKGRFT ISKTSSTAVT LQMSSLTAAD TATYFCAREG FAETGGYGYA AYFNLWGPPT LVTVSSGQPK APSVFPLAPC CGDTPSSTVT LGCLVKGYLP EPVTVTNWNSG TLTNGVTRTFP SVRQSSGLYS LSSVSVSTSS SQPVTCNVAH PATNTKVDKT VAPSTCSKPT HHHHHHP
199	rb.14H11c Light Chain Fab (amino acids 23-237, when numbered beginning with signal sequence)	AIEMTQSPPS LSASVGETVR IRCLASEDIA NSVSWYQQKP GKPPTLLIYG ASNLESGVPP RFTGSGSGTD YTLTIGGVQA EDAATYYCLG GYSYSTGTA FGAGTKVEIK RDPVAPSVLL FPFSKEELTT GTATIVCVAN KFYPSPDITVT WKVDGTTQSS GIENSKTPQS PEDNTYNLSS TLTLTSTQYN SHKEYTCKVT QGTTSVVQSF NRGDC
15	hu.14H11c.V3-53*1.H1 VH	EQQLVESGGG LIQPGGSLRL SCAASGFSFS SSYYMSWVRQ APGKGLEWIA SIYAGSSGAP YYAGWAKGRF TISKDSSKNT VYLQMNSLRA EDTAVYFCAR EGFAETGGYG YAAYFNLWGP GTLVTVSS
16	hu.14H11c.V3-53*1.H2 VH	EQQLVESGGG LIQPGGSLRL SCAASGFSFS SSYYMSWVRQ APGKGLEWIA SIYAGSSGAP YYAGWAKGRF TISKDSSKNT VYLQMNSLRA EDTAVYFCAR EGFAETGGYG YAAYFNLWGP GTLVTVSS
17	hu.14H11c.V3-53*1.H3 VH	EQQLVESGGG LIQPGGSLRL SCAASGFSFS SSYYMSWVRQ APGKGLEWVA SIYAGSSGAP YYAGWAKGRF TISKDSSKNT VYLQMNSLRA EDTAVYFCAR EGFAETGGYG YAAYFNLWGP GTLVTVSS
18	hu.14H11c.V3-53*1.H4 VH	EQQLVESGGG LIQPGGSLRL SCAASGFSFS SSYYMSWVRQ APGKGLEWIS SIYAGSSGAP YYAGWAKGRF TISKDSSKNT VYLQMNSLRA EDTAVYFCAR EGFAETGGYG YAAYFNLWGP GTLVTVSS
19	hu.14H11c.V3-53*1.H5 VH	EQQLVESGGG LIQPGGSLRL SCAASGFSFS SSYYMSWVRQ APGKGLEWIA SIYAGSSGAP YYAGWAKGRF TISRDSSKNT VYLQMNSLRA EDTAVYFCAR EGFAETGGYG YAAYFNLWGP GTLVTVSS
20	hu.14H11c.V3-53*1.H6 VH	EQQLVESGGG LIQPGGSLRL SCAASGFSFS SSYYMSWVRQ APGKGLEWIA SIYAGSSGAP YYAGWAKGRF TISKDSSKNT VYLQMNSLRA EDTAVYFCAR EGFAETGGYG YAAYFNLWGP GTLVTVSS
21	hu.14H11c.V3-53*1.H7 VH	EQQLVESGGG LIQPGGSLRL SCAASGFSFS SSYYMSWVRQ APGKGLEWIA SIYAGSSGAP YYAGWAKGRF TISKDSSKNT LYLQMNSLRA EDTAVYFCAR EGFAETGGYG YAAYFNLWGP GTLVTVSS
22	hu.14H11c.V3-53*1.H8 VH	EQQLVESGGG LIQPGGSLRL SCAASGFSFS SSYYMSWVRQ APGKGLEWIA SIYAGSSGAP YYAGWAKGRF TISKDSSKNT VYLQMNSLRA EDTAVYFCAR EGFAETGGYG YAAYFNLWGP GTLVTVSS
23	hu.14H11c.V3-53*1.H9 VH	EQQLVESGGG LIQPGGSLRL SCAASGFSFS SSYYMSWVRQ APGKGLEWIA SIYAGSSGAP YYAGWAKGRF TISKDSSKNT VYLQMNSLRA EDTAVYFCAR EGFAETGGYG YAAYFNLWGP GTLVTVSS
24	hu.14H11c.V3-53*1.H10 VH	EQQLVESGGG LIQPGGSLRL SCAASGFSFS SSYYMSWVRQ APGKGLEWVS SIYAGSSGAP YYAGWAKGRF TISRDSSKNT LYLQMNSLRA EDTAVYFCAR EGFAETGGYG YAAYFNLWGP GTLVTVSS

25	hu.14H11c.V3-53*4.H1 VH	EQQLVESGGG LVQPGGSLRL SCAASGFSFS SSYYMSWVRQ APGKGLEWIA SIYAGSSGAP YYAGWAKGRF TISKHSSKNT VYLQMNLSRA EDTAVYFCAR EGFAETGGYG YAAYFNLWGP GTLVTVSS
26	hu.14H11c.V3-23.H1 VH	EQQLLES GGG LVQPGGSLRL SCAASGFSFS SSYYMSWVRQ APGKGLEWIA SIYAGSSGAP YYAGWAKGRF TISKDSSKNT VYLQMNLSRA EDTAVYFCAR EGFAETGGYG YAAYFNLWGP GTLVTVSS
27	hu.14H11c.V3-33*2.H1 VH	EQQLVESGGG VVQPGGSLRL SCAASGFSFS SSYYMSWVRQ APGKGLEWIA SIYAGSSGAP YYAGWAKGRF TISKDSSNT VFLQMNLSRA EDTAVYFCAR EGFAETGGYG YAAYFNLWGP GTLVTVSS
28	hu.14H11c.V3-21.H1 VH	EQQLVESGGG LVKPGGSLRL SCAASGFSFS SSYYMSWVRQ APGKGLEWIA SIYAGSSGAP YYAGWAKGRF TISKDTASTS VYLQMNLSRA EDTAVYFCAR EGFAETGGYG YAAYFNLWGP GTLVTVSS
29	hu.14H11c-H11 VH	EQQLVESGGG LIQPGGSLRL SCAASGFSFS SSYYMSWVRQ APGKGLEWVS SIYAGSSGAP YYAGWAKGRF TISRDNKNT LYLQMNLSRA EDTAVYYCAR EGFAETGGYG YAAYFNLWGP GTLVTVSS
30	hu.14H11c-H11.Q39E VH	EQQLVESGGG LIQPGGSLRL SCAASGFSFS SSYYMSWVRE APGKGLEWVS SIYAGSSGAP YYAGWAKGRF TISRDNKNT LYLQMNLSRA EDTAVYYCAR EGFAETGGYG YAAYFNLWGP GTLVTVSS
31	hu.14H11c.K1-39.L1 VL	DIQMTQSPSS LSASVGDRVT ITCLASEDIA SSVSWYQQKP GKPPKLLIYG ASNLESGVPS RFGSGSGTD YTLTISSLQP EDFATYYCLG GYSYSTGTGTA FGGGTKVEIK
32	hu.14H11c.K1-39.L2 VL	DIQMTQSPSS LSASVGDRVT ITCLASEDIA SSVSWYQQKP GKAPKLLIYG ASNLESGVPS RFGSGSGTD YTLTISSLQP EDFATYYCLG GYSYSTGTGTA FGGGTKVEIK
33	hu.14H11c.K1-39.L3 VL	DIQMTQSPSS LSASVGDRVT ITCLASEDIA SSVSWYQQKP GKPPKLLIYG ASNLESGVPS RFGSGSGTD FTLTISSLQP EDFATYYCLG GYSYSTGTGTA FGGGTKVEIK
34	hu.14H11c.K1-39.L4 VL	DIQMTQSPSS LSASVGDRVT ITCLASEDIA SSVSWYQQKP GKAPKLLIYG ASNLESGVPS RFGSGSGTD FTLTISSLQP EDFATYYCLG GYSYSTGTGTA FGGGTKVEIK
35	hu.14H11c.K1-5.L1 VL	DIQMTQSPST LSASVGDRVT ITCLASEDIA SSVSWYQQKP GKPPKLLIYG ASNLESGVPS RFGSGSGTE YTLTISSLQP DDFATYYCLG GYSYSTGTGTA FGGGTKVEIK
36	hu.14H11c.K1-8.L1 VL	AIQMTQSPSS FSASTGDRVT ITCLASEDIA SSVSWYQQKP GKPPKLLIYG ASNLESGVPS RFGSGSGTD YTLTISSLQP EDFATYYCLG GYSYSTGTGTA FGGGTKVEIK
37	hu.14H11c.K1-6.L1 VL	AIQMTQSPSS LSASVGDRVT ITCLASEDIA SSVSWYQQKP GKPPKLLIYG ASNLESGVPS RFGSGSGTD YTLTISSLQP EDFATYYCLG GYSYSTGTGTA FGGGTKVEIK
38	hu.14H11c-L2.Q38K VL	DIQMTQSPSS LSASVGDRVT ITCLASEDIA SSVSWYQKKP GKAPKLLIYG ASNLESGVPS RFGSGSGTD YTLTISSLQP EDFATYYCLG GYSYSTGTGTA FGGGTKVEIK
39	hu.10C5-H28L5 CDRH1 hu.10C5-H28.N53V CDRH1 hu.10C5-H28.Q39K.N53V CDRH1	SYGVT
107	hu.10C5-H28.G33P CDRH1 hu.10C5-H28.G33P.N53V CDRH1	SYPVT
40	hu.10C5-H28L5 CDRH2 hu.10C5-H28.G33P CDRH2	YITSNYGVSYASWAKS
41	hu.10C5-H28.N53V CDRH2 hu.10C5-H28.Q39K.N53V CDRH2	YITSVYGVSYASWAKS

	hu.10C5-H28.G33P.N53V CDRH2	
42	hu.10C5-H28L5 CDRH3 hu.10C5-H28.N53V CDRH3 hu.10C5-H28.Q39K.N53V CDRH3 hu.10C5-H28.G33P CDRH3 hu.10C5-H28.G33P.N53V CDRH3	ENPDYGYAYDA
43	hu.10C5-H28L5 CDRL1 hu.10C5-L5.F92Y CDRL1 hu.10C5-L5.S95F CDRL1 hu.10C5-L5.F92Y.S95F CDRL1 hu.10C5-L5.Q38E.F92Y CDRL1 hu.10C5-L5.Q38E.S95F CDRL1 hu.10C5-L5.Q38E.F92Y.S95F CDRL1	QASESISNELS
44	hu.10C5-L5.S34K CDRL1 hu.10C5-L5.S34K.F92Y CDRL1 hu.10C5-L5.S34K.S95F CDRL1 hu.10C5-L5.S34K.F92Y.S95F CDRL1 hu.10C5-L5.Q38E.S34K CDRL1 hu.10C5-L5.Q38E.S34K.F92Y CDRL1 hu.10C5-L5.Q38E.S34K.S95F CDRL1 hu.10C5- L5.Q38E.S34K.F92Y.S95F CDRL1	QASESISNELK
45	hu.10C5-H28L5 CDRL2 hu.10C5-L5.S34K CDRL2 hu.10C5-L5.F92Y CDRL2 hu.10C5-L5.S95F CDRL2 hu.10C5-L5.S34K.F92Y CDRL2 hu.10C5-L5.S34K.S95F CDRL2 hu.10C5-L5.F92Y.S95F CDRL2 hu.10C5-L5.S34K.F92Y.S95F CDRL2 hu.10C5-L5.Q38E.S34K CDRL2 hu.10C5-L5.Q38E.F92Y CDRL2 hu.10C5-L5.Q38E.S95F CDRL2 hu.10C5-L5.Q38E.S34K.F92Y CDRL2 hu.10C5-L5.Q38E.S34K.S95F CDRL2 hu.10C5-L5.Q38E.F92Y.S95F CDRL2	YASTLAS

	hu.10C5-L5.Q38E.S34K.F92Y.S95F CDRL2	
46	hu.10C5-H28L5 CDRL3 hu.10C5-L5.S34K CDRL3 hu.10C5-L5.Q38E.S34K CDRL3	AQGFGSSGVENV
47	hu.10C5-L5.F92Y CDRL3 hu.10C5-L5.S34K.F92Y CDRL3 hu.10C5-L5.Q38E.F92Y CDRL3 hu.10C5-L5.Q38E.S34K.F92Y CDRL3	AQGYGSSGVENV
48	hu.10C5-L5.S95F CDRL3 hu.10C5-L5.S34K.S95F CDRL3 hu.10C5-L5.Q38E.S95F CDRL3 hu.10C5-L5.Q38E.S34K.S95F CDRL3	AQGFSGSGVENV
49	hu.10C5-L5.F92Y.S95F CDRL3 10C5-L5.S34K.F92Y.S95F CDRL3 hu.10C5-L5.Q38E.F92Y.S95F CDRL3 hu.10C5-L5.Q38E.S34K.F92Y.S95F CDRL3	AQGYGSGGVENV
161	hu.10C5-H28L5 VH FR1 hu.10C5-H28.G33P VH FR1 hu.10C5-H28.N54V VH FR1 hu.10C5-H28.G33P.N54V VH FR1 hu.10C5-H28.Q39K.N54V VH FR1	EVQLVESGGGLVQPGGSLRLSCAASGFSLS
162	hu.10C5-H28L5 VH FR2 hu.10C5-H28.G33P VH FR2 hu.10C5-H28.N54V VH FR2 hu.10C5-H28.G33P.N54V VH FR2	WVRQAPGKGLEWIG
163	hu.10C5-H28.Q39K.N54V VH FR2	WVRKAPGKGLEWIG
164	hu.10C5-H28L5 VH FR3 hu.10C5-H28.G33P VH FR3 hu.10C5-H28.N54V VH FR3 hu.10C5-H28.G33P.N54V VH FR3 hu.10C5-H28.Q39K.N54V VH FR3	RSTISRDTSKNTVYLQMGSRAEDMAVYYCAR
165	hu.10C5-H28L5 VH FR4 hu.10C5-H28.G33P VH FR4 hu.10C5-H28.N54V VH FR4 hu.10C5-H28.G33P.N54V VH FR4 hu.10C5-H28.Q39K.N54V VH FR4	WGQGTTVTVSS

166	hu.10C5-H28L5 VL FR1 hu.10C5-L5.S34K VL FR1 hu.10C5-L5.F92Y VL FR1 hu.10C5-L5.S95F VL FR1 hu.10C5-L5.S34.KF92Y VL FR1 hu.10C5-L5.S34K.S95F VL FR1 hu.10C5-L5.F92Y.S95F VL FR1 hu.10C5-L5.S34K.F92Y.S95F VL FR1 hu.10C5-L5.Q38E.S34K VL FR1 hu.10C5-L5.Q38E.F92Y VL FR1 hu.10C5-L5.Q38E.S95F VL FR1 hu.10C5-L5.Q38E.S34K.F92Y VL FR1 hu.10C5-L5.Q38E.S34K.S95F VL FR1 hu.10C5-L5.Q38E.F92Y.S95F VL FR1 hu.10C5-L5.Q38E.S34K.F92Y.S95F VL FR1	AIRMTQSPSSFSASTGDRVITTC
167	hu.10C5-H28L5 VL FR2 hu.10C5-L5.S34K VL FR2 hu.10C5-L5.F92Y VL FR2 hu.10C5-L5.S95F VL FR2 hu.10C5-L5.S34.KF92Y VL FR2 hu.10C5-L5.S34K.S95F VL FR2 hu.10C5-L5.F92Y.S95F VL FR2 hu.10C5-L5.S34K.F92Y.S95F VL FR2	WYQQKPGKAPKLLIY
168	hu.10C5-L5.Q38E.S34K VL FR2 hu.10C5-L5.Q38E.F92Y VL FR2 hu.10C5-L5.Q38E.S95F VL FR2 hu.10C5-L5.Q38E.S34K.F92Y VL FR2 hu.10C5-L5.Q38E.S34K.S95F VL FR2 hu.10C5-L5.Q38E.F92Y.S95F VL FR2 hu.10C5-L5.Q38E.S34K.F92Y.S95F VL FR2	WYQEKPGRKAPKLLIY
169	hu.10C5-H28L5 VL FR3 hu.10C5-L5.S34K VL FR3	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC

	hu.10C5-L5.F92Y VL FR3 hu.10C5-L5.S95F VL FR3 hu.10C5-L5.S34.KF92Y VL FR3 hu.10C5-L5.S34K.S95F VL FR3 hu.10C5-L5.F92Y.S95F VL FR3 hu.10C5-L5.S34K.F92Y.S95F VL FR3 hu.10C5-L5.Q38E.S34K VL FR3 hu.10C5-L5.Q38E.F92Y VL FR3 hu.10C5-L5.Q38E.S95F VL FR3 hu.10C5-L5.Q38E.S34K.F92Y VL FR3 hu.10C5-L5.Q38E.S34K.S95F VL FR3 hu.10C5-L5.Q38E.F92Y.S95F VL FR3 hu.10C5-L5.Q38E.S34K.F92Y.S95F VL FR3	
170	hu.10C5-H28L5 VL FR4 hu.10C5-L5.S34K VL FR4 hu.10C5-L5.F92Y VL FR4 hu.10C5-L5.S95F VL FR4 hu.10C5-L5.S34.KF92Y VL FR4 hu.10C5-L5.S34K.S95F VL FR4 hu.10C5-L5.F92Y.S95F VL FR4 hu.10C5-L5.S34K.F92Y.S95F VL FR4 hu.10C5-L5.Q38E.S34K VL FR4 hu.10C5-L5.Q38E.F92Y VL FR4 hu.10C5-L5.Q38E.S95F VL FR4 hu.10C5-L5.Q38E.S34K.F92Y VL FR4 hu.10C5-L5.Q38E.S34K.S95F VL FR4 hu.10C5-L5.Q38E.F92Y.S95F VL FR4 hu.10C5-L5.Q38E.S34K.F92Y.S95F VL FR4	FGGGTKVEIK
50	hu.10C5-H28L5 VH	EVQLVESGGG LVQPGGSLRL SCAASGFSLs SYGVTWVRQA PGKGLEWIGY ITSNYGVSY ASWAKSRSTI SRDTSKNTVY LQMGS LRAED MAVYYCAREN PDYGYAYDAW GQGTTVTVSS
51	hu.10C5-H28L5 VL	AIRMTQSPSS FSASTGDRVT ITCQASESIS NELSWYQQKP

		GKAPKLLIYY EDFATYYCAQ	ASTLASGVPS GFGSSGVENV	RFSGSGSGTD FGGGTKVEIK	FTLTISLQ
52	hu.10C5-H28.N53V VH	EVQLVESGGG PGKGLEWIGY LQMGSRAED	LVQPGGSLRL ITSVYGVSY MAVYYCAREN	SCAASGFSL ASWAKSRSTI PDYGYAYDAW	SYGVTWVRQA SRDTSKNTVY QGQTTVTVSS
53	hu.10C5-H28.Q39K.N53V VH	EVQLVESGGG PGKGLEWIGY LQMGSRAED	LVQPGGSLRL ITSVYGVSY MAVYYCAREN	SCAASGFSL ASWAKSRSTI PDYGYAYDAW	SYGVTWVRKA SRDTSKNTVY QGQTTVTVSS
105	hu.10C5-H28.G33P VH	EVQLVESGGG PGKGLEWIGY LQMGSRAED	LVQPGGSLRL ITSNYGVSY MAVYYCAREN	SCAASGFSL ASWAKSRSTI PDYGYAYDAW	SYFVTWVRQA SRDTSKNTVY QGQTTVTVSS
106	hu.10C5-H28.G33P.N53V VH	EVQLVESGGG PGKGLEWIGY LQMGSRAED	LVQPGGSLRL ITSVYGVSY MAVYYCAREN	SCAASGFSL ASWAKSRSTI PDYGYAYDAW	SYFVTWVRQA SRDTSKNTVY QGQTTVTVSS
54	hu.10C5-L5.S34K VL	AIRMTQSPSS GKAPKLLIYY EDFATYYCAQ	FSASTGDRVT ASTLASGVPS GFGSSGVENV	ITCQASESIS RFSGSGSGTD FGGGTKVEIK	NELKWWQKP FTLTISLQ
55	hu.10C5-L5.F92Y VL	AIRMTQSPSS GKAPKLLIYY EDFATYYCAQ	FSASTGDRVT ASTLASGVPS GYGSSGVENV	ITCQASESIS RFSGSGSGTD FGGGTKVEIK	NELSWYQKP FTLTISLQ
56	hu.10C5-L5.S95F VL	AIRMTQSPSS GKAPKLLIYY EDFATYYCAQ	FSASTGDRVT ASTLASGVPS GFGSFGVENV	ITCQASESIS RFSGSGSGTD FGGGTKVEIK	NELSWYQKP FTLTISLQ
57	hu.10C5-L5.S34K.F92Y VL	AIRMTQSPSS GKAPKLLIYY EDFATYYCAQ	FSASTGDRVT ASTLASGVPS GYGSSGVENV	ITCQASESIS RFSGSGSGTD FGGGTKVEIK	NELKWWQKP FTLTISLQ
58	hu.10C5-L5.S34K.S95F VL	AIRMTQSPSS GKAPKLLIYY EDFATYYCAQ	FSASTGDRVT ASTLASGVPS GFGSFGVENV	ITCQASESIS RFSGSGSGTD FGGGTKVEIK	NELKWWQKP FTLTISLQ
59	hu.10C5-L5.F92Y.S95F VL	AIRMTQSPSS GKAPKLLIYY EDFATYYCAQ	FSASTGDRVT ASTLASGVPS GYGSSGVENV	ITCQASESIS RFSGSGSGTD FGGGTKVEIK	NELSWYQKP FTLTISLQ
60	hu.10C5-L5.S34K.F92Y.S95F VL	AIRMTQSPSS GKAPKLLIYY EDFATYYCAQ	FSASTGDRVT ASTLASGVPS GYGSSGVENV	ITCQASESIS RFSGSGSGTD FGGGTKVEIK	NELKWWQKP FTLTISLQ
61	hu.10C5-L5.Q38E.S34K VL	AIRMTQSPSS GKAPKLLIYY EDFATYYCAQ	FSASTGDRVT ASTLASGVPS GFGSSGVENV	ITCQASESIS RFSGSGSGTD FGGGTKVEIK	NELKWWQKP FTLTISLQ
62	hu.10C5-L5.Q38E.F92Y VL	AIRMTQSPSS GKAPKLLIYY EDFATYYCAQ	FSASTGDRVT ASTLASGVPS GYGSSGVENV	ITCQASESIS RFSGSGSGTD FGGGTKVEIK	NELSWYQKP FTLTISLQ
63	hu.10C5-L5.Q38E.S95F VL	AIRMTQSPSS GKAPKLLIYY EDFATYYCAQ	FSASTGDRVT ASTLASGVPS GFGSFGVENV	ITCQASESIS RFSGSGSGTD FGGGTKVEIK	NELSWYQKP FTLTISLQ
64	hu.10C5-L5.Q38E.S34K.F92Y VL	AIRMTQSPSS GKAPKLLIYY EDFATYYCAQ	FSASTGDRVT ASTLASGVPS GYGSSGVENV	ITCQASESIS RFSGSGSGTD FGGGTKVEIK	NELKWWQKP FTLTISLQ
65	hu.10C5-L5.Q38E.S34K.S95F VL	AIRMTQSPSS GKAPKLLIYY EDFATYYCAQ	FSASTGDRVT ASTLASGVPS GFGSFGVENV	ITCQASESIS RFSGSGSGTD FGGGTKVEIK	NELKWWQKP FTLTISLQ
66	hu.10C5-L5.Q38E.F92Y.S95F VL	AIRMTQSPSS GKAPKLLIYY EDFATYYCAQ	FSASTGDRVT ASTLASGVPS GYGSSGVENV	ITCQASESIS RFSGSGSGTD FGGGTKVEIK	NELSWYQKP FTLTISLQ
67	hu.10C5-L5.Q38E.S34K.F92Y.S95F VL	AIRMTQSPSS GKAPKLLIYY EDFATYYCAQ	FSASTGDRVT ASTLASGVPS GYGSSGVENV	ITCQASESIS RFSGSGSGTD FGGGTKVEIK	NELKWWQKP FTLTISLQ
68	hu.9H5-H14L4 CDRH1 hu.9H5-H14.G54A CDRH1 hu.9H5-H14.G98Q CDRH1 hu.9H5-H14.G54A.G98Q CDRH1	SYGVS			

	hu.9H5-H14.Q39K.CDRH1 hu.9H5-H14.Q39K.G54A.CDRH1 hu.9H5-H14.Q39K.G98Q.CDRH1 hu.9H5-H14.Q39K.G54A.G98Q.CDRH1	
69	hu.9H5-H14L4.CDRH2 hu.9H5-H14.G98Q.CDRH2 hu.9H5-H14.Q39K.CDRH2 hu.9H5-H14.Q39K.G98Q.CDRH2	FIGSGGFAYYASWAKS
70	hu.9H5-H14.G54A.CDRH2 hu.9H5-H14.G54A.G98Q.CDRH2 hu.9H5-H14.Q39K.G54A.CDRH2 hu.9H5-H14.Q39K.G54A.G98Q.CDRH2	FIGSAGFAYYASWAKS
71	hu.9H5-H14L4.CDRH3 hu.9H5-H14.G54A.CDRH3 hu.9H5-H14.Q39K.CDRH3 hu.9H5-H14.Q39K.G54A.CDRH3	DDVGGGKSLDI
72	hu.9H5-H14.G98Q.CDRH3 hu.9H5-H14.G54A.G98Q.CDRH3 hu.9H5-H14.Q39K.G98Q.CDRH3 hu.9H5-H14.Q39K.G54A.G98Q.CDRH3	DDVQGGKSLDI
73	hu.9H5-H14L4.CDRL1 hu.9H5-L4.H89V.CDRL1 hu.9H5-L4.S95Y.CDRL1 hu.9H5-L4.H89V.S95Y.CDRL1 hu.9H5-L4.Q38E.CDRL1 hu.9H5-L4.Q38E.H89V.CDRL1 hu.9H5-L4.Q38E.S95Y.CDRL1 hu.9H5-L4.Q38E.H89V.S95Y.CDRL1	QASQSISSYLS
74	hu.9H5-H14L4.CDRL2 hu.9H5-L4.H89V.CDRL2 hu.9H5-L4.S95Y.CDRL2 hu.9H5-L4.H89V.S95Y.CDRL2 hu.9H5-L4.Q38E.CDRL2 hu.9H5-L4.Q38E.H89V.CDRL2 hu.9H5-L4.Q38E.S95Y.CDRL2 hu.9H5-L4.Q38E.H89V.S95Y.CDRL2	SASTLAS
75	hu.9H5-H14L4.CDRL3 hu.9H5-L4.Q38E.CDRL3	HQDYTSSNVDNT
76	hu.9H5-L4.H89V.CDRL3 hu.9H5-L4.Q38E.H89V.CDRL3	VQDYTSSNVDNT
77	hu.9H5-L4.S95Y.CDRL3 hu.9H5-L4.Q38E.S95Y.CDRL3	HQDYTSYNVDNT
78	hu.9H5-L4.H89V.S95Y.CDRL3	VQDYTSYNVDNT

	hu.9H5-L4.Q38E.H89V.S95Y CDRL3	
171	hu.9H5-H14L4 VH FR1 hu.9H5-H14.G54A VH FR1 hu.9H5-H14.G98Q VH FR1 hu.9H5-H14.G54A.G98Q VH FR1 hu.9H5-H14.Q39K VH FR1 hu.9H5-H14.Q39K.G54A VH FR1 hu.9H5-H14.Q39K.G98Q VH FR1 hu.9H5-H14.Q39K.G54A.G98Q VH FR1	EVQLVESGGGLIQPGGSLRLSCAASGFSLS
172	hu.9H5-H14L4 VH FR2 hu.9H5-H14.G54A VH FR2 hu.9H5-H14.G98Q VH FR2 hu.9H5-H14.G54A.G98Q VH FR2	WVRQAPGKGGLEYVG
173	hu.9H5-H14.Q39K VH FR2 hu.9H5-H14.Q39K.G54A VH FR2 hu.9H5-H14.Q39K.G98Q VH FR2 hu.9H5-H14.Q39K.G54A.G98Q VH FR2	WVRKAPGKGGLEYVG
174	hu.9H5-H14L4 VH FR3 hu.9H5-H14.G54A VH FR3 hu.9H5-H14.G98Q VH FR3 hu.9H5-H14.G54A.G98Q VH FR3 hu.9H5-H14.Q39K VH FR3 hu.9H5-H14.Q39K.G54A VH FR3 hu.9H5-H14.Q39K.G98Q VH FR3 hu.9H5-H14.Q39K.G54A.G98Q VH FR3	RFTISRDN SKNTLYLQMNSLRAEDTAVYYCAR
175	hu.9H5-H14L4 VH FR4 hu.9H5-H14.G54A VH FR4 hu.9H5-H14.G98Q VH FR4 hu.9H5-H14.G54A.G98Q VH FR4 hu.9H5-H14.Q39K VH FR4 hu.9H5-H14.Q39K.G54A VH FR4 hu.9H5-H14.Q39K.G98Q VH FR4 hu.9H5-H14.Q39K.G54A.G98Q VH FR4	WGQGTLVTVSS
176	hu.9H5-H14L4 VL FR1 hu.9H5-L4.H89V VL FR1 hu.9H5-L4.S95Y VL FR1 hu.9H5-L4.H89V.S95Y VL FR1 hu.9H5-L4.Q38E VL FR1 hu.9H5-L4.Q38E.H89V VL	DIQMTQSPSSLSASVGDRVITTC

	FR1 hu.9H5-L4.Q38E.S95Y VL FR1 hu.9H5-L4.Q38E.H89V.S95Y VL FR1	
177	hu.9H5-H14L4 VL FR2 hu.9H5-L4.H89V VL FR2 hu.9H5-L4.S95Y VL FR2 hu.9H5-L4.H89V.S95Y VL FR2	WYQQKPGKAPKLLIY
178	hu.9H5-L4.Q38E VL FR2 hu.9H5-L4.Q38E.H89V VL FR2 hu.9H5-L4.Q38E.S95Y VL FR2 hu.9H5-L4.Q38E.H89V.S95Y VL FR2	WYQEKPFGKAPKLLIY
179	hu.9H5-H14L4 VL FR3 hu.9H5-L4.H89V VL FR3 hu.9H5-L4.S95Y VL FR3 hu.9H5-L4.H89V.S95Y VL FR3 hu.9H5-L4.Q38E VL FR3 hu.9H5-L4.Q38E.H89V VL FR3 hu.9H5-L4.Q38E.S95Y VL FR3 hu.9H5-L4.Q38E.H89V.S95Y VL FR3	GVPSRFSGSGSGTDFTLTISLQPEDFATYYC
180	hu.9H5-H14L4 VL FR4 hu.9H5-L4.H89V VL FR4 hu.9H5-L4.S95Y VL FR4 hu.9H5-L4.H89V.S95Y VL FR4 hu.9H5-L4.Q38E VL FR4 hu.9H5-L4.Q38E.H89V VL FR4 hu.9H5-L4.Q38E.S95Y VL FR4 hu.9H5-L4.Q38E.H89V.S95Y VL FR4	FGGGTKVEIK
79	hu.9H5-H14L4 VH	EVQLVESGGG LIQPGGSLRL SCAASGFSLs SYGVSWVRQA PGKGLYVGF IGSAGFAYYA SWAKSRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCARDVV GGGKSLDIWG QGTLVTVSS
80	hu.9H5-H14L4 VL	DIQMTQSPSS LSASVGDRVT ITCQASQSI SYLSWYQQK GKAPKLLIYS ASTLASGVPS RFSGSGSGTD FTLTISLQ EDFATYYCHQ DYTSSNVDNT FGGGKVEIK
81	hu.9H5-H14.G54A VH	EVQLVESGGG LIQPGGSLRL SCAASGFSLs SYGVSWVRQA PGKGLYVGF IGSAGFAYYA SWAKSRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCARDVV GGGKSLDIWG QGTLVTVSS
82	hu.9H5-H14.G98Q VH	EVQLVESGGG LIQPGGSLRL SCAASGFSLs SYGVSWVRQA PGKGLYVGF IGSAGFAYYA SWAKSRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCARDVV GGGKSLDIWG QGTLVTVSS
83	hu.9H5-H14.G54A.G98Q VH	EVQLVESGGG LIQPGGSLRL SCAASGFSLs SYGVSWVRQA PGKGLYVGF IGSAGFAYYA SWAKSRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCARDVV GGGKSLDIWG QGTLVTVSS
84	hu.9H5-H14.Q39K VH	EVQLVESGGG LIQPGGSLRL SCAASGFSLs SYGVSWVRKA PGKGLYVGF IGSAGFAYYA SWAKSRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCARDVV GGGKSLDIWG QGTLVTVSS
85	hu.9H5-H14.Q39K.G54A VH	EVQLVESGGG LIQPGGSLRL SCAASGFSLs SYGVSWVRKA PGKGLYVGF IGSAGFAYYA SWAKSRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCARDVV GGGKSLDIWG QGTLVTVSS
86	hu.9H5-H14.Q39K.G98Q VH	EVQLVESGGG LIQPGGSLRL SCAASGFSLs SYGVSWVRKA PGKGLYVGF IGSAGFAYYA SWAKSRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCARDVV GGGKSLDIWG QGTLVTVSS

87	hu.9H5-H14.Q39K.G54A.G98Q VH	EVQLVESGGG LIQPGGSLRL SCAASGFSLS SYGVSWVRKA PGKGLLEYVGF IGSAGFAYYA SWAKSRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCARDVV QGGKSLDIWG QGTLTVTSS
88	hu.9H5-L4.H89V VL	DIQMTQSPSS LSASVGDRVT ITCQASQSS SYLSWYQQKP GKAPKLLIYS ASTLASGVPS RFGSGSGSGTD FTLTISSLQP EDFATYYCVQ DYTSSNVDNT FGGGTKVEIK
89	hu.9H5-L4.S95Y VL	DIQMTQSPSS LSASVGDRVT ITCQASQSS SYLSWYQQKP GKAPKLLIYS ASTLASGVPS RFGSGSGSGTD FTLTISSLQP EDFATYYCHQ DYTSYNVDNT FGGGTKVEIK
90	hu.9H5-L4.H89V.S95Y VL	DIQMTQSPSS LSASVGDRVT ITCQASQSS SYLSWYQQKP GKAPKLLIYS ASTLASGVPS RFGSGSGSGTD FTLTISSLQP EDFATYYCVQ DYTSYNVDNT FGGGTKVEIK
91	hu.9H5-L4.Q38E VL	DIQMTQSPSS LSASVGDRVT ITCQASQSS SYLSWYQEK GKAPKLLIYS ASTLASGVPS RFGSGSGSGTD FTLTISSLQP EDFATYYCHQ DYTSSNVDNT FGGGTKVEIK
92	hu.9H5-L4.Q38E.H89V VL	DIQMTQSPSS LSASVGDRVT ITCQASQSS SYLSWYQEK GKAPKLLIYS ASTLASGVPS RFGSGSGSGTD FTLTISSLQP EDFATYYCVQ DYTSSNVDNT FGGGTKVEIK
93	hu.9H5-L4.Q38E.S95Y VL	DIQMTQSPSS LSASVGDRVT ITCQASQSS SYLSWYQEK GKAPKLLIYS ASTLASGVPS RFGSGSGSGTD FTLTISSLQP EDFATYYCHQ DYTSYNVDNT FGGGTKVEIK
94	hu.9H5-L4.Q38E.H89V.S95Y VL	DIQMTQSPSS LSASVGDRVT ITCQASQSS SYLSWYQEK GKAPKLLIYS ASTLASGVPS RFGSGSGSGTD FTLTISSLQP EDFATYYCVQ DYTSYNVDNT FGGGTKVEIK
95	Human IgG1 heavy chain constant region (hIgG1)	ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LSDSGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
183	Human IgG1 heavy chain constant region (hIgG1) ΔGK	ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LSDSGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSP
96	hIgG1.N297G.Knob(T366W). S183K	ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLKSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYG STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLWC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LSDSGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
184	hIgG1.N297G.Knob(T366W). S183K ΔGK	ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLKSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYG STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLWC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LSDSGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSP
97	hIgG1.N297G.Hole(T366S. L368A.Y407V). S183E	ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLESVVT VPSSSLGTQT

		YICNVNHNKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNF YVDGVEVHNA KTKPREEQYGSTYRVVSVLT VLNQDNLGNK EYKCKVSNKA LPAPIEKTISKAKGQPREPQ VYTLPPSREE MTKNQVSLSC AVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSGDGSFFLV SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
185	hlgG1.N297G.Hole(T366S. L368A.Y407V). S183E ΔGK	ASTKGPSVFPLAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGVHTFPAVLQSS GLYSLESVVT VPSSSLGTQT YICNVNHNKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNF YVDGVEVHNA KTKPREEQYGSTYRVVSVLT VLNQDNLGNK EYKCKVSNKA LPAPIEKTISKAKGQPREPQ VYTLPPSREE MTKNQVSLSC AVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSGDGSFFLV SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSP
98	hlgG1.N297G.Knob(T366W). S183K.M428L.N434S	ASTKGPSVFPLAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGVHTFPAVLQSS GLYSLSKVVT VPSSSLGTQT YICNVNHNKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNF YVDGVEVHNA KTKPREEQYGSTYRVVSVLT VLNQDNLGNK EYKCKVSNKA LPAPIEKTISKAKGQPREPQ VYTLPPSREE MTKNQVSLWC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSGDGSFFLY SKLTVDKSRW QQGNVFSCSV LHEALHSHYT QKSLSLSPGK
186	hlgG1.N297G.Knob(T366W). S183K.M428L.N434S ΔGK	ASTKGPSVFPLAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGVHTFPAVLQSS GLYSLSKVVT VPSSSLGTQT YICNVNHNKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNF YVDGVEVHNA KTKPREEQYGSTYRVVSVLT VLNQDNLGNK EYKCKVSNKA LPAPIEKTISKAKGQPREPQ VYTLPPSREE MTKNQVSLWC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSGDGSFFLY SKLTVDKSRW QQGNVFSCSV LHEALHSHYT QKSLSLSP
99	hlgG1.N297G.Hole(T366S. L368A.Y407V).S183E. M428L.N434S	ASTKGPSVFPLAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGVHTFPAVLQSS GLYSLESVVT VPSSSLGTQT YICNVNHNKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNF YVDGVEVHNA KTKPREEQYGSTYRVVSVLT VLNQDNLGNK EYKCKVSNKA LPAPIEKTISKAKGQPREPQ VYTLPPSREE MTKNQVSLSC AVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSGDGSFFLV SKLTVDKSRW QQGNVFSCSV LHEALHSHYT QKSLSLSPGK
187	hlgG1.N297G.Hole(T366S. L368A.Y407V).S183E. M428L.N434S ΔGK	ASTKGPSVFPLAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGVHTFPAVLQSS GLYSLESVVT VPSSSLGTQT YICNVNHNKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNF YVDGVEVHNA KTKPREEQYGSTYRVVSVLT VLNQDNLGNK EYKCKVSNKA LPAPIEKTISKAKGQPREPQ VYTLPPSREE MTKNQVSLSC AVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSGDGSFFLV SKLTVDKSRW QQGNVFSCSV LHEALHSHYT QKSLSLSP
117	hlgG1.N297G.Knob(T366W). S183E	ASTKGPSVFPLAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGVHTFPAVLQSS GLYSLESVVT VPSSSLGTQT YICNVNHNKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNF YVDGVEVHNA KTKPREEQYGSTYRVVSVLT VLNQDNLGNK EYKCKVSNKA LPAPIEKTISKAKGQPREPQ VYTLPPSREE MTKNQVSLWC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSGDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
188	hlgG1.N297G.Knob(T366W).	ASTKGPSVFPLAPSSKSTSG GTAALGCLVK DYFPEPVTVS

	S183E ΔGK	WNSGALTSGV HTFPAVLQSS GLYSLESVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMIS RTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYG STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLWC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LSDSGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSP
118	hIgG1.N297G.Hole(T366S. L368A.Y407V). S183K	ASTKGPSVFAPLAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLKSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMIS RTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYG STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLSC AVKGFYPSDI AVEWESNGQP ENNYKTTPPV LSDSGSFFLV SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
189	hIgG1.N297G.Hole(T366S. L368A.Y407V). S183K ΔGK	ASTKGPSVFAPLAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLKSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMIS RTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYG STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLSC AVKGFYPSDI AVEWESNGQP ENNYKTTPPV LSDSGSFFLV SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSP
119	hIgG1.N297G.Knob(T366W). S183E.M428L.N434S	ASTKGPSVFAPLAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLESVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMIS RTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYG STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLWC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LSDSGSFFLY SKLTVDKSRW QQGNVFSCSV LHEALHSHYT QKSLSLSPGK
190	hIgG1.N297G.Knob(T366W). S183E.M428L.N434S ΔGK	ASTKGPSVFAPLAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLESVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMIS RTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYG STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLWC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LSDSGSFFLY SKLTVDKSRW QQGNVFSCSV LHEALHSHYT QKSLSLSP
120	hIgG1.N297G.Hole(T366S. L368A.Y407V).S183K. M428L.N434S	ASTKGPSVFAPLAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLKSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMIS RTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYG STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLSC AVKGFYPSDI AVEWESNGQP ENNYKTTPPV LSDSGSFFLV SKLTVDKSRW QQGNVFSCSV LHEALHSHYT QKSLSLSPGK
191	hIgG1.N297G.Hole(T366S. L368A.Y407V).S183K. M428L.N434S ΔGK	ASTKGPSVFAPLAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLKSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMIS RTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYG STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLSC AVKGFYPSDI AVEWESNGQP ENNYKTTPPV LSDSGSFFLV SKLTVDKSRW QQGNVFSCSV LHEALHSHYT QKSLSLSP

102	Human kappa light chain constant region (hKappa)	RTVAAPSVFI WKVDNALQSG KHKVYACEVT	FPPSDEQLKS NSQESVTEQD HQGLSSPVTK	GTASVVCLLN SKDSTYSLSS SFNRGEC	NFYFPREAKVQ TLTLSKADYE
103	hKappa.V133E	RTVAAPSVFI WKVDNALQSG KHKVYACEVT	FPPSDEQLKS NSQESVTEQD HQGLSSPVTK	GTASVECLLN SKDSTYSLSS SFNRGEC	NFYFPREAKVQ TLTLSKADYE
104	hKappa.V133K	RTVAAPSVFI WKVDNALQSG KHKVYACEVT	FPPSDEQLKS NSQESVTEQD HQGLSSPVTK	GTASVKCLLN SKDSTYSLSS SFNRGEC	NFYFPREAKVQ TLTLSKADYE
108	hu14H11c heavy chain (HC) in hu.10C5VY.hu14H11c.L2H11 WT	EQQLVESGGG APGKGLEWVS LYLQMNSLRA GTLVTVSSAS FPEPVTVSWN SSSLGTQTYI PAPELLGGPS DPEVKFNWYV HQDWLNGKEY TLPPSREEMT NYKTTTPPVL D EALHNHYTQK	LIQPGGSLRL SIYAGSSGAP EDTAVYYCAR TKGPSVFPLA SGALTSGVHT CNVNHKPSNT VFLFPPKPKD DGVEVHNAKT KCKVSNKALP KNQVSLWCLV SDGSFFLYSK SLSLSPGK	SCAASGFSFS YYAGWAKGRF EGFAETGGYG PSSKSTSGGT FPAVLQSSGL YSLKSVVTVP KVDKKVEPKS TLMISRTPEV KPREEQYGST YRVVSVLTVL APIEKTISKA KGQPREPQVY KGFYPSDI AV LTVDKSRWQQ	SSYYMSWVRE TISRDNSKNT YAAYFNLWGP AALGCLVKDY YSLKSVVTVP CDKTHTCPPC TCVVVDVSHE YRVVSVLTVL KGQPREPQVY EWESNGQPEN GNVFSCSVMH
192	hu14H11c heavy chain (HC) in hu.10C5VY.hu14H11c.L2H11 WT ΔGK	EQQLVESGGG APGKGLEWVS LYLQMNSLRA GTLVTVSSAS FPEPVTVSWN SSSLGTQTYI PAPELLGGPS DPEVKFNWYV HQDWLNGKEY TLPPSREEMT NYKTTTPPVL D EALHNHYTQK	LIQPGGSLRL SIYAGSSGAP EDTAVYYCAR TKGPSVFPLA SGALTSGVHT CNVNHKPSNT VFLFPPKPKD DGVEVHNAKT KCKVSNKALP KNQVSLWCLV SDGSFFLYSK SLSLSP	SCAASGFSFS YYAGWAKGRF EGFAETGGYG PSSKSTSGGT FPAVLQSSGL YSLKSVVTVP KVDKKVEPKS TLMISRTPEV KPREEQYGST YRVVSVLTVL APIEKTISKA KGQPREPQVY KGFYPSDI AV LTVDKSRWQQ	SSYYMSWVRE TISRDNSKNT YAAYFNLWGP AALGCLVKDY YSLKSVVTVP CDKTHTCPPC TCVVVDVSHE YRVVSVLTVL KGQPREPQVY EWESNGQPEN GNVFSCSVMH
109	hu14H11c light chain (LC) in hu.10C5VY.hu14H11c.L2H11 WT	DIQMTQSPSS GKAPKLLIYG EDFATYYCLG FPPSDEQLKS NSQESVTEQD HQGLSSPVTK	LSASVGDRV T ASNLESGVPS GYSYSTGT A FGGGTKEI K GTASVECLLN SKDSTYSLSS TLTLSKADYE SFNRGEC	ITCLASEDIA RFSGSGSGTD FGGGTKEI K NFYFPREAKVQ TLTLSKADYE	SSVSWYQKKP YTLTISSLQ P RTVAAPSVFI WKVDNALQSG KHKVYACEVT
110	hu.10C5VY heavy chain (HC) in hu.10C5VY.hu14H11c.L2H11 WT	EVQLVESGGG PGKGLEWIGY LQMGS LRAED ASTKGPSVFP WNSGALTSGV YICNVNHKPS PSVFLFPPKP YVDGVEVHNA EYKCKVSNKA MTKNQVSLSC LDSDGSFFLV QKSLSLSPGK	LVQPGGSLRL ITS VYGVSY Y MAVYYCAREN LAPSSKSTSG HTFPAVLQSS NTKVDKKVEP KDTLMISRTP KTKPREEQYG LPAPIEKTIS AVKGFYPSDI SKLTVDKSRW	SCAASGFSLS ASWAKSRSTI PDYGYAYDAW GTAALGCLVK GLYSLESVVT KSCDKTHTCP EVTCVVVDVS STYRVVSVLT KAKGQPREPQ AVEWESNGQP QQGNVFSCSV	SYGVTWVRKA SRDTSKNTVY GQGT TTVTVSS DYFPEPVTVS VPSSSLGTQT PCPAPELLGG HEDPEVKFNW VLHQDWLNGK VYTLPPSREE ENNYKTTTPV MHEALHNHYT
193	hu.10C5VY heavy chain (HC) in hu.10C5VY.hu14H11c.L2H11 WT ΔGK	EVQLVESGGG PGKGLEWIGY LQMGS LRAED ASTKGPSVFP WNSGALTSGV YICNVNHKPS PSVFLFPPKP YVDGVEVHNA EYKCKVSNKA MTKNQVSLSC LDSDGSFFLV	LVQPGGSLRL ITS VYGVSY Y MAVYYCAREN LAPSSKSTSG HTFPAVLQSS NTKVDKKVEP KDTLMISRTP KTKPREEQYG LPAPIEKTIS AVKGFYPSDI SKLTVDKSRW	SCAASGFSLS ASWAKSRSTI PDYGYAYDAW GTAALGCLVK GLYSLESVVT KSCDKTHTCP EVTCVVVDVS STYRVVSVLT KAKGQPREPQ AVEWESNGQP QQGNVFSCSV	SYGVTWVRKA SRDTSKNTVY GQGT TTVTVSS DYFPEPVTVS VPSSSLGTQT PCPAPELLGG HEDPEVKFNW VLHQDWLNGK VYTLPPSREE ENNYKTTTPV MHEALHNHYT

		QKSLSLSP	
111	hu.10C5VY light chain (LC) in hu.10C5VY.hu14H11c.L2H11 WT	AIRMTQSPSS FSASTGDRVIT ITCQASESIS NELSWYQEKP GKAPKLLIYY ASTLASGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCAQ GYGSSGVENV FGGGTKEVEIK RTVAAPSVFI FPPSDEQLKS GTASVKCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVT K SFNRGEC	
112	hu14H11c heavy chain (HC) in hu.10C5VY.hu14H11c.L2H11 LS	EQQLVESGGG LIQPGGSLRL SCAASGFSFS SSYYMSWVRE APGKGLEWVS SIYAGSSGAP YYAGWAKGRF TISRDN SKNT LYLQMNSLRA EDTAVYYCAR EGFAETGGYG YAAYFNLWGP GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVT VSWN SGALTSGVHT FPAVLQSSGL YSLKSVVTV SSSLGTQTYI CNVNHKPSNT KVDKKVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYGST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSREEMT KNQVSLWCLV KGFYPSDI AV EWESNGQPEN NYKTTTPPVL SDGSFFLYSK LTVDKSRWQQ GNVFSCSVLH EALHSHYTQK SLSLSPGK	
194	hu14H11c heavy chain (HC) in hu.10C5VY.hu14H11c.L2H11 LS ΔGK	EQQLVESGGG LIQPGGSLRL SCAASGFSFS SSYYMSWVRE APGKGLEWVS SIYAGSSGAP YYAGWAKGRF TISRDN SKNT LYLQMNSLRA EDTAVYYCAR EGFAETGGYG YAAYFNLWGP GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVT VSWN SGALTSGVHT FPAVLQSSGL YSLKSVVTV SSSLGTQTYI CNVNHKPSNT KVDKKVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYGST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSREEMT KNQVSLWCLV KGFYPSDI AV EWESNGQPEN NYKTTTPPVL SDGSFFLYSK LTVDKSRWQQ GNVFSCSVLH EALHSHYTQK SLSLSPGK	
113	hu14H11c light chain (LC) in hu.10C5VY.hu14H11c.L2H11 LS	DIQMTQSPSS LSASVGDRVIT ITCLASEDIA SSVSWYQKKP GKAPKLLIYG ASNLESGVPS RFSGSGSGTD YTLTISSLQP EDFATYYCLG GYSYSTGTA FGGGTKEVEIK RTVAAPSVFI FPPSDEQLKS GTASVECLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVT K SFNRGEC	
114	hu.10C5VY heavy chain (HC) in hu.10C5VY.hu14H11c.L2H11 LS	EVQLVESGGG LVQPGGSLRL SCAASGFSLS SYGVTWVRKA PGKLEWIGY ITSIVYGVSY ASWAKSRSTI SRDTSKNTVY LQMGSLRAED MAVYICAREN PDYGYAYDAW GQGTITVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLESVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTPEVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYG STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLSC AVKGFYPSDI AVEWESNGQP ENNYKTTTPV LSDSGSFFLV SKLTVDKSRW QQGNVFSCSV LHEALHSHYT QKSLSLSPGK	
195	hu.10C5VY heavy chain (HC) in hu.10C5VY.hu14H11c.L2H11 LS ΔGK	EVQLVESGGG LVQPGGSLRL SCAASGFSLS SYGVTWVRKA PGKLEWIGY ITSIVYGVSY ASWAKSRSTI SRDTSKNTVY LQMGSLRAED MAVYICAREN PDYGYAYDAW GQGTITVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLESVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTPEVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYG STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLSC AVKGFYPSDI AVEWESNGQP ENNYKTTTPV LSDSGSFFLV SKLTVDKSRW QQGNVFSCSV LHEALHSHYT QKSLSLSPGK	
115	hu.10C5VY light chain (LC) in	AIRMTQSPSS FSASTGDRVIT ITCQASESIS NELSWYQEKP	

	hu.10C5VY.hu14H11c.L2H11 LS	GKAPKLLIYY ASTLASGVPS RFSGSGSGTD FTLTISLQPF EDFATYYCAQ GYGSSGVENV FGGGTKVEIK RTVAAPSVFI FPPSDEQLKS GTASVKCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS TLTLKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC
121	KLK7 substrate; Nval is norvaline	RPKPVE-Nval-WRK
181	“dummy” hIgG1.N297G.Knob(T366W). S183K for one-armed constructs	DKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTF EVTCCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYG STYRVVSVLT VLHQDWLNGK EYCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLWC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSEFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
182	“dummy” hIgG1. N297G.Hole(T366S. L368A.Y407V). S183E for one- armed constructs	DKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTF EVTCCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYG STYRVVSVLT VLHQDWLNGK EYCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLWC AVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSEFFLV SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
196	SFTI 21705 (also referred to as SFTI-KLK7)	GKCLFSNPPICFPN
197	SPINK9.SRE.Fc	GSIESAKQTK QMVDCSHYKK LPPGQQRFCF REYDPICGSD GKTYKNDCEFF CSKVKKT DGT LKRVHFGKCG NSRAQVTDKK IEPRGPTIKP CPPCKCPAPN LLGGPSVFIF PPKIKDVLMI SLSPIVTCVV VDVSEDDPDV QISWFEVNNVE VHTAQTQTHR EDYNSTLRVV SALPIQHQQDW MSGKEFKCKV NNKDLPAPIE RTISKPKGSV RAPQVYVLPP PEEEMTKKQV TLTCMVTDQM PEDIYVEWTN NGKTELNYKN TEPVLDSDGS YFMYSKLRVE KKNWVERNSY SCSVVHEGLH NHHTTKSFSSR TPGK

WHAT IS CLAIMED IS:

1. An isolated antibody that binds to human kallikrein related peptidase 7 (KLK7), wherein the antibody:
 - a) inhibits human KLK7-mediated cleavage of a substrate comprising the amino acid sequence RPKPVE-Nval-WRK (SEQ ID NO: 121), wherein Nval is norvaline; and/or
 - b) binds human KLK7 with an K_D of less than 10 pM, or less than 9 pM, or less than 8 pM, or less than 7 pM, or less than 6 pM, or less than 5 pM as measured by surface plasmon resonance;
 - c) binds an epitope within amino acids R71-N82, K152-S158, and/or Q211-K222 of KLK7 (SEQ ID NO: 4); and/or
 - d) binds an epitope comprising one or more of amino acids H72, P73, G74, S76, Q78, N82, N157, K211, and/or T213 of KLK7 (SEQ ID NO: 4).
2. An antibody that binds to human KLK7, wherein the antibody comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12.
3. The antibody of claim 1, comprising a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12.
4. The antibody of any one of claims 1 to 3, which is a monoclonal antibody.
5. The antibody of any one of claims 1 to 4, which is a humanized, or chimeric antibody.
6. The antibody of any one of claims 1 to 5, which is an antibody fragment that binds to human KLK7.

7. The antibody of any of claims 1 to 6, wherein the antibody binds human KLK7 with a K_D of less than 10 pM, or less than 9 pM, or less than 8 pM, or less than 7 pM, or less than 6 pM, or less than 5 pM as measured by surface plasmon resonance; and/or binds to cynomolgus monkey KLK7 with a K_D of less than 10 pM, or less than 9 pM, or less than 8 pM, or less than 7 pM, or less than 6 pM, or less than 5 pM as measured by surface plasmon resonance.

8. The antibody of any one of claims 1 to 7, wherein the heavy chain variable region comprises an FR1 comprising an amino acid sequence selected from SEQ ID NO: 123-128, an FR2 comprising an amino acid sequence selected from SEQ ID NO: 130-133, an FR3 comprising an amino acid sequence of SEQ ID NO: 135-143, and/or an FR4 comprising an amino acid sequence selected from SEQ ID NO: 144-145.

9. The antibody of any one of claims 1 to 8, wherein the light chain variable region comprises an FR1 comprising an amino acid sequence selected from SEQ ID NO: 147-150, an FR2 comprising an amino acid sequence selected from SEQ ID NO: 152-154, an FR3 comprising an amino acid sequence selected from SEQ ID NO: 156-158, and/or an FR4 comprising an amino acid sequence selected from SEQ ID NO: 160.

10. The antibody of any of claims 1 to 9, comprising a sequence selected from:

(a) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 15-30;

(b) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NO:31-38; and

(c) a VH sequence as defined in (a) and a VL sequence as defined in (b).

11. The antibody of any of claims 1 to 10, comprising a sequence selected from:

(a) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 15-30;

(b) a VL sequence comprising an amino acid sequence selected from SEQ ID NO:31-38; and

(c) a VH sequence as defined in (a) and a VL sequence as defined in (b).

12. The antibody of any of claims 1 to 11, comprising a VH sequence of SEQ ID NO: 29 and a VL sequence of SEQ ID NO: 32.

13. The antibody of any of claims 1 to 11, comprising a VH sequence of SEQ ID NO: 30 and a VL sequence of SEQ ID NO: 38.

14. An antibody that specifically binds to human KLK7 comprising a VH sequence of SEQ ID NO: 29 and a VL sequence of SEQ ID NO: 32.

15. An antibody that specifically binds to human KLK7 comprising a VH sequence of SEQ ID NO: 30 and a VL sequence of SEQ ID NO: 38.

16. The antibody of any one of claims 1 to 15, wherein the antibody comprises a heavy chain constant region and a light chain constant region, wherein the heavy chain constant region comprises a S183K substitution (EU numbering) and/or an S183E substitution (EU numbering); and/or the light chain constant region comprises a V133K substitution (EU numbering) and/or a V133E substitution (EU numbering).

17. The antibody of any of claims 1 to 16, which is a full length IgG1 antibody.

18. The antibody of claim 17, wherein the antibody comprises a N297G substitution (EU numbering).

19. The antibody of any one of claims 16 to 18, wherein the antibody comprises a M428L substitution (EU numbering) and/or an N434S substitution (EU numbering).

20. The antibody of any one of claims 1 to 19, wherein the antibody binds human KLK7 with a K_D of less than 20 pM, or less than 15 pM, or less than 10 pM, less than 5 pM, or less than 3 pM, or less than 2 pM, or less than 1 pM, as measured by surface plasmon resonance.

21. The antibody of any one of claims 1 to 20, wherein the antibody inhibits human KLK7 protease activity with an IC_{50} of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM.

22. The antibody of any one of claims 1 to 21, wherein the antibody binds human KLK7 with a K_D of less than 20 pM, or less than 15 pM, or less than 10 pM, less than 5 pM, or less than 3 pM, or less than 2 pM, or less than 1 pM, as measured by surface plasmon resonance; and wherein the antibody inhibits human KLK7 protease activity with an IC_{50} of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM.

23. The antibody of claim 21 or claim 22, wherein inhibition of human KLK7 protease activity is inhibition of human KLK7-mediated cleavage of a substrate comprising the amino acid sequence RPKPVE-Nval-WRK (SEQ ID NO: 121), wherein Nval is norvaline.

24. The antibody of any of claims 1 to 23, wherein the antibody is a multispecific antibody.

25. The antibody of claim 24, which is a bispecific antibody.

26. An antibody that specifically binds human KLK7, which competes for binding to human KLK7 with the antibody of any one of claims 1 to 25.
27. The antibody of claim 26, wherein the antibody:
- c) inhibits human KLK7-mediated cleavage of a substrate comprising the amino acid sequence RPKPVE-Nval-WRK (SEQ ID NO: 121), wherein Nval is norvaline, with an IC₅₀ of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM; and/or
 - d) binds human KLK7 with a K_D of less than 10 pM, or less than 9 pM, or less than 8 pM, or less than 7 pM, or less than 6 pM, or less than 5 pM as measured by surface plasmon resonance.
28. An isolated nucleic acid encoding the antibody of any of claims 1 to 27.
29. An isolated host cell comprising the nucleic acid of claim 28.
30. An isolated host cell that expresses the antibody of any one of claims 1 to 27.
31. A method of producing an antibody that binds to human KLK7 comprising culturing the host cell of claim 29 or claim 30 under conditions suitable for the expression of the antibody.
32. The method of claim 31, further comprising recovering the antibody from the host cell.
33. An antibody produced by the method of claim 32.
34. An antibody that binds to human KLK5, wherein the antibody comprises:
- a) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 43 and 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49; or
 - b) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 39 and 107, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising an amino acid sequence selected

from SEQ ID NOs: 43 and 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49; or

c) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 39 and 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NOs: 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49; or

d) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 39 and 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 43 and 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 47-49; or

e) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 70, and (c) CDR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 71 and 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 75-78; or

f) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 69 and 70, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 75-78; or

g) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 69 and 70, and (c) CDR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 71 and 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 76-78.

35. The antibody of claim 34, wherein the antibody comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NOs: 43, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 47.

36. The antibody of claim 34, wherein the antibody comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 70, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 76.

37. The antibody of any one of claims 34 to 36, which is a monoclonal antibody.

38. The antibody of any one of claims 34 to 37, which is a humanized, or chimeric antibody.

39. The antibody of any one of claims 34 to 38, which is an antibody fragment that binds human KLK5.

40. The antibody of any of claims 34 to 39, wherein the antibody binds human KLK5 with a K_D of less than 1 nM, or less than 500 pM, or less than 300 pM, or less than 200 pM, or less than 100 pM, or less than 50 pM as measured by surface plasmon resonance; and/or binds to cynomolgus monkey KLK5 with a K_D of less than 1 nM, or less than 500 pM, or less than 300 pM, or less than 200 pM, or less than 100 pM, or less than 50 pM as measured by surface plasmon resonance.

41. The antibody of any one of claims 34 to 40, wherein the heavy chain variable region comprises:

- a) an FR1 comprising the amino acid sequence selected of SEQ ID NO: 161, an FR2 comprising the amino acid sequence of SEQ ID NO: 162-163, an FR3 comprising the amino acid sequence of SEQ ID NO: 164, and/or an FR4 comprising the amino acid sequence of SEQ ID NO: 165; or
- b) an FR1 comprising the amino acid sequence of SEQ ID NO: 171, an FR2 comprising an amino acid sequence selected from SEQ ID NO: 172-173, an FR3 comprising the amino acid sequence of SEQ ID NO: 174, and/or an FR4 comprising the amino acid sequence of SEQ ID NO: 175.

42. The antibody of any one of claims 34 to 41, wherein the light chain variable region comprises:

- a) an FR1 comprising the amino acid sequence of SEQ ID NO: 166, an FR2 comprising an amino acid sequence selected from SEQ ID NO: 167-168, an FR3 comprising the amino acid sequence of SEQ ID NO: 169, and/or an FR4 comprising the amino acid sequence of SEQ ID NO: 170; or
- b) an FR1 comprising the amino acid sequence of SEQ ID NO: 176, an FR2 comprising an amino acid sequence selected from SEQ ID NO: 177-178, an FR3 comprising the amino acid sequence of SEQ ID NO: 179, and/or an FR4 comprising the amino acid sequence of SEQ ID NO: 180.

43. The antibody of any of claims 34 to 42, comprising a sequence selected from:

- a) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 50, 52, 53, 105, and 106;
- b) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 51 and 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 79 and 81-87;
- e) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 80 and 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

44. The antibody of any of claims 34 to 43, comprising a sequence selected from:
- a) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 50, 52, 53, 105, and 106;
 - b) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 51 and 54-67; and
 - c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
 - d) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 79 and 81-87;
 - e) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 80 and 88-94; and
 - f) a VH sequence as defined in (d) and a VL sequence as defined in (e).
45. The antibody of any of claims 34 to 44, comprising a VH sequence of SEQ ID NO: 52 and a VL sequence of SEQ ID NO: 55.
46. The antibody of any of claims 34 to 44, comprising a VH sequence of SEQ ID NO: 53 and a VL sequence of SEQ ID NO: 62.
47. An antibody that specifically binds to human KLK5 comprising a VH sequence of SEQ ID NO: 52 and a VL sequence of SEQ ID NO: 55.
48. An antibody that specifically binds to human KLK5 comprising a VH sequence of SEQ ID NO: 53 and a VL sequence of SEQ ID NO: 62.
49. The antibody of any of claims 34 to 44, comprising a VH sequence of SEQ ID NO: 83 and a VL sequence of SEQ ID NO: 88.
50. The antibody of any of claims 34 to 44, comprising a VH sequence of SEQ ID NO: 87 and a VL sequence of SEQ ID NO: 92.
51. An antibody that specifically binds to human KLK5 comprising a VH sequence of SEQ ID NO: 83 and a VL sequence of SEQ ID NO: 88.
52. An antibody that specifically binds to human KLK5 comprising a VH sequence of SEQ ID NO: 87 and a VL sequence of SEQ ID NO: 92.
53. The antibody of any one of claims 34 to 52, wherein the antibody comprises a heavy chain constant region and a light chain constant region, wherein the heavy chain constant region comprises a S183K substitution (EU numbering) and/or an S183E substitution (EU numbering);

and/or the light chain constant region comprises a V133K substitution (EU numbering) and/or a V133E substitution (EU numbering).

54. The antibody of any of claims 34 to 53, which is a full length IgG1 antibody.
55. The antibody of claim 54, wherein the antibody comprises a N297G substitution (EU numbering).
56. The antibody of any one of claims 53 to 55, wherein the antibody comprises a M428L substitution (EU numbering) and/or an N434S substitution (EU numbering).
57. The antibody of any of claims 34 to 56, wherein the antibody binds human KLK5 with a K_D of less than 60 pM, less than 30 pM, less than 20 pM, less than 10 pM, or less than 5 pM, as measured by surface plasmon resonance.
58. The antibody of any one of claims 34 to 57, wherein the antibody inhibits human KLK5 protease activity with an IC_{50} of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM.
59. The antibody of any one of claims 34 to 58, wherein the antibody binds human KLK5 with a K_D of less than 60 pM, less than 30 pM, less than 20 pM, less than 10 pM, or less than 5 pM, as measured by surface plasmon resonance; and wherein the antibody inhibits human KLK5 protease activity with an IC_{50} of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM.
60. The antibody of claim 58 or claim 59, wherein inhibition of human KLK5 protease activity is inhibition of human KLK5-mediated cleavage of the substrate Boc-Val-Pro-Arg-AMC.
61. The antibody of any of claims 34 to 60, wherein the antibody is a multispecific antibody.
62. The antibody of claim 61, wherein the antibody is a bispecific antibody.
63. An isolated nucleic acid encoding the antibody of any of claims 34 to 62.
64. An isolated host cell comprising the nucleic acid of claim 63.
65. An isolated host cell that expresses the antibody of any one of claims 34 to 62.
66. A method of producing an antibody that binds to human KLK5 comprising culturing the host cell of claim 64 or claim 65 under conditions suitable for the expression of the antibody.

67. The method of claim 66, further comprising recovering the antibody from the host cell.

68. An antibody produced by the method of claim 67.

69. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 7, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 8, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 9, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12.

70. The bispecific antibody of claim 69, wherein the first binding domain is humanized.

71. The bispecific antibody of claim 69 or claim 70, wherein the first binding domain comprises a sequence selected from:

(a) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 15-30;

(b) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NO:31-38; and

(c) a VH sequence as defined in (a) and a VL sequence as defined in (b).

72. The bispecific antibody of any one of claims 69 to 71, wherein the first binding domain comprises a sequence selected from:

(a) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 15-30;

(b) a VL sequence comprising an amino acid sequence selected from SEQ ID NO: 31-38; and

(c) a VH sequence as defined in (a) and a VL sequence as defined in (b).

73. The bispecific antibody of any one of claims 69 to 72, wherein the first binding domain comprises a VH sequence of SEQ ID NO: 29 and a VL sequence of SEQ ID NO: 32.

74. The bispecific antibody of any one of claims 69 to 72, wherein the first binding domain comprises a VH sequence of SEQ ID NO: 30 and a VL sequence of SEQ ID NO: 38.

75. The bispecific antibody of any one of claims 69 to 74, wherein the second binding domain comprises:

- a) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 39 and 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 43 and 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49; or
- b) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 69 and 70, and (c) CDR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 71 and 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 75-78.

76. The bispecific antibody of any one of claims 69 to 75, wherein the second binding domain comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NOs: 43, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 47.

77. The bispecific antibody of any one of claims 69 to 75, wherein the second binding domain comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 70, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 76.

78. The bispecific antibody of any one of claims 69 to 77, wherein the second binding domain is humanized.

79. The bispecific antibody of any one of claims 75 to 78, wherein the second binding domain comprises a sequence selected from:

- a) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 50, 52, 53, 105, and 106;
- b) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 51 and 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 79 and 81-87;
- e) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 80 and 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

80. The bispecific antibody of any one of claims 75 to 78, wherein the second binding domain comprises a sequence selected from:

- a) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 52, 53, 105, and 106;
- b) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 81-87;
- e) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

81. The bispecific antibody of any one of claims 69 to 78, wherein the second binding domain comprises a sequence selected from:

- a) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 50, 52, 53, 105, and 106;

- b) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 51 and 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 79 and 81-87;
- e) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 80 and 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

82. The bispecific antibody of any one of claims 69 to 78, wherein the second binding domain comprises a sequence selected from:

- a) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 52, 53, 105, and 106;
- b) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 81-87;
- e) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

83. The bispecific antibody of any one of claims 69 to 79, wherein the first binding domain comprises a VH amino acid sequence of SEQ ID NO: 29 or SEQ ID NO: 30 and a VL amino acid sequence of SEQ ID NO: 32 or SEQ ID NO: 38, and the second binding domain comprises a VH sequence of SEQ ID NO: 52 or SEQ ID NO: 53 and a VL amino acid sequence of SEQ ID NO: 55 or SEQ ID NO: 62.

84. The bispecific antibody of claim 83, wherein (i) the first binding domain comprises a VH amino acid sequence of SEQ ID NO: 29 and a VL amino acid sequence of SEQ ID NO: 32, or a VH amino acid sequence of SEQ ID NO: 30 and a VL amino acid sequence of SEQ ID NO: 38; and (ii) the second binding domain comprises a VH sequence of SEQ ID NO: 52 and a VL amino acid sequence of SEQ ID NO: 55; or a VH sequence of SEQ ID NO: 53 and a VL amino acid sequence of SEQ ID NO: 62.

85. The bispecific antibody of any one of claims 69 to 79, wherein the first binding domain comprises a VH sequence of SEQ ID NO: 30 and a VL sequence of SEQ ID NO: 38, and the second binding domain comprises a VH sequence of SEQ ID NO: 53 and a VL sequence of SEQ ID NO: 62.

86. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain variable domain (VH) amino acid sequence of SEQ ID NO: 30 and a light chain variable domain (VL) amino acid sequence of SEQ ID NO: 38, and the second binding domain comprises a VH amino acid sequence of SEQ ID NO: 53 and a VL amino acid sequence of SEQ ID NO: 62.

87. The bispecific antibody of any one of claims 69 to 86, wherein the first binding domain comprises a first heavy chain variable domain and a first light chain variable domain, wherein the first heavy chain variable domain is linked to a first heavy chain constant region and the first light chain variable domain is linked to a first light chain constant region; and the second binding domain comprises a second heavy chain variable domain and a second light chain variable domain, wherein the second heavy chain variable domain is linked to a second heavy chain constant region and the second light chain variable domain is linked to a second light chain constant region.

88. The bispecific antibody of claim 87, wherein the first heavy chain constant region comprises a knob mutation and the second heavy chain constant region comprises a hole mutation; or wherein the first heavy chain constant region comprises a hole mutation and the second heavy chain constant region comprises a knob mutation.

89. The bispecific antibody of claim 88, wherein the antibody is an IgG1 antibody and wherein the knob mutation comprises a T366W substitution.

90. The bispecific antibody of claim 88 or claim 89, wherein the antibody is an IgG1 antibody and wherein the hole mutation comprises at least one, at least two, or three substitutions selected from T366S, L368A, and Y407V.

91. The bispecific antibody of claim 90, wherein the antibody is an IgG1 antibody and wherein the hole mutation comprises T366S, L368A, and Y407V substitutions.

92. The bispecific antibody of any one of claims 87 to 91, wherein the first heavy chain constant region and/or the second heavy chain constant region comprises a N297G substitution (EU numbering).

93. The bispecific antibody of claim 92, wherein the first heavy chain constant region and the second heavy chain constant region each comprises a N297G substitution (EU numbering).

94. The bispecific antibody of any one of claims 87 to 93, wherein:

a) the first heavy chain constant region further comprises a S183K substitution (EU numbering) and the first light chain constant region comprises a V133E substitution (EU numbering), and the second heavy chain constant region further comprises a S183E substitution (EU numbering) and the second light chain constant region comprises a V133K substitution (EU numbering); or

b) the first heavy chain constant region further comprises a S183E substitution (EU numbering) and the first light chain constant region comprises a V133K substitution (EU numbering), and the second heavy chain constant region further comprises a S183K substitution (EU numbering) and the second light chain constant region comprises a V133E substitution (EU numbering).

95. The bispecific antibody of any one of claims 87 to 94, wherein the first heavy chain constant region and/or the second heavy chain constant region further comprises at least one substitution selected from M428L and N434S (EU numbering).

96. The bispecific antibody of claim 95, wherein the first heavy chain constant region and the second heavy chain constant region each further comprises at least one substitution selected from M428L and N434S (EU numbering).

97. The bispecific antibody of claim 96, wherein the first heavy chain constant region and the second heavy chain constant region each further comprises M428L and N434S substitutions (EU numbering).

98. The bispecific antibody of any one of claims 87 to 97, wherein:

a) the first heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 96, 184, 98, 186, 117, 188, 119, and 190 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103; and the heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 97, 185, 99, 187, 118, 189, 120, and 191 and the second light chain constant region comprising the amino acid sequence of SEQ ID NO: 104; or

b) the second heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 96, 184, 98, 186, 117, 188, 119, and 190 and the second

light chain constant region comprises the amino acid sequence of SEQ ID NO: 103; and the first heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 97, 185, 99, 187, 118, 189, 120, and 191 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104.

99. The bispecific antibody of claim 98, wherein:

a) the first heavy chain constant region comprises the amino acid sequence of SEQ ID NOs: 96 or 184 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 97 or 185 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

b) the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 98 or 186 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 99 or 187 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

c) the second heavy chain constant region comprises the amino acid sequence of SEQ ID NOs: 96 or 184 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 97 or 185 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

d) the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 98 or 186 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 99 or 187 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

e) the first heavy chain constant region comprises the amino acid sequence of SEQ ID NOs: 118 or 189 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 117 or 188 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

f) the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 120 or 191 and the first light chain constant region comprises the amino acid

sequence of SEQ ID NO: 103, and the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 119 or 190 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

g) the second heavy chain constant region comprises the amino acid sequence of SEQ ID NOs: 118 or 189 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 117 or 188 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

h) the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 120 or 191 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 119 or 190 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104.

100. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 108 or 192, and a light chain amino acid sequence of SEQ ID NO: 109, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 110 or 193, and a light chain amino acid sequence of SEQ ID NO: 111.

101. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 112 or 194, and a light chain amino acid sequence of SEQ ID NO: 113, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 114 or 195, and a light chain amino acid sequence of SEQ ID NO: 115.

102. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 108 and a light chain amino acid sequence of SEQ ID NO: 109, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 110 and a light chain amino acid sequence of SEQ ID NO: 111.

103. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain

binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 112 and a light chain amino acid sequence of SEQ ID NO: 113, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 114 and a light chain amino acid sequence of SEQ ID NO: 115.

104. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the second binding domain comprises

- a) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NOs: 43 or 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49; or
- b) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 39 and 107, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 43 and 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49; or
- c) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39 or 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NOs: 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49; or
- d) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 39 and 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain

variable domain (VL) comprising (d) CDR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 43 and 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 47-49; or

e) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 70, and (c) CDR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 71 and 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 75-78; or

f) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 69 and 70, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 75-78; or

g) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 69 and 70, and (c) CDR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 71 and 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 76-78.

105. The bispecific antibody of claim 104, wherein the second binding domain comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NOs: 43, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 47.

106. The bispecific antibody of claim 104, wherein the second binding domain comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 70, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 76.

107. The bispecific antibody of any one of claims 104 to 106, wherein the second binding domain is humanized.

108. The bispecific antibody of any one of claims 104 to 107, wherein the second binding domain comprises a sequence selected from:

- a) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 50, 52, 53, 105, and 106;
- b) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 51 and 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 79 and 81-87;
- e) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 80 and 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

109. The bispecific antibody of any one of claims 104 to 107, wherein the second binding domain comprises a sequence selected from:

- a) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 52, 53, 105, and 106;
- b) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 81-87;

- e) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

110. The bispecific antibody of any one of claims 104 to 107, wherein the second binding domain comprises a sequence selected from:

- a) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 50, 52, 53, 105, and 106;
- b) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 51 and 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 79 and 81-87;
- e) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 80 and 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

111. The bispecific antibody of any one of claims 104 to 107, wherein the second binding domain comprises a sequence selected from:

- a) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 52, 53, 105, and 106;
- b) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 81-87;
- e) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

112. The bispecific antibody of any one of claims 104 to 107, wherein the second half amino acid antibody comprises a VH sequence of SEQ ID NO: 52 or SEQ ID NO: 53 and a VL amino acid sequence of SEQ ID NO: 55 or SEQ ID NO: 62.

113. The bispecific antibody of claim 112, wherein the second half amino acid antibody comprises a VH sequence of SEQ ID NO: 52 and a VL amino acid sequence of SEQ ID NO: 55; or a VH sequence of SEQ ID NO: 53 and a VL amino acid sequence of SEQ ID NO: 62.

114. The bispecific antibody of any one of claims 104 to 113, wherein the first binding domain is humanized.

115. The bispecific antibody of any one of claims 104 to 114, wherein the first binding domain comprises a first heavy chain variable domain and a first light chain variable domain, wherein the first heavy chain variable domain is linked to a first heavy chain constant region and the first light chain variable domain is linked to a first light chain constant region; and the second binding domain comprises a second heavy chain variable domain and a second light chain variable domain, wherein the second heavy chain variable domain is linked to a second heavy chain constant region and the second light chain variable domain is linked to a second light chain constant region.

116. The bispecific antibody of claim 115, wherein the first heavy chain constant region comprises a knob mutation and the second heavy chain constant region comprises a hole mutation; or wherein the first heavy chain constant region comprises a hole mutation and the second heavy chain constant region comprises a knob mutation.

117. The bispecific antibody of claim 116, wherein the antibody is an IgG1 antibody and wherein the knob mutation comprises a T366W mutation.

118. The bispecific antibody of claim 116 or claim 117, wherein the antibody is an IgG1 antibody and wherein the hole mutation comprises at least one, at least two, or three mutations selected from T366S, L368A, and Y407V.

119. The bispecific antibody of claim 118, wherein the antibody is an IgG1 antibody and wherein the hole mutation comprises T366S, L368A, and Y407V mutations.

120. The bispecific antibody of any one of claims 115 to 119, wherein the first heavy chain constant region and/or the second heavy chain constant region comprises a N297G substitution (EU numbering).

121. The bispecific antibody of claim 120, wherein the first heavy chain constant region and the second heavy chain constant region each comprises a N297G substitution (EU numbering).

122. The bispecific antibody of any one of claims 115 to 121, wherein:

a) the first heavy chain constant region further comprises a S183K substitution (EU numbering) and the first light chain constant region comprises a V133E substitution (EU numbering), and the second heavy chain constant region further comprises a S183E substitution (EU numbering) and the second light chain constant region comprises a V133K substitution (EU numbering); or

b) the first heavy chain constant region further comprises a S183E substitution (EU numbering) and the first light chain constant region comprises a V133K substitution (EU numbering), and the second heavy chain constant region further comprises a S183K substitution (EU numbering) and the second light chain constant region comprises a V133E substitution (EU numbering).

123. The bispecific antibody of any one of claims 115 to 122, wherein the first heavy chain constant region and/or the second heavy chain constant region further comprises at least one substitution selected from M428L and N434S (EU numbering).

124. The bispecific antibody of claim 123, wherein the first heavy chain constant region and the second heavy chain constant region each further comprises at least one substitution selected from M428L and N434S (EU numbering).

125. The bispecific antibody of claim 124, wherein the first heavy chain constant region and the second heavy chain constant region each further comprises M428L and N434S substitutions (EU numbering).

126. The bispecific antibody of any one of claims 115 to 125, wherein:

a) the first heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 96, 184, 98, 186, 117, 188, 119, and 190 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103; and the heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 97, 185, 99, 187, 118, 189, 120, and 191 and the second light chain constant region comprising the amino acid sequence of SEQ ID NO: 104; or

b) the second heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 96, 184, 98, 186, 117, 188, 119, and 190 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 103; and the first heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 97, 185, 99, 187, 118, 189, 120, and 191 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104.

127. The bispecific antibody of claim 126, wherein:

a) the first heavy chain constant region comprises the amino acid sequence of SEQ ID NOs: 96 or 184 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 97 or 185 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

b) the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 98 or 186 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 99 or 187 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

c) the second heavy chain constant region comprises the amino acid sequence of SEQ ID NOs: 96 or 184 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 97 or 185 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

d) the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 98 or 186 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 99 or 187 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

e) the first heavy chain constant region comprises the amino acid sequence of SEQ ID NOs: 118 or 189 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 117 or 188 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

f) the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 120 or 191 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 119 or 190 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

g) the second heavy chain constant region comprises the amino acid sequence of SEQ ID NOs: 118 or 189 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 117 or 188 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104; or

h) the second heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 120 or 191 and the second light chain constant region comprises the amino acid sequence of SEQ ID NO: 103, and the first heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 119 or 190 and the first light chain constant region comprises the amino acid sequence of SEQ ID NO: 104.

128. The bispecific antibody of any one of claims 69 to 127, wherein the antibody binds human KLK5 with a K_D of less than 60 pM, less than 30 pM, less than 20 pM, less than 10 pM, or less than 5 pM, as measured by surface plasmon resonance.

129. The bispecific antibody of any one of claims 69 to 128, wherein the antibody inhibits human KLK5 protease activity with an IC_{50} of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM.

130. The antibody of any one of claims 69 to 129, wherein the antibody binds human KLK5 with a K_D of less than 60 pM, less than 30 pM, less than 20 pM, less than 10 pM, or less than 5 pM, as measured by surface plasmon resonance; and wherein the antibody inhibits human KLK5 protease activity with an IC_{50} of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM.

131. The bispecific antibody of claim 129 or claim 130, wherein inhibition of human KLK5 protease activity is inhibition of human KLK5-mediated cleavage of the substrate Boc-Val-Pro-Arg-AMC.

132. The bispecific antibody of any one of claims 69 to 131, wherein the antibody binds human KLK7 with a K_D of less than 20 pM, or less than 15 pM, or less than 10 pM, less than 5 pM, or less than 3 pM, or less than 2 pM, or less than 1 pM, as measured by surface plasmon resonance.

133. The bispecific antibody of any one of claims 69 to 132, wherein the antibody inhibits human KLK7 protease activity with an IC_{50} of less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM.

134. The bispecific antibody of any one of claims 69 to 133, wherein the antibody binds human KLK7 with a K_D of less than 20 pM, or less than 15 pM, or less than 10 pM, less than 5 pM, or less than 3 pM, or less than 2 pM, or less than 1 pM, as measured by surface plasmon resonance; and wherein the antibody inhibits human KLK7 protease activity with an IC_{50} of less than less than 5 nM, or less than 3 nM, or less than 2 nM, or less than 1 nM.

135. The bispecific antibody of claim 133 or claim 134, wherein inhibition of human KLK7 protease activity is inhibition of human KLK7-mediated cleavage of a substrate comprising the amino acid sequence RPKPVE- Nval-WRK (SEQ ID NO: 121), wherein Nval is norvaline.

136. The bispecific antibody of any one of claims 69 to 135, wherein the K_D of the bispecific antibody for human KLK5 and the K_D of the antibody for human KLK7 are within 3-fold, or within 2.5-fold, or within 2-fold, or within 1.5-fold of one another.

137. An isolated nucleic acid encoding the bispecific antibody of any one of claims 69 to 136.

138. An isolated nucleic acid encoding the first binding domain of the bispecific antibody of any one of claims 69 to 136.

139. An isolated nucleic acid encoding the second binding domain of the bispecific antibody of any one of claims 69 to 136.

140. An isolated host cell comprising the isolated nucleic acid of claim 137.

141. An isolated host cell comprising the isolated nucleic acid of claim 138.

142. An isolated host cell comprising the isolated nucleic acid of claim 139.

143. An isolated host cell that expresses the bispecific antibody of any one of claims 69 to 136.

144. An isolated host cell that expresses the first binding domain of the bispecific antibody of any one of claims 69 to 136.

145. An isolated host cell that expresses the second binding domain of the bispecific antibody of any one of claims 69 to 136.

146. A method of producing a bispecific antibody that binds to human KLK5 and human KLK7, comprising culturing the host cell of claim 140 or claim 143 under conditions suitable for the expression of the antibody.

147. The method of claim 146, further comprising recovering the antibody from the host cell.

148. A method of producing a bispecific antibody that binds to human KLK5 and human KLK7, comprising (i) culturing the host cell of claim 141 or claim 144 under conditions suitable for the expression of the first binding domain; and (ii) culturing the host cell of claim 142 or claim 145 under conditions suitable for expression of the second binding domain.

149. The method of claim 148, further comprising recovering the first binding domain and the second binding domain and assembling the bispecific antibody.

150. A pharmaceutical composition comprising the antibody of any of claims 1 to 27 and a pharmaceutically acceptable carrier.

151. The pharmaceutical composition of claim 150, further comprising an additional therapeutic agent.

152. The pharmaceutical composition of claim 151, wherein the additional therapeutic agent is a KLK5 inhibitor.

153. The pharmaceutical composition of claim 152, wherein the KLK5 inhibitor is an anti-KLK5 antibody.

154. The pharmaceutical composition of claim 153, wherein the anti-KLK5 antibody comprises:

a) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 39 and 107, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 40 and 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 43 and 44, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 46-49; or

b) a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 69 and 70, and (c) CDR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 71 and 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID

NO: 74, and (f) CDR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 75-78.

155. The pharmaceutical composition of claim 153 or claim 154, wherein the anti-KLK5 antibody comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 41, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NOs: 43, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 47.

156. The pharmaceutical composition of claim 153 or claim 154, wherein the anti-KLK5 antibody comprises a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 68, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 70, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 72, and a light chain variable domain (VL) comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 76.

157. The pharmaceutical composition of any one of claims 153 to 156, wherein the anti-KLK5 antibody is a monoclonal antibody.

158. The pharmaceutical composition of any one of claims 153 to 157, wherein the anti-KLK5 antibody is a humanized, or chimeric antibody.

159. The pharmaceutical composition of any one of claims 153 to 158, wherein the anti-KLK5 antibody is an antibody fragment that binds human KLK5.

160. The pharmaceutical composition of any one of claims 153-159, wherein the anti-KLK5 antibody comprises a sequence selected from:

a) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 50, 52, 53, 105 and 106;

b) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 51 and 54-67; and

c) a VH sequence as defined in (a) and a VL sequence as defined in (b);

d) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 79 and 81-87;

- e) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 80 and 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

161. The pharmaceutical composition of any one of claims 153-159, wherein the anti-KLK5 antibody comprises a sequence selected from:

- a) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 52, 53, 105 and 106;
- b) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 81-87;
- e) a VL sequence having at least 95% sequence identity to an amino acid sequence selected from SEQ ID NOs: 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

162. The pharmaceutical composition of any one of claims 153-159, wherein the anti-KLK5 antibody comprises a sequence selected from:

- a) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 50, 52, 53, 105, and 106;
- b) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 51 and 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 79 and 81-87;
- e) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 80 and 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

163. The pharmaceutical composition of any one of claims 153-159, wherein the anti-KLK5 antibody comprises a sequence selected from:

- a) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 52, 53, 105, and 106;
- b) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 54-67; and
- c) a VH sequence as defined in (a) and a VL sequence as defined in (b);
- d) a VH sequence comprising an amino acid sequence selected from SEQ ID NOs: 81-87;
- e) a VL sequence comprising an amino acid sequence selected from SEQ ID NOs: 88-94; and
- f) a VH sequence as defined in (d) and a VL sequence as defined in (e).

164. The pharmaceutical composition of claim 153, wherein the anti-KLK5 antibody is an antibody of any one of claims 34 to 62.

165. The pharmaceutical composition of claim 153, wherein the anti-KLK5 antibody is an antibody of any one of claims 47, 48, 51, and 52.

166. A pharmaceutical composition comprising the antibody of any of claims 34 to 62 and a pharmaceutically acceptable carrier.

167. The pharmaceutical composition of claim 166, further comprising an additional therapeutic agent.

168. The pharmaceutical composition of claim 167, wherein the additional therapeutic agent is a KLK7 inhibitor.

169. The pharmaceutical composition of claim 168, wherein the KLK7 inhibitor is an anti-KLK7 antibody.

170. The pharmaceutical composition of claim 169, wherein the anti-KLK7 antibody is an antibody of any one of claims 1 to 27.

171. A pharmaceutical composition comprising the antibody of any of claims 1 to 27 and an antibody of any one of claims 34 to 62, and a pharmaceutically acceptable carrier.

172. The pharmaceutical composition of any one of claims 150 to 171, comprising an additional therapeutic agent selected from an anti-inflammatory agent and an antibiotic.

173. A pharmaceutical composition comprising the bispecific antibody of any one of claims 69 to 136.

174. The pharmaceutical composition of claim 173, further comprising an additional therapeutic agent.

175. The pharmaceutical composition of claim 174, wherein the additional therapeutic agent is an anti-inflammatory agent.

176. The pharmaceutical composition of any one of claims 150 to 175, wherein the pharmaceutical composition is for topical administration.

177. The pharmaceutical composition of any one of claims 150 to 175, wherein the pharmaceutical composition is for subcutaneous or intravenous administration.

178. The antibody of any one of claims 1 to 27 and 34 to 62, the bispecific antibody of any one of claims 69 to 136, or the pharmaceutical composition of any one of claims 150 to 177 for use as a medicament.

179. The antibody of any one of claims 1 to 27 and 34 to 62, the bispecific antibody of any one of claims 69 to 136, or the pharmaceutical composition of any one of claims 150 to 177 for use in treating disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea.

180. The antibody, bispecific antibody, or pharmaceutical composition for use of claim 179, wherein the asthma is selected from atopic asthma, allergic asthma, non-allergic asthma, exercise-induced asthma, aspirin sensitive/exacerbated asthma, mild asthma, moderate to severe asthma, corticosteroid naïve asthma, chronic asthma, corticosteroid resistant asthma, corticosteroid refractory asthma, newly diagnosed and untreated asthma, asthma due to smoking, asthma uncontrolled on corticosteroids, T helper lymphocyte type 2 (Th2) or type 2 (Th2) high, or Type 2 (T2)-driven asthma, eosinophilic asthma, periostin-high asthma, eosinophil-high asthma, Th2-low asthma or nonTh2-driven asthma, periostin-low asthma, and eosinophil-low asthma.

181. The antibody, bispecific antibody, or pharmaceutical composition for use of claim 180, wherein the asthma is eosinophil-low asthma.

182. A combination of an antibody of any one of claims 1 to 27 and an antibody of any one of claims 34 to 62, for use as a medicament.

183. A combination of an antibody of any one of claims 1 to 27 and an antibody of any one of claims 34 to 62, for use in treating disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea.

184. The combination for use of claim 183, wherein the asthma is selected from atopic asthma, allergic asthma, non-allergic asthma, exercise-induced asthma, aspirin sensitive/exacerbated asthma, mild asthma, moderate to severe asthma, corticosteroid naïve asthma, chronic asthma, corticosteroid resistant asthma, corticosteroid refractory asthma, newly diagnosed and untreated asthma, asthma due to smoking, asthma uncontrolled on corticosteroids, T helper lymphocyte type 2 (Th2) or type 2 (Th2) high, or Type 2 (T2)-driven asthma, eosinophilic asthma, periostin-high asthma, eosinophil-high asthma, Th2-low asthma or nonTh2-driven asthma, periostin-low asthma, and eosinophil-low asthma.

185. The combination of claim 184, wherein the asthma is eosinophil-low asthma.

186. Use of the antibody of any one of claims 1 to 27 and 34 to 62, the bispecific antibody of any one of claims 69 to 136, or the pharmaceutical composition of any one of claims 150 to 177 in the manufacture of a medicament for treating disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea.

187. The use of claim 186, wherein the asthma is selected from atopic asthma, allergic asthma, non-allergic asthma, exercise-induced asthma, aspirin sensitive/exacerbated asthma, mild asthma, moderate to severe asthma, corticosteroid naïve asthma, chronic asthma, corticosteroid resistant asthma, corticosteroid refractory asthma, newly diagnosed and untreated asthma, asthma due to smoking, asthma uncontrolled on corticosteroids, T helper lymphocyte type 2 (Th2) or type 2 (Th2) high, or Type 2 (T2)-driven asthma, eosinophilic asthma, periostin-high asthma, eosinophil-high asthma, Th2-low asthma or nonTh2-driven asthma, periostin-low asthma, and eosinophil-low asthma.

188. The use of claim 187, wherein the asthma is eosinophil-low asthma.

189. Use of a combination of the antibody of any one of claims 1 to 27 and the antibody of any one of claims 34 to 62 in the manufacture of a medicament for treating disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea.

190. The use of claim 189, wherein the asthma is selected from atopic asthma, allergic asthma, non-allergic asthma, exercise-induced asthma, aspirin sensitive/exacerbated asthma, mild asthma, moderate to severe asthma, corticosteroid naïve asthma, chronic asthma, corticosteroid resistant asthma, corticosteroid refractory asthma, newly diagnosed and untreated asthma, asthma due to smoking, asthma uncontrolled on corticosteroids, T helper lymphocyte type 2 (Th2) or type 2 (Th2) high, or Type 2 (T2)-driven asthma, eosinophilic asthma, periostin-

high asthma, eosinophil-high asthma, Th2-low asthma or nonTh2-driven asthma, periostin-low asthma, and eosinophil-low asthma.

191. The use of claim 190, wherein the asthma is eosinophil-low asthma.

192. Use of the antibody of any one of claims 1 to 27 and 34 to 62, the bispecific antibody of any one of claims 69 to 136, or the pharmaceutical composition of any one of claims 150 to 177 in the manufacture of a medicament for reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines.

193. Use of a combination of the antibody of any one of claims 1 to 27 and the antibody of any one of claims 34 to 62 in the manufacture of a medicament for reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines.

194. A method of treating an individual having a disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea, comprising administering to the individual an effective amount of the antibody of any one of claims 1 to 27 and 34 to 62, the bispecific antibody of any one of claims 69 to 136, or the pharmaceutical composition of any one of claims 150 to 177.

195. A method of treating an individual having a disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea, comprising administering to the individual a) an effective amount of the antibody of any one of claims 1 to 27; and b) an effective amount of the antibody of any one of claims 34 to 62.

196. The method of claim 195, wherein the antibody of (a) and the antibody of (b) are administered simultaneously.

197. The method of claim 195, wherein the antibody of (a) and the antibody of (b) are administered sequentially.

198. A method of treating an individual having a disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea, comprising administering to the individual an effective amount of the bispecific antibody of any one of claims 69 to 136, or an effective amount of the pharmaceutical composition of any one of claims 150 to 177.

199. The method of any one of claims 194 to 198, wherein the asthma is selected from atopic asthma, allergic asthma, non-allergic asthma, exercise-induced asthma, aspirin sensitive/exacerbated asthma, mild asthma, moderate to severe asthma, corticosteroid naïve asthma, chronic asthma, corticosteroid resistant asthma, corticosteroid refractory asthma, newly diagnosed and untreated asthma, asthma due to smoking, asthma uncontrolled on corticosteroids, T helper lymphocyte type 2 (Th2) or type 2 (Th2) high, or Type 2 (T2)-driven asthma, eosinophilic asthma, periostin-high asthma, eosinophil-high asthma, Th2-low asthma or nonTh2-driven asthma, periostin-low asthma, and eosinophil-low asthma.

200. The method of claim 199, wherein the asthma is eosinophil-low asthma.

201. The method of any one of claims 194 to 198, wherein the individual has Netherton Syndrome.

202. The method of any one of claims 194 to 198, wherein the individual has rosacea.

203. The method of any one of claims 194 to 202, further comprising administering an additional therapeutic agent to the individual.

204. The method of claim 203 wherein the additional therapeutic agent is an anti-inflammatory agent.

205. A method of reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines in an individual comprising administering to the individual an effective amount of the antibody of any one of claims 1 to 27 and 34 to 62, the bispecific antibody of any one of claims 69 to 136, or the pharmaceutical composition of any one of claims 150 to 177 to reduce epithelium inflammation, reduce epithelium permeability, reduce transepidermal water loss, reduce dermal infiltrates, reduce parakeratosis, and/or restore the epithelial barrier.

206. A method of reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines in an individual comprising administering to the individual a) an effective amount of the antibody of any one of claims 1 to 27; and b) an effective amount of the antibody of any one of claims 34 to 62, to reduce epithelium inflammation, reduce epithelium permeability, reduce transepidermal water loss, reduce dermal infiltrates, reduce parakeratosis, and/or restore the epithelial barrier.

207. The method of claim 206, wherein the antibody of (a) and the antibody of (b) are administered simultaneously.

208. The method of claim 206, wherein the antibody of (a) and the antibody of (b) are administered sequentially.

209. A method of reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines in an individual comprising administering to the individual the bispecific antibody of any one of claims 69 to 136, or an effective amount of the pharmaceutical composition of any one of claims 150 to 177, to reduce epithelium inflammation, reduce epithelium permeability, reduce transepidermal water loss, reduce dermal infiltrates, reduce parakeratosis, and/or restore the epithelial barrier.

210. The method of any one of claims 194 to 209, wherein the administering is subcutaneous or intravenous administration.

211. The method of any one of claims 194 to 209, wherein the administering is topical administration.

212. The method of any one of claims 194 to 209, wherein the administering is intravenous administration.

213. An isolated antibody that binds human KLK7, wherein when bound to human KLK7 results in a conformational change of human KLK7, wherein the conformational change allosterically results in the disruption of the substrate binding site and/or the active site of human KLK7.

214. The isolated antibody of claim 213, which is a bispecific antibody.

215. The isolated antibody of claim 214, wherein the bispecific antibody binds human KLK7 and human KLK5.

216. The isolated antibody of claim 215, wherein when bound to human KLK5 results in a conformational change of human KLK5, wherein the conformational change allosterically results in the disruption of the substrate binding site and/or the active site of human KLK5.

217. The isolated antibody of claim 216, wherein the antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from Pro130, Ser131, Ala132, Gly133, Val162, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Tyr172, Pro173, Arg174, Gln174A, Ile176, Asp177, Asp178, Gly184, Asp185, Lys186,

Ala186A, Arg188, Asn223, Arg224, Pro225, and Lys233 according to standard protease numbering.

218. The isolated antibody of claim 217, wherein the antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from the group consisting of Pro130, Ser131, Ala132, Val162, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Tyr172, Pro173, Arg174, Gln174A, Ile176, Asp177, Asp178, Arg224, and Lys233 according to standard protease numbering.

219. The isolated antibody of claim 217, wherein the antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from Pro130, Ser131, Ala132, Gly133, Val162, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Tyr172, Pro173, Arg174, Gln174A, Ile176, Asp177, and Lys233 according to standard protease numbering.

220. The isolated antibody of claim 217, wherein the antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from Ser131, Ala132, Gly133, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Pro173, Arg174, Gly184, Asp185, Lys186, Ala186A, Arg188, Asn223, Arg224, and Pro225 according to standard protease numbering.

221. The isolated antibody of any one of claims 213-220, wherein the antibody binds an epitope within amino acids R71-N82, K152-S158, and/or Q211-K222 of KLK7 (SEQ ID NO: 4).

222. The isolated antibody of any one of claims 213-221, wherein the antibody binds an epitope comprising one or more of amino acids H72, P73, G74, S76, Q78, N82, N157, K211, and/or T213 of KLK7 (SEQ ID NO: 4).

223. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein when bound to human KLK7 results in a conformational change of human KLK7, wherein the conformational change allosterically results in the disruption of the substrate binding site and/or the active site of human KLK7.

224. The bispecific antibody of claim 223, wherein when bound to human KLK5 results in a conformational change of human KLK5, wherein the conformational change allosterically results in the disruption of the substrate binding site and/or the active site of human KLK5.

225. A bispecific antibody comprising a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein when bound to human KLK5 results in a conformational change of human KLK5, wherein the conformational change allosterically results in the disruption of the substrate binding site and/or the active site of human KLK5.

226. The bispecific antibody of claim 224 or claim 225, wherein the antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from Pro130, Ser131, Ala132, Gly133, Val162, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Tyr172, Pro173, Arg174, Gln174A, Ile176, Asp177, Asp178, Gly184, Asp185, Lys186, Ala186A, Arg188, Asn223, Arg224, Pro225, and Lys233 according to standard protease numbering.

227. The isolated antibody of claim 226, wherein the antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from the group consisting of Pro130, Ser131, Ala132, Val162, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Tyr172, Pro173, Arg174, Gln174A, Ile176, Asp177, Asp178, Arg224, and Lys233 according to standard protease numbering.

228. The isolated antibody of claim 226, wherein the antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from Pro130, Ser131, Ala132, Gly133, Val162, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Tyr172, Pro173, Arg174, Gln174A, Ile176, Asp177, and Lys233 according to standard protease numbering.

229. The isolated antibody of claim 226, wherein the antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from Ser131, Ala132, Gly133, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Pro173, Arg174, Gly184, Asp185, Lys186, Ala186A, Arg188, Asn223, Arg224, and Pro225 according to standard protease numbering.

230. The bispecific antibody of any one of claims 223 to 229, wherein the antibody binds an epitope within amino acids R71-N82, K152-S158, and/or Q211-K222 of KLK7 (SEQ ID NO: 4).

231. The bispecific antibody of any one of claims 223 to 230, wherein the antibody binds an epitope comprising one or more of amino acids H72, P73, G74, S76, Q78, N82, N157, K211, and/or T213 of KLK7 (SEQ ID NO: 4).

232. A pharmaceutical composition comprising the antibody of any one of claims 213 to 222 and a pharmaceutically acceptable carrier.

233. A pharmaceutical composition comprising the bispecific antibody of any one of claims 223 to 231 and a pharmaceutically acceptable carrier.

234. The antibody of any one of claims 213 to 222, the bispecific antibody of any one of claims 223 to 231, or the pharmaceutical composition of claim 232 or claim 233 for use as a medicament.

235. The antibody of any one of claims 213 to 222, the bispecific antibody of any one of claims 223 to 231, or the pharmaceutical composition of claim 232 or claim 233 for use in treating disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea.

236. The antibody, bispecific antibody, or pharmaceutical composition for use of claim 235, wherein the asthma is selected from atopic asthma, allergic asthma, non-allergic asthma, exercise-induced asthma, aspirin sensitive/exacerbated asthma, mild asthma, moderate to severe asthma, corticosteroid naïve asthma, chronic asthma, corticosteroid resistant asthma, corticosteroid refractory asthma, newly diagnosed and untreated asthma, asthma due to smoking, asthma uncontrolled on corticosteroids, T helper lymphocyte type 2 (Th2) or type 2 (Th2) high, or Type 2 (T2)-driven asthma, eosinophilic asthma, periostin-high asthma, eosinophil-high asthma, Th2-low asthma or nonTh2-driven asthma, periostin-low asthma, and eosinophil-low asthma.

237. The antibody of any one of claims 213 to 222, the bispecific antibody of any one of claims 223 to 231, or the pharmaceutical composition of claim 232 or claim 233 for use in reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines.

238. Use of the antibody of any one of claims 213 to 222, the bispecific antibody of any one of claims 223 to 231, or the pharmaceutical composition of claim 232 or claim 233 in the manufacture of a medicament for treating disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea.

239. The use of claim 238, wherein the asthma is selected from atopic asthma, allergic asthma, non-allergic asthma, exercise-induced asthma, aspirin sensitive/exacerbated asthma, mild asthma, moderate to severe asthma, corticosteroid naïve asthma, chronic asthma,

corticosteroid resistant asthma, corticosteroid refractory asthma, newly diagnosed and untreated asthma, asthma due to smoking, asthma uncontrolled on corticosteroids, T helper lymphocyte type 2 (Th2) or type 2 (Th2) high, or Type 2 (T2)-driven asthma, eosinophilic asthma, periostin-high asthma, eosinophil-high asthma, Th2-low asthma or nonTh2-driven asthma, periostin-low asthma, and eosinophil-low asthma.

240. Use of the antibody of any one of claims 213 to 222, the bispecific antibody of any one of claims 223 to 231, or the pharmaceutical composition of claim 232 or claim 233 in the manufacture of a medicament for reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines.

241. A method of treating an individual having a disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea, comprising administering to the individual an effective amount of the antibody of any one of 213 to 222, the bispecific antibody of any one of claims 223 to 231, or the pharmaceutical composition of claim 232 or claim 233.

242. The method of claim 241, wherein the asthma is selected from atopic asthma, allergic asthma, non-allergic asthma, exercise-induced asthma, aspirin sensitive/exacerbated asthma, mild asthma, moderate to severe asthma, corticosteroid naïve asthma, chronic asthma, corticosteroid resistant asthma, corticosteroid refractory asthma, newly diagnosed and untreated asthma, asthma due to smoking, asthma uncontrolled on corticosteroids, T helper lymphocyte type 2 (Th2) or type 2 (Th2) high, or Type 2 (T2)-driven asthma, eosinophilic asthma, periostin-high asthma, eosinophil-high asthma, Th2-low asthma or nonTh2-driven asthma, periostin-low asthma, and eosinophil-low asthma.

243. A method of reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines in an individual comprising administering to the individual an effective amount of the antibody of any one of 213 to 222, the bispecific antibody of any one of claims 223 to 231, or the pharmaceutical composition of claim 232 or claim 233 to reduce epithelium inflammation, reduce epithelium permeability, reduce transepidermal water loss, reduce dermal infiltrates, reduce parakeratosis, and/or restore the epithelial barrier.

244. The antibody, bispecific antibody, or pharmaceutical composition for use of claim 179 or claim 235, wherein the disease is Netherton Syndrome.

245. The combination for use of claim 183, wherein the disease is Netherton Syndrome.

246. The use of any one of claims 186, 189, and 238, wherein the disease is Netherton Syndrome.

247. The use of any one of claims 192, 193, and 240, wherein the medicament is for reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier, and/or reducing skin inflammatory cytokines in an individual with Netherton Syndrome.

248. A bispecific antibody for use in treating Netherton Syndrome, wherein the bispecific antibody comprises a first binding domain and a second binding domain, wherein the first binding domain binds human KLK7 and the second binding domain binds human KLK5, wherein the first binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 112 or 194, and a light chain amino acid sequence of SEQ ID NO: 113, and the second binding domain comprises a heavy chain amino acid sequence of SEQ ID NO: 114 or 195, and a light chain amino acid sequence of SEQ ID NO: 115.

249. An anti-KLK5 antibody for use in treating Netherton Syndrome, wherein the anti-KLK5 antibody comprises (a) a VH sequence of SEQ ID NO: 52 and a VL sequence of SEQ ID NO: 55; or (b) a VH sequence of SEQ ID NO: 53 and a VL sequence of SEQ ID NO: 62.

250. An anti-KLK7 antibody for use in treating Netherton Syndrome, wherein the anti-KLK7 antibody comprises (a) a VH sequence of SEQ ID NO: 29 and a VL sequence of SEQ ID NO: 32; or (b) a VH sequence of SEQ ID NO: 30 and a VL sequence of SEQ ID NO: 38.

251. An antibody combination for use in treating Netherton Syndrome, wherein the antibody combination comprises an anti-KLK5 antibody and an anti-KLK7 antibody, wherein the anti-KLK5 antibody comprises a VH sequence of SEQ ID NO: 52 and a VL sequence of SEQ ID NO: 55, or a VH sequence of SEQ ID NO: 53 and a VL sequence of SEQ ID NO: 62; and wherein the anti-KLK7 antibody comprises a VH sequence of SEQ ID NO: 29 and a VL sequence of SEQ ID NO: 32, or a VH sequence of SEQ ID NO: 30 and a VL sequence of SEQ ID NO: 38.

252. A method of treating an individual having a disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea,

comprising administering to the individual an effective amount of the bispecific antibody, wherein the bispecific antibody comprises a first binding domain and second binding domain, wherein the first binding domain binds human KLK7 and inhibits KLK7 protease activity and the second binding domain binds human KLK5 and inhibits KLK5 protease activity.

253. A method of treating an individual having a disease selected from Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis, and rosacea, comprising administering to the individual an anti-KLK5 antibody and an anti-KLK7 antibody, wherein the anti-KLK5 antibody inhibits KLK5 protease activity, and wherein the anti-KLK7 antibody inhibits KLK7 protease activity.

254. A method of reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier and/or reducing skin inflammatory cytokines in an individual comprising administering to the individual a KLK5 antagonist and a KLK7 antagonist.

255. The method of claim 254, wherein the KLK5 antagonist is an anti-KLK5 antibody and/or the KLK7 antagonist is an anti-KLK7 antibody.

256. A method of reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier and/or reducing skin inflammatory cytokines in an individual comprising administering to the individual an effective amount of the bispecific antibody, wherein the bispecific antibody comprises a first binding domain and second binding domain, wherein the first binding domain binds human KLK7 and inhibits KLK7 protease activity and the second binding domain binds human KLK5 and inhibits KLK5 protease activity.

257. A method of reducing epithelium inflammation, reducing epithelium permeability, reducing transepidermal water loss, reducing dermal infiltrates, reducing parakeratosis, restoring the epithelial barrier and/or reducing skin inflammatory cytokines in an individual comprising administering to the individual an anti-KLK5 antibody and an anti-KLK7 antibody, wherein the anti-KLK5 antibody inhibits KLK5 protease activity, and wherein the anti-KLK7 antibody inhibits KLK7 protease activity.

258. A method of ameliorating skin rash and/or scaling in an individual with Netherton Syndrome comprising administering to the individual an effective amount of the bispecific antibody, wherein the bispecific antibody comprises a first binding domain and second binding domain, wherein the first binding domain binds human KLK7 and inhibits

KLK7 protease activity and the second binding domain binds human KLK5 and inhibits KLK5 protease activity.

259. A method of ameliorating skin rash and/or scaling in an individual with Netherton Syndrome comprising administering to the individual an anti-KLK5 antibody and an anti-KLK7 antibody, wherein the anti-KLK5 antibody inhibits KLK5 protease activity, and wherein the anti-KLK7 antibody inhibits KLK7 protease activity.

260. The use of any one of claims 192, 193, 240, or 247 or the method of any one of claims 205, 206, 209, 243, or 254-257, or the antibody, bispecific antibody, or pharmaceutical composition for use of claim 237, wherein the skin inflammatory cytokines are one or more of IL-8, TNF α , IL-6, IL-4, and/or G-CSF.

Kabat number	CDRL1-Contig		SEQ ID NO
	CDRL1-Contig	CDRL1-Kabat	
rb.14H11c-LC			
hu.14H11c.K1-39.L1	A I E M T Q S P S S L S A S V G E T V R I R C L A S E D I A S S V S W Y Q Q K P G K	1	14
hu.14H11c.K1-39.L2	D I Q M T Q S P S S L S A S V G D R V T I T C L A S E D I A S S V S W Y Q Q K P G K	2	31
hu.14H11c.K1-39.L3	D I Q M T Q S P S S L S A S V G D R V T I T C L A S E D I A S S V S W Y Q Q K P G K	3	32
hu.14H11c.K1-39.L4	D I Q M T Q S P S S L S A S V G D R V T I T C L A S E D I A S S V S W Y Q Q K P G K	4	33
hu.14H11c.K1-5.L1	D I Q M T Q S P S S L S A S V G D R V T I T C L A S E D I A S S V S W Y Q Q K P G K	5	34
hu.14H11c.K1-8.L1	A I Q M T Q S P S S L S A S V G D R V T I T C L A S E D I A S S V S W Y Q Q K P G K	6	35
hu.14H11c.K1-6.L1	A I Q M T Q S P S S L S A S V G D R V T I T C L A S E D I A S S V S W Y Q Q K P G K	7	36
hu.14H11c-L2.Q38K	D I Q M T Q S P S S L S A S V G D R V T I T C L A S E D I A S S V S W Y Q Q K P G K	8	37
Kabat number	CDRL2-Contig		SEQ ID NO
	CDRL2-Contig	CDRL2-Kabat	
rb.14H11c-LC			
hu.14H11c.K1-39.L1	P P T L L I Y G A S N L E S G V P S R R F S G S G S G T D Y T L T I S S L Q P E D F A	1	14
hu.14H11c.K1-39.L2	P P K L L I Y G A S N L E S G V P S R R F S G S G S G T D Y T L T I S S L Q P E D F A	2	31
hu.14H11c.K1-39.L3	P P K L L I Y G A S N L E S G V P S R R F S G S G S G T D Y T L T I S S L Q P E D F A	3	32
hu.14H11c.K1-39.L4	P P K L L I Y G A S N L E S G V P S R R F S G S G S G T D Y T L T I S S L Q P E D F A	4	33
hu.14H11c.K1-5.L1	P P K L L I Y G A S N L E S G V P S R R F S G S G S G T D Y T L T I S S L Q P E D F A	5	34
hu.14H11c.K1-8.L1	P P K L L I Y G A S N L E S G V P S R R F S G S G S G T D Y T L T I S S L Q P E D F A	6	35
hu.14H11c.K1-6.L1	P P K L L I Y G A S N L E S G V P S R R F S G S G S G T D Y T L T I S S L Q P E D F A	7	36
hu.14H11c-L2.Q38K	A P K L L I Y G A S N L E S G V P S R R F S G S G S G T D Y T L T I S S L Q P E D F A	8	37
Kabat number	CDRL3-Contig		SEQ ID NO
	CDRL3-Contig	CDRL3-Kabat	
rb.14H11c-LC			
hu.14H11c.K1-39.L1	T Y Y C L G G Y S Y S S T G T A F G G G T K V E I K	1	14
hu.14H11c.K1-39.L2	T Y Y C L G G Y S Y S S T G T A F G G G T K V E I K	2	31
hu.14H11c.K1-39.L3	T Y Y C L G G Y S Y S S T G T A F G G G T K V E I K	3	32
hu.14H11c.K1-39.L4	T Y Y C L G G Y S Y S S T G T A F G G G T K V E I K	4	33
hu.14H11c.K1-5.L1	T Y Y C L G G Y S Y S S T G T A F G G G T K V E I K	5	34
hu.14H11c.K1-8.L1	T Y Y C L G G Y S Y S S T G T A F G G G T K V E I K	6	35
hu.14H11c.K1-6.L1	T Y Y C L G G Y S Y S S T G T A F G G G T K V E I K	7	36
hu.14H11c-L2.Q38K	T Y Y C L G G Y S Y S S T G T A F G G G T K V E I K	8	37

FIG. 1A

CDR H2 - Constant

CDR H3 - Variable

CSA K3 - Contingency

Knot number	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200	201	202	203	204	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220	221	222	223	224	225	226	227	228	229	230	231	232	233	234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	251	252	253	254	255	256	257	258	259	260	261	262	263	264	265	266	267	268	269	270	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324	325	326	327	328	329	330	331	332	333	334	335	336	337	338	339	340	341	342	343	344	345	346	347	348	349	350	351	352	353	354	355	356	357	358	359	360	361	362	363	364	365	366	367	368	369	370	371	372	373	374	375	376	377	378	379	380	381	382	383	384	385	386	387	388	389	390	391	392	393	394	395	396	397	398	399	400	401	402	403	404	405	406	407	408	409	410	411	412	413	414	415	416	417	418	419	420	421	422	423	424	425	426	427	428	429	430	431	432	433	434	435	436	437	438	439	440	441	442	443	444	445	446	447	448	449	450	451	452	453	454	455	456	457	458	459	460	461	462	463	464	465	466	467	468	469	470	471	472	473	474	475	476	477	478	479	480	481	482	483	484	485	486	487	488	489	490	491	492	493	494	495	496	497	498	499	500	501	502	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	518	519	520	521	522	523	524</
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CA 03150999 2022-3-11

		CDR1 - Contd.																																														
Kabat number		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40							
	hu.10C5-H2BL5	A	I	R	M	T	Q	S	P	S	S	F	G	A	S	T	G	D	R	V	T	I	T	C	Q	A	S	E	S	I	S	N	E	L	S	W	Y	Q	Q	K	P	G	K					
	hu.10C5-L5.S34K	A	I	R	M	T	Q	S	P	S	S	F	G	A	S	T	G	D	R	V	T	I	T	C	Q	A	S	E	S	I	S	N	E	L	K	W	Y	Q	Q	K	P	G	K					
	hu.10C5-L5.F92Y	A	I	R	M	T	Q	S	P	S	S	F	G	A	S	T	G	D	R	V	T	I	T	C	Q	A	S	E	S	I	S	N	E	L	S	W	Y	Q	Q	K	P	G	K					
	hu.10C5-L5.S95F	A	I	R	M	T	Q	S	P	S	S	F	G	A	S	T	G	D	R	V	T	I	T	C	Q	A	S	E	S	I	S	N	E	L	S	W	Y	Q	Q	K	P	G	K					
	hu.10C5-L5.S34K.F92Y	A	I	R	M	T	Q	S	P	S	S	F	G	A	S	T	G	D	R	V	T	I	T	C	Q	A	S	E	S	I	S	N	E	L	K	W	Y	Q	Q	K	P	G	K					
	hu.10C5-L5.S34K.S95F	A	I	R	M	T	Q	S	P	S	S	F	G	A	S	T	G	D	R	V	T	I	T	C	Q	A	S	E	S	I	S	N	E	L	K	W	Y	Q	Q	K	P	G	K					
	hu.10C5-L5.F92Y.S95F	A	I	R	M	T	Q	S	P	S	S	F	G	A	S	T	G	D	R	V	T	I	T	C	Q	A	S	E	S	I	S	N	E	L	S	W	Y	Q	Q	K	P	G	K					
	hu.10C5-L5.Q38E.S34K	A	I	R	M	T	Q	S	P	S	S	F	G	A	S	T	G	D	R	V	T	I	T	C	Q	A	S	E	S	I	S	N	E	L	K	W	Y	Q	Q	K	P	G	K					
	hu.10C5-L5.Q38E.F92Y	A	I	R	M	T	Q	S	P	S	S	F	G	A	S	T	G	D	R	V	T	I	T	C	Q	A	S	E	S	I	S	N	E	L	S	W	Y	Q	Q	K	P	G	K					
	hu.10C5-L5.Q38E.S95F	A	I	R	M	T	Q	S	P	S	S	F	G	A	S	T	G	D	R	V	T	I	T	C	Q	A	S	E	S	I	S	N	E	L	S	W	Y	Q	Q	K	P	G	K					
	hu.10C5-L5.Q38E.S34K.F92Y	A	I	R	M	T	Q	S	P	S	S	F	G	A	S	T	G	D	R	V	T	I	T	C	Q	A	S	E	S	I	S	N	E	L	K	W	Y	Q	Q	K	P	G	K					
	hu.10C5-L5.Q38E.S34K.S95F	A	I	R	M	T	Q	S	P	S	S	F	G	A	S	T	G	D	R	V	T	I	T	C	Q	A	S	E	S	I	S	N	E	L	K	W	Y	Q	Q	K	P	G	K					
	hu.10C5-L5.Q38E.F92Y.S95F	A	I	R	M	T	Q	S	P	S	S	F	G	A	S	T	G	D	R	V	T	I	T	C	Q	A	S	E	S	I	S	N	E	L	S	W	Y	Q	Q	K	P	G	K					
	hu.10C5-L5.Q38E.S34K.F92Y.S95F	A	I	R	M	T	Q	S	P	S	S	F	G	A	S	T	G	D	R	V	T	I	T	C	Q	A	S	E	S	I	S	N	E	L	K	W	Y	Q	Q	K	P	G	K					
		CDR2 - Contd.																																														
Kabat number		41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84			
	hu.10C5-H2BL5	A	P	K	L	L	I	Y	A	S	T	L	A	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P	E	D	F	A						
	hu.10C5-L5.S34K	A	P	K	L	L	I	Y	A	S	T	L	A	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P	E	D	F	A						
	hu.10C5-L5.F92Y	A	P	K	L	L	I	Y	A	S	T	L	A	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P	E	D	F	A						
	hu.10C5-L5.S95F	A	P	K	L	L	I	Y	A	S	T	L	A	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P	E	D	F	A						
	hu.10C5-L5.S34K.F92Y	A	P	K	L	L	I	Y	A	S	T	L	A	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P	E	D	F	A						
	hu.10C5-L5.S34K.S95F	A	P	K	L	L	I	Y	A	S	T	L	A	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P	E	D	F	A						
	hu.10C5-L5.Q38E.S34K	A	P	K	L	L	I	Y	A	S	T	L	A	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P	E	D	F	A						
	hu.10C5-L5.Q38E.F92Y	A	P	K	L	L	I	Y	A	S	T	L	A	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P	E	D	F	A						
	hu.10C5-L5.Q38E.S95F	A	P	K	L	L	I	Y	A	S	T	L	A	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P	E	D	F	A						
	hu.10C5-L5.Q38E.S34K.F92Y	A	P	K	L	L	I	Y	A	S	T	L	A	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P	E	D	F	A						
	hu.10C5-L5.Q38E.S34K.S95F	A	P	K	L	L	I	Y	A	S	T	L	A	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P	E	D	F	A						
	hu.10C5-L5.Q38E.F92Y.S95F	A	P	K	L	L	I	Y	A	S	T	L	A	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P	E	D	F	A						
	hu.10C5-L5.Q38E.S34K.F92Y.S95F	A	P	K	L	L	I	Y	A	S	T	L	A	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P	E	D	F	A						
		CDR3 - Contd.																																														
Kabat number		85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130	
	hu.10C5-H2BL5	T	Y	Y	C	A	Q	G	F	G	S	S	G	V	E	N	V	F	G	G	G	T	K	V	E	I	K																					
	hu.10C5-L5.S34K	T	Y	Y	C	A	Q	G	F	G	S	S	G	V	E	N	V	F	G	G	G	T	K	V	E	I	K																					
	hu.10C5-L5.F92Y	T	Y	Y	C	A	Q	G	F	G	S	S	G	V	E	N	V	F	G	G	G	T	K	V	E	I	K																					
	hu.10C5-L5.S95F	T	Y	Y	C	A	Q	G	F	G	S	S	G	V	E	N	V	F	G	G	G	T	K	V	E	I	K																					
	hu.10C5-L5.S34K.F92Y	T	Y	Y	C	A	Q	G	F	G	S	S	G	V	E	N	V	F	G	G	G	T	K	V	E	I	K																					
	hu.10C5-L5.S34K.S95F	T	Y	Y	C	A	Q	G	F	G	S	S	G	V	E	N	V	F	G	G	G	T	K	V	E	I	K																					
	hu.10C5-L5.Q38E.S34K	T	Y	Y	C	A	Q	G	F	G	S	S	G	V	E	N	V	F	G	G	G	T	K	V	E	I	K																					
	hu.10C5-L5.Q38E.F92Y	T	Y	Y	C	A	Q	G	F	G	S	S	G	V	E	N	V	F	G	G	G	T	K	V	E	I	K																					
	hu.10C5-L5.Q38E.S95F	T	Y	Y	C	A	Q	G	F	G	S	S	G	V	E	N	V	F	G	G	G	T	K	V	E	I	K																					
	hu.10C5-L5.Q38E.S34K.F92Y	T	Y	Y	C	A	Q	G	F	G	S	S	G	V	E	N	V	F	G	G	G	T	K	V	E	I	K																					
	hu.10C5-L5.Q38E.S34K.S95F	T	Y	Y	C	A	Q	G	F	G	S	S	G	V	E	N	V	F	G	G	G	T	K	V	E	I	K																					
	hu.10C5-L5.Q38E.F92Y.S95F	T	Y	Y	C	A	Q	G	F	G	S	S	G	V	E	N	V	F	G	G	G	T	K	V	E	I	K																					
	hu.10C5-L5.Q38E.S34K.F92Y.S95F	T	Y	Y	C	A	Q	G	F	G	S	S	G	V	E	N	V	F	G	G	G	T	K	V	E	I	K																					

Kabat number hu.10C5-H28.L5	42	CDR H1 - Contact	39	CDR H1 - Kabat	82a	Kabat number hu.10C5-H28.L5	82a	SEQ ID NO
	41	CDR H1 - Contact	38	CDR H1 - Kabat	82		82	
	40	CDR H1 - Contact	37	CDR H1 - Kabat	81		81	
	39	CDR H1 - Contact	36	CDR H1 - Kabat	80		80	
	38	CDR H1 - Contact	35	CDR H1 - Kabat	79		79	
	37	CDR H1 - Contact	34	CDR H1 - Kabat	78		78	
	36	CDR H1 - Contact	33	CDR H1 - Kabat	77		77	
	35	CDR H1 - Contact	32	CDR H1 - Kabat	76		76	
	34	CDR H1 - Contact	31	CDR H1 - Kabat	75		75	
	33	CDR H1 - Contact	30	CDR H1 - Kabat	74		74	
Kabat number hu.10C5-H28.G33P	32	CDR H1 - Contact	29	CDR H1 - Kabat	73		73	
	31	CDR H1 - Contact	28	CDR H1 - Kabat	72		72	
	30	CDR H1 - Contact	27	CDR H1 - Kabat	71		71	
	29	CDR H1 - Contact	26	CDR H1 - Kabat	70		70	
	28	CDR H1 - Contact	25	CDR H1 - Kabat	69		69	
	27	CDR H1 - Contact	24	CDR H1 - Kabat	68		68	
	26	CDR H1 - Contact	23	CDR H1 - Kabat	67		67	
	25	CDR H1 - Contact	22	CDR H1 - Kabat	66		66	
	24	CDR H1 - Contact	21	CDR H1 - Kabat	65		65	
	23	CDR H1 - Contact	20	CDR H1 - Kabat	64		64	
Kabat number hu.10C5-H28.N53V	22	CDR H1 - Contact	19	CDR H1 - Kabat	63		63	
	21	CDR H1 - Contact	18	CDR H1 - Kabat	62		62	
	20	CDR H1 - Contact	17	CDR H1 - Kabat	61		61	
	19	CDR H1 - Contact	16	CDR H1 - Kabat	60		60	
	18	CDR H1 - Contact	15	CDR H1 - Kabat	59		59	
	17	CDR H1 - Contact	14	CDR H1 - Kabat	58		58	
	16	CDR H1 - Contact	13	CDR H1 - Kabat	57		57	
	15	CDR H1 - Contact	12	CDR H1 - Kabat	56		56	
	14	CDR H1 - Contact	11	CDR H1 - Kabat	55		55	
	13	CDR H1 - Contact	10	CDR H1 - Kabat	54		54	
Kabat number hu.10C5-H28.G33P.N53V	12	CDR H1 - Contact	9	CDR H1 - Kabat	53		53	
	11	CDR H1 - Contact	8	CDR H1 - Kabat	52a		52a	
	10	CDR H1 - Contact	7	CDR H1 - Kabat	52		52	
	9	CDR H1 - Contact	6	CDR H1 - Kabat	51		51	
	8	CDR H1 - Contact	5	CDR H1 - Kabat	50		50	
	7	CDR H1 - Contact	4	CDR H1 - Kabat	49		49	
	6	CDR H1 - Contact	3	CDR H1 - Kabat	48		48	
	5	CDR H1 - Contact	2	CDR H1 - Kabat	47		47	
	4	CDR H1 - Contact	1	CDR H1 - Kabat	46		46	
	3	CDR H1 - Contact	0	CDR H1 - Kabat	45		45	
Kabat number hu.10C5-H28.N53V	2	CDR H1 - Contact	0	CDR H1 - Kabat	44		44	
	1	CDR H1 - Contact	0	CDR H1 - Kabat	43		43	
	0	CDR H1 - Contact	0	CDR H1 - Kabat	42		42	
	0	CDR H1 - Contact	0	CDR H1 - Kabat	41		41	
	0	CDR H1 - Contact	0	CDR H1 - Kabat	40		40	
	0	CDR H1 - Contact	0	CDR H1 - Kabat	39		39	
	0	CDR H1 - Contact	0	CDR H1 - Kabat	38		38	
	0	CDR H1 - Contact	0	CDR H1 - Kabat	37		37	
	0	CDR H1 - Contact	0	CDR H1 - Kabat	36		36	
	0	CDR H1 - Contact	0	CDR H1 - Kabat	35		35	

FIG. 2B

Kabat number	CDRL1 - Contact	
	CDRL1 - Kabat	CDRL1 - Contact
hu.9H5-H14L4	DIQMTQSPSSLSASSVGDRVTITCQASQSISSYLSWYQKPKGK	DIQMTQSPSSLSASSVGDRVTITCQASQSISSYLSWYQKPKGK
hu.9H5-L4.H89V	DIQMTQSPSSLSASSVGDRVTITCQASQSISSYLSWYQKPKGK	DIQMTQSPSSLSASSVGDRVTITCQASQSISSYLSWYQKPKGK
hu.9H5-L4.S95Y	DIQMTQSPSSLSASSVGDRVTITCQASQSISSYLSWYQKPKGK	DIQMTQSPSSLSASSVGDRVTITCQASQSISSYLSWYQKPKGK
hu.9H5-L4.H89V.S95Y	DIQMTQSPSSLSASSVGDRVTITCQASQSISSYLSWYQKPKGK	DIQMTQSPSSLSASSVGDRVTITCQASQSISSYLSWYQKPKGK
hu.9H5-L4.Q38E	DIQMTQSPSSLSASSVGDRVTITCQASQSISSYLSWYQKPKGK	DIQMTQSPSSLSASSVGDRVTITCQASQSISSYLSWYQKPKGK
hu.9H5-L4.Q38E.H89V	DIQMTQSPSSLSASSVGDRVTITCQASQSISSYLSWYQKPKGK	DIQMTQSPSSLSASSVGDRVTITCQASQSISSYLSWYQKPKGK
hu.9H5-L4.Q38E.S95Y	DIQMTQSPSSLSASSVGDRVTITCQASQSISSYLSWYQKPKGK	DIQMTQSPSSLSASSVGDRVTITCQASQSISSYLSWYQKPKGK
hu.9H5-L4.Q38E.H89V.S95Y	DIQMTQSPSSLSASSVGDRVTITCQASQSISSYLSWYQKPKGK	DIQMTQSPSSLSASSVGDRVTITCQASQSISSYLSWYQKPKGK
Kabat number	CDRL2 - Contact	
	CDRL2 - Kabat	CDRL2 - Contact
hu.9H5-H14L4	APKLLIYSSASTLASGVPSRFSGSGSGTDFTLTISSSLQPEDEFA	APKLLIYSSASTLASGVPSRFSGSGSGTDFTLTISSSLQPEDEFA
hu.9H5-L4.H89V	APKLLIYSSASTLASGVPSRFSGSGSGTDFTLTISSSLQPEDEFA	APKLLIYSSASTLASGVPSRFSGSGSGTDFTLTISSSLQPEDEFA
hu.9H5-L4.S95Y	APKLLIYSSASTLASGVPSRFSGSGSGTDFTLTISSSLQPEDEFA	APKLLIYSSASTLASGVPSRFSGSGSGTDFTLTISSSLQPEDEFA
hu.9H5-L4.H89V.S95Y	APKLLIYSSASTLASGVPSRFSGSGSGTDFTLTISSSLQPEDEFA	APKLLIYSSASTLASGVPSRFSGSGSGTDFTLTISSSLQPEDEFA
hu.9H5-L4.Q38E	APKLLIYSSASTLASGVPSRFSGSGSGTDFTLTISSSLQPEDEFA	APKLLIYSSASTLASGVPSRFSGSGSGTDFTLTISSSLQPEDEFA
hu.9H5-L4.Q38E.H89V	APKLLIYSSASTLASGVPSRFSGSGSGTDFTLTISSSLQPEDEFA	APKLLIYSSASTLASGVPSRFSGSGSGTDFTLTISSSLQPEDEFA
hu.9H5-L4.Q38E.S95Y	APKLLIYSSASTLASGVPSRFSGSGSGTDFTLTISSSLQPEDEFA	APKLLIYSSASTLASGVPSRFSGSGSGTDFTLTISSSLQPEDEFA
hu.9H5-L4.Q38E.H89V.S95Y	APKLLIYSSASTLASGVPSRFSGSGSGTDFTLTISSSLQPEDEFA	APKLLIYSSASTLASGVPSRFSGSGSGTDFTLTISSSLQPEDEFA
Kabat number	CDRL3 - Contact	
	CDRL3 - Kabat	CDRL3 - Contact
hu.9H5-H14L4	TY YCHQDYTSNVDNNTFGGGTKVEIK	TY YCHQDYTSNVDNNTFGGGTKVEIK
hu.9H5-L4.H89V	TY YCHQDYTSNVDNNTFGGGTKVEIK	TY YCHQDYTSNVDNNTFGGGTKVEIK
hu.9H5-L4.S95Y	TY YCHQDYTSNVDNNTFGGGTKVEIK	TY YCHQDYTSNVDNNTFGGGTKVEIK
hu.9H5-L4.H89V.S95Y	TY YCHQDYTSNVDNNTFGGGTKVEIK	TY YCHQDYTSNVDNNTFGGGTKVEIK
hu.9H5-L4.Q38E	TY YCHQDYTSNVDNNTFGGGTKVEIK	TY YCHQDYTSNVDNNTFGGGTKVEIK
hu.9H5-L4.Q38E.H89V	TY YCHQDYTSNVDNNTFGGGTKVEIK	TY YCHQDYTSNVDNNTFGGGTKVEIK
hu.9H5-L4.Q38E.S95Y	TY YCHQDYTSNVDNNTFGGGTKVEIK	TY YCHQDYTSNVDNNTFGGGTKVEIK
hu.9H5-L4.Q38E.H89V.S95Y	TY YCHQDYTSNVDNNTFGGGTKVEIK	TY YCHQDYTSNVDNNTFGGGTKVEIK

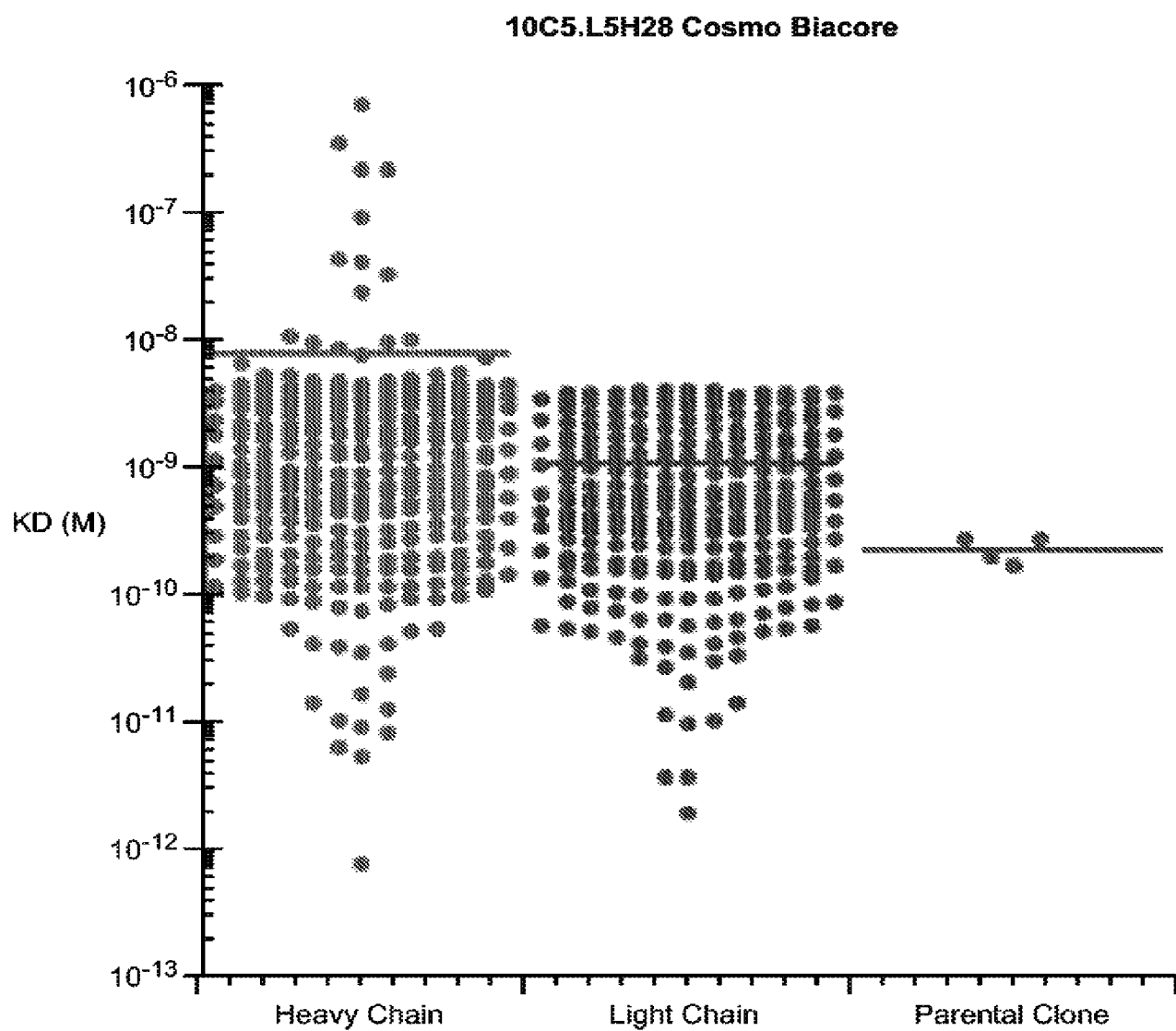
FIG. 3A

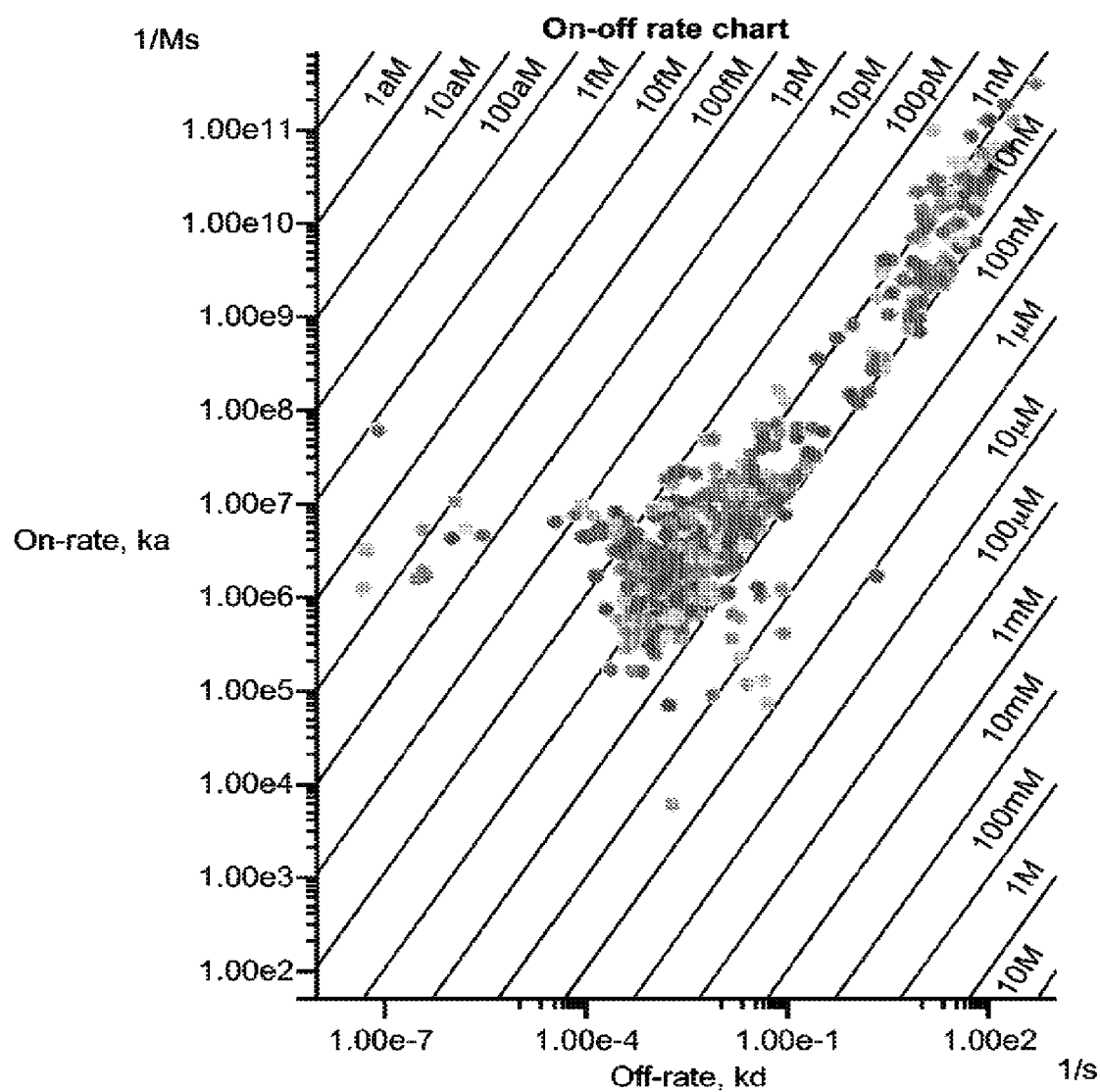
Kabat number	CDR H1 - Contact	CDR H1 - Kabat
hu.9H5-H14L4	EVQLVESGGGLIQPGGSLRLSCAASGFFSLSSYGVSWVRQA	PG
hu.9H5-H14.G54A	EVQLVESGGGLIQPGGSLRLSCAASGFFSLSSYGVSWVRQA	PG
hu.9H5-H14.G98Q	EVQLVESGGGLIQPGGSLRLSCAASGFFSLSSYGVSWVRQA	PG
hu.9H5-H14.G54A.G98Q	EVQLVESGGGLIQPGGSLRLSCAASGFFSLSSYGVSWVRQA	PG
hu.9H5-H14.Q39K	EVQLVESGGGLIQPGGSLRLSCAASGFFSLSSYGVSWVRQA	PG
hu.9H5-H14.Q39K.G54A	EVQLVESGGGLIQPGGSLRLSCAASGFFSLSSYGVSWVRQA	PG
hu.9H5-H14.Q39K.G98Q	EVQLVESGGGLIQPGGSLRLSCAASGFFSLSSYGVSWVRQA	PG
hu.9H5-H14.Q39K.G54A.G98Q	EVQLVESGGGLIQPGGSLRLSCAASGFFSLSSYGVSWVRQA	PG

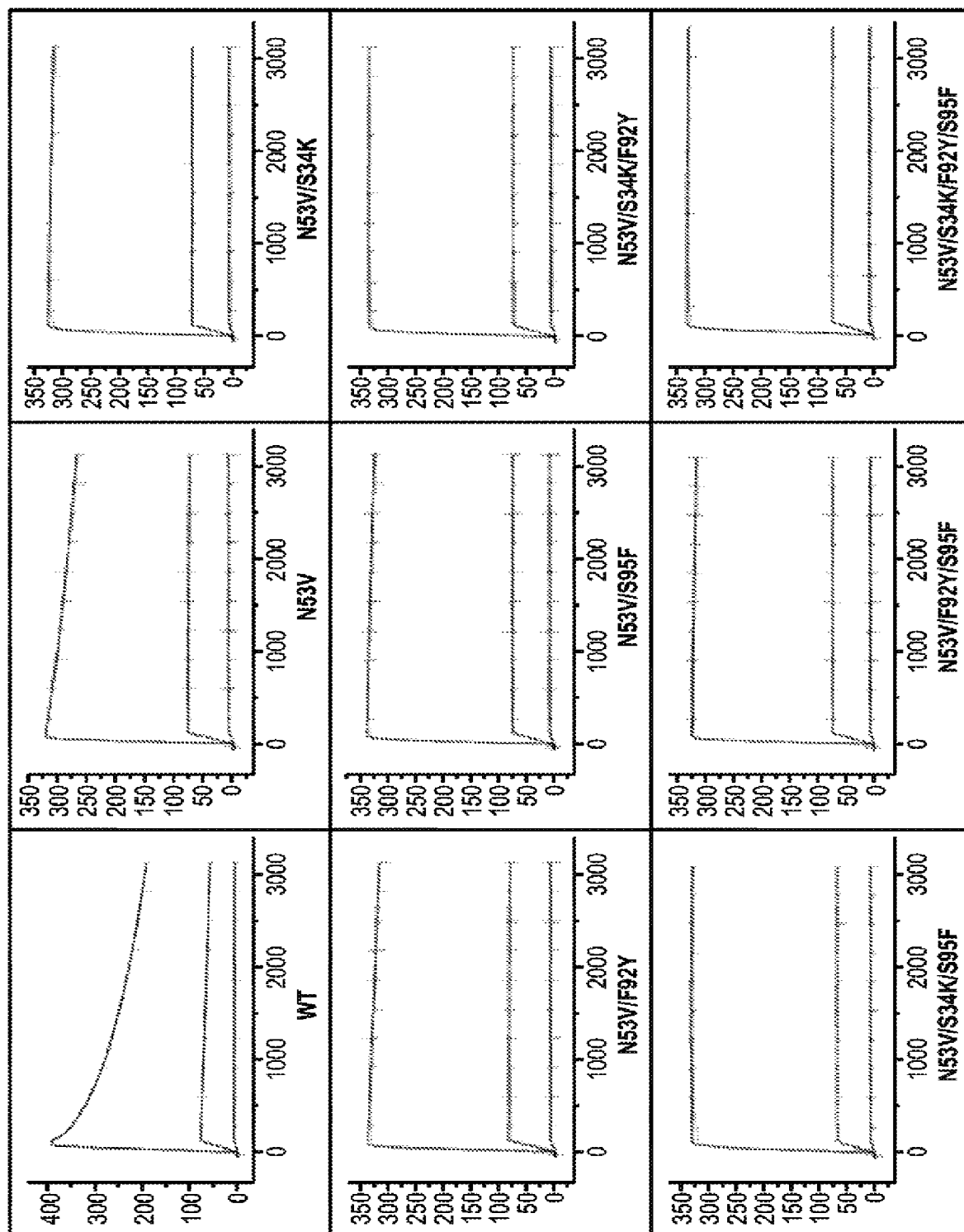
Kabat number	CDR H2 - Contact	CDR H2 - Kabat
hu.9H5-H14L4	KGLEYYVGFIGSGGFAFYASWAKSRFTISRDN	SKNTLYLQMN
hu.9H5-H14.G54A	KGLEYYVGFIGSGGFAFYASWAKSRFTISRDN	SKNTLYLQMN
hu.9H5-H14.G98Q	KGLEYYVGFIGSGGFAFYASWAKSRFTISRDN	SKNTLYLQMN
hu.9H5-H14.G54A.G98Q	KGLEYYVGFIGSGGFAFYASWAKSRFTISRDN	SKNTLYLQMN
hu.9H5-H14.Q39K	KGLEYYVGFIGSGGFAFYASWAKSRFTISRDN	SKNTLYLQMN
hu.9H5-H14.Q39K.G54A	KGLEYYVGFIGSGGFAFYASWAKSRFTISRDN	SKNTLYLQMN
hu.9H5-H14.Q39K.G98Q	KGLEYYVGFIGSGGFAFYASWAKSRFTISRDN	SKNTLYLQMN
hu.9H5-H14.Q39K.G54A.G98Q	KGLEYYVGFIGSGGFAFYASWAKSRFTISRDN	SKNTLYLQMN

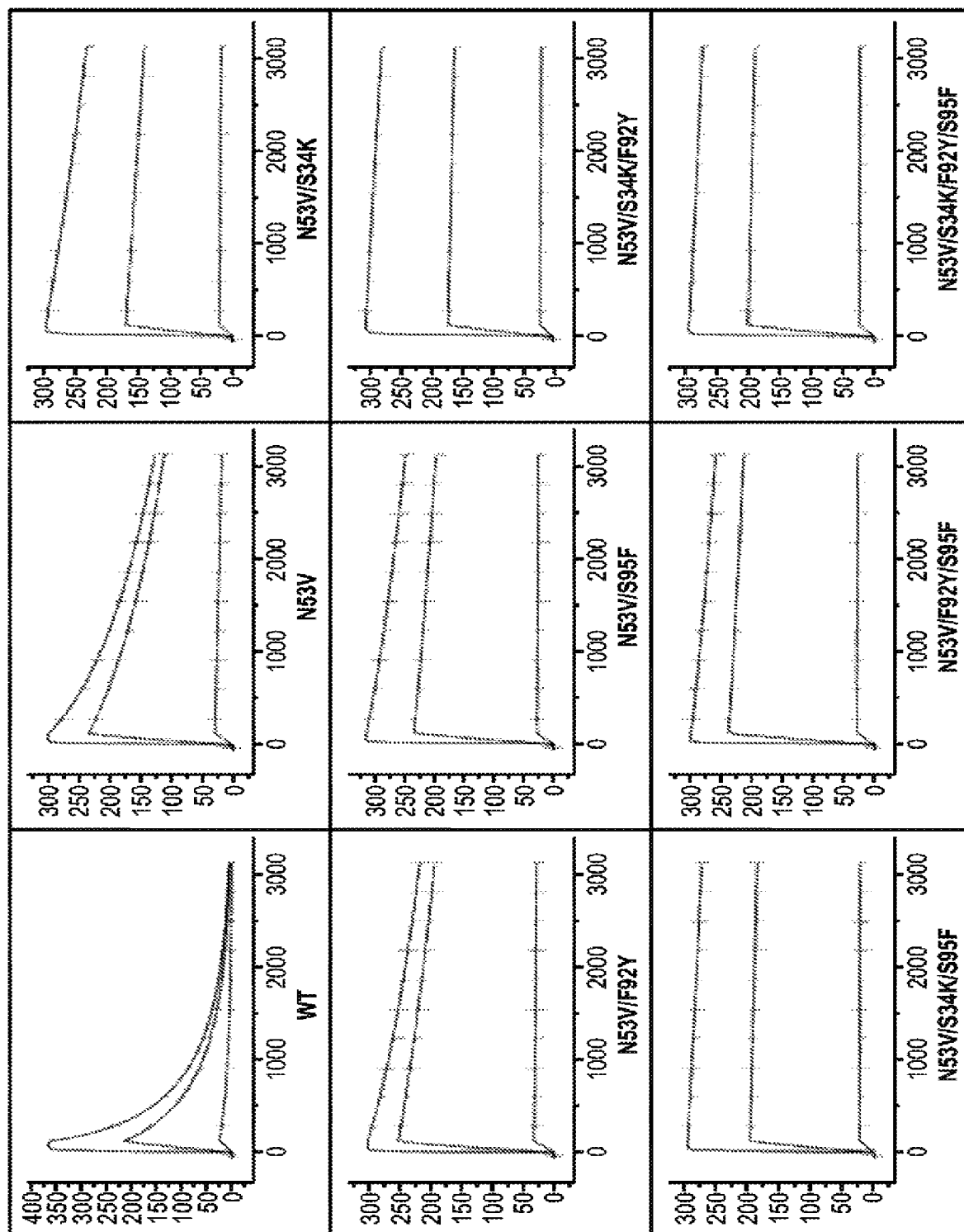
Kabat number	CDR H3 - Contact	CDR H3 - Kabat	SEQ ID NO
hu.9H5-H14L4	LRAEDTAVYYCARDDVGGGKSLDIWGQGT	LVTVSS	79
hu.9H5-H14.G54A	LRAEDTAVYYCARDDVGGGKSLDIWGQGT	LVTVSS	81
hu.9H5-H14.G98Q	LRAEDTAVYYCARDDVGGGKSLDIWGQGT	LVTVSS	82
hu.9H5-H14.G54A.G98Q	LRAEDTAVYYCARDDVGGGKSLDIWGQGT	LVTVSS	83
hu.9H5-H14.Q39K	LRAEDTAVYYCARDDVGGGKSLDIWGQGT	LVTVSS	84
hu.9H5-H14.Q39K.G54A	LRAEDTAVYYCARDDVGGGKSLDIWGQGT	LVTVSS	85
hu.9H5-H14.Q39K.G98Q	LRAEDTAVYYCARDDVGGGKSLDIWGQGT	LVTVSS	86
hu.9H5-H14.Q39K.G54A.G98Q	LRAEDTAVYYCARDDVGGGKSLDIWGQGT	LVTVSS	87

FIG. 3B



**FIG. 5**

**FIG. 6A**

**FIG. 6B**

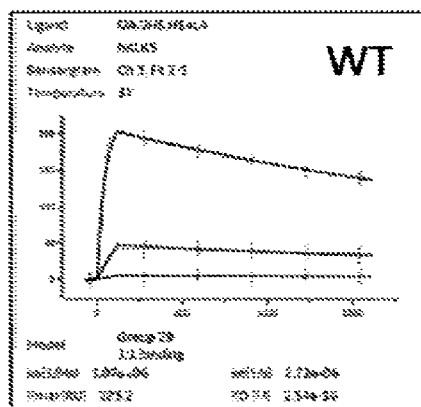
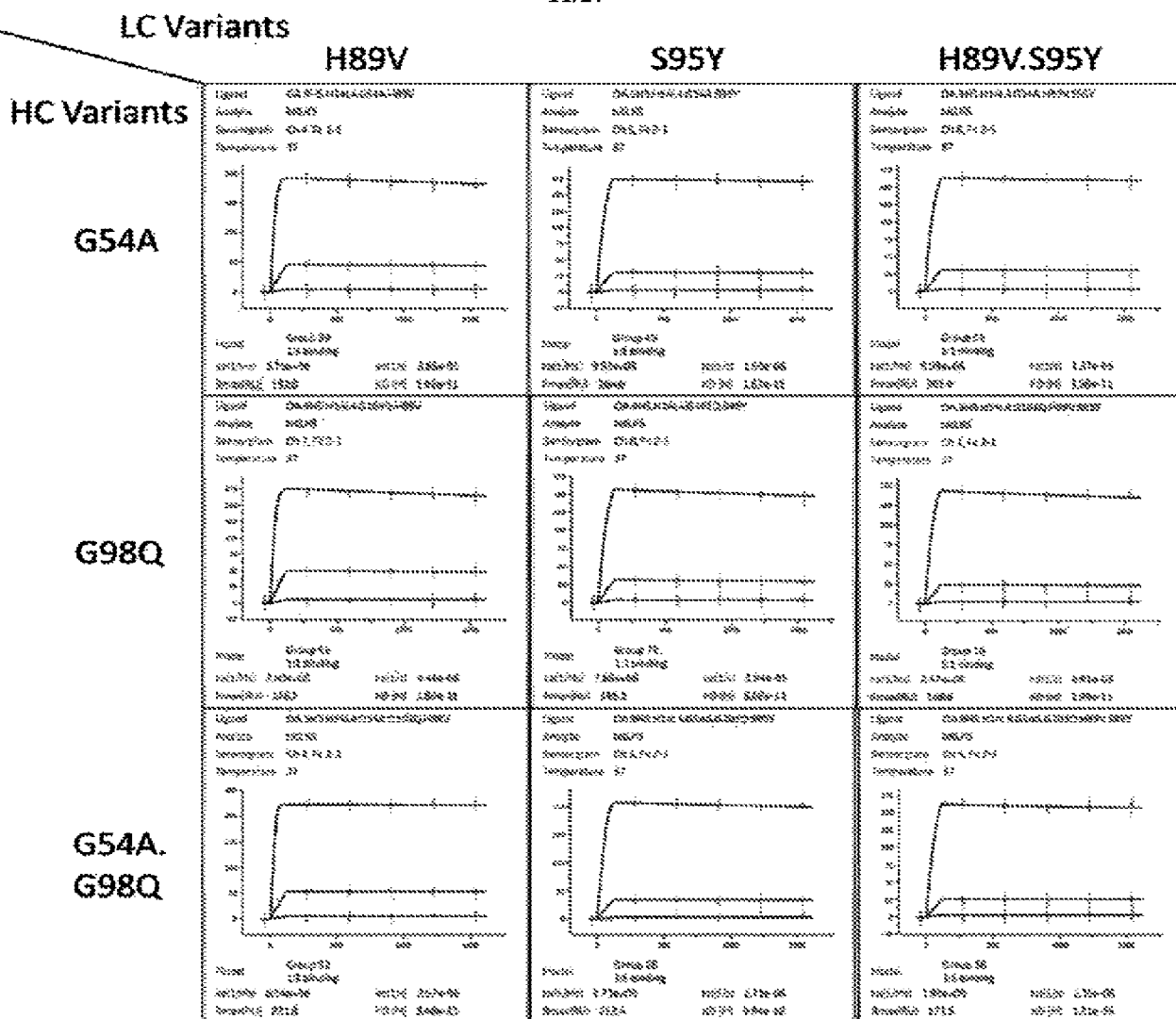


FIG. 7A

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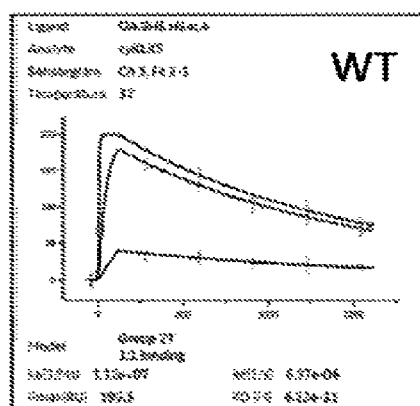
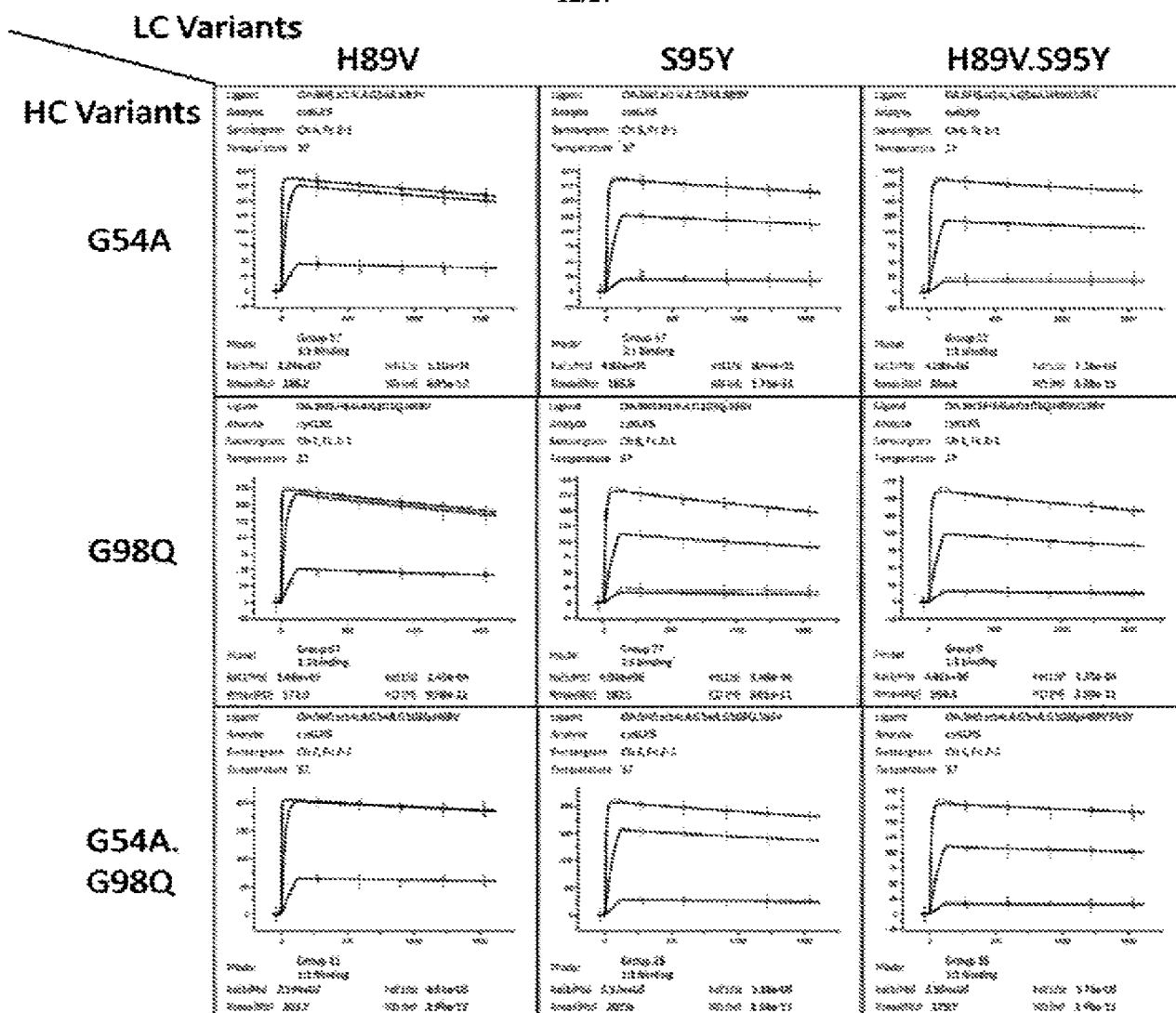
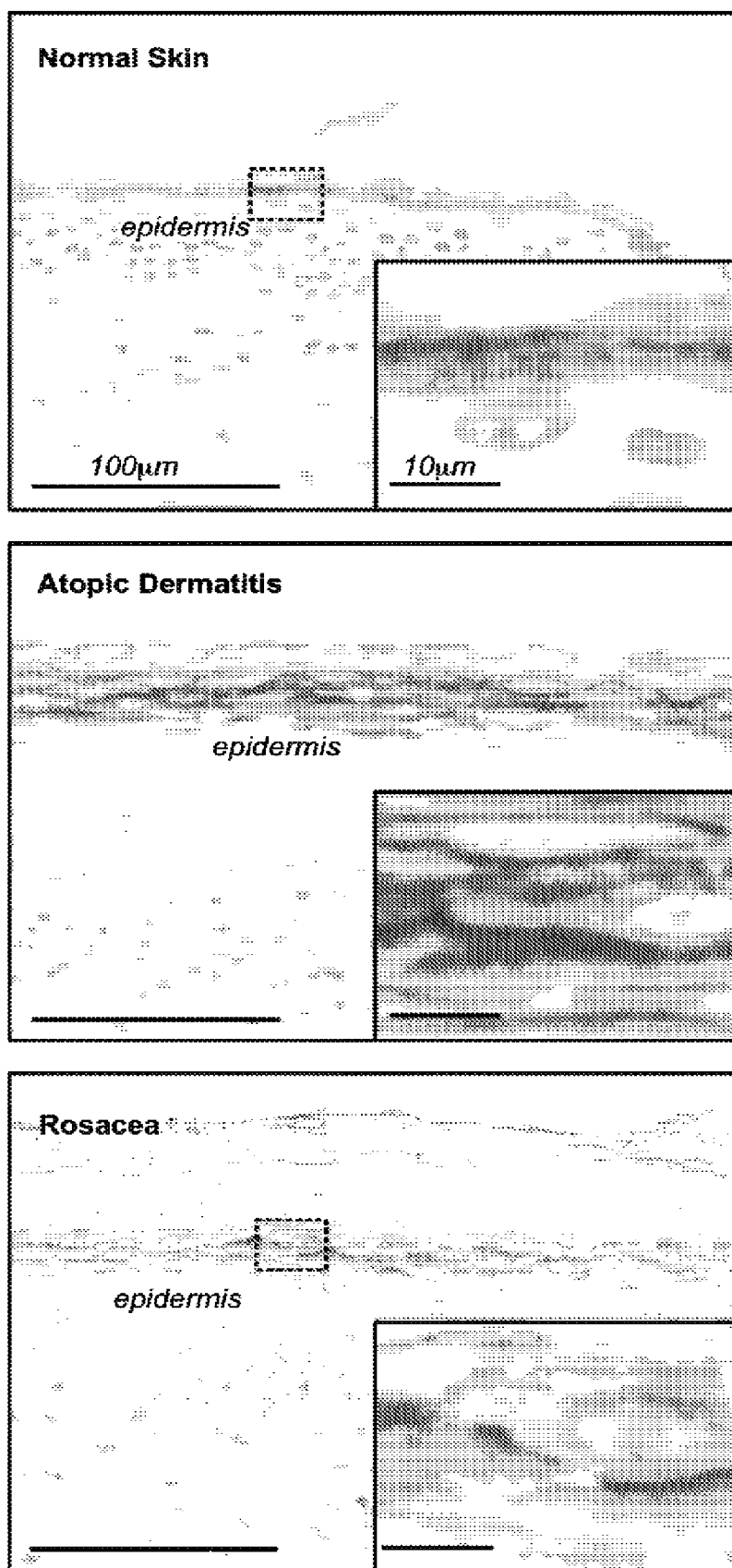


FIG. 7B

FIG. 8

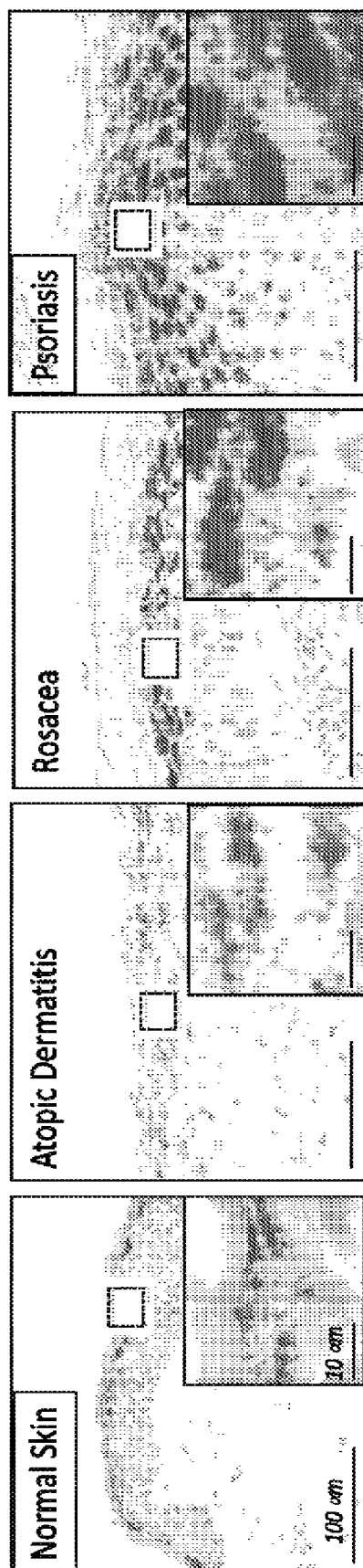


FIG. 9

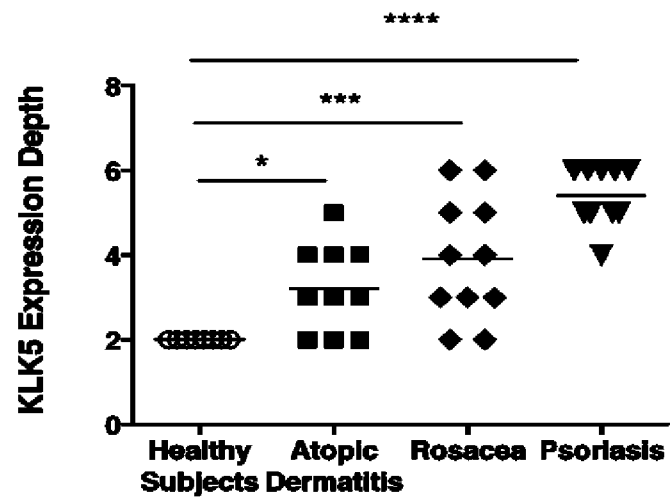
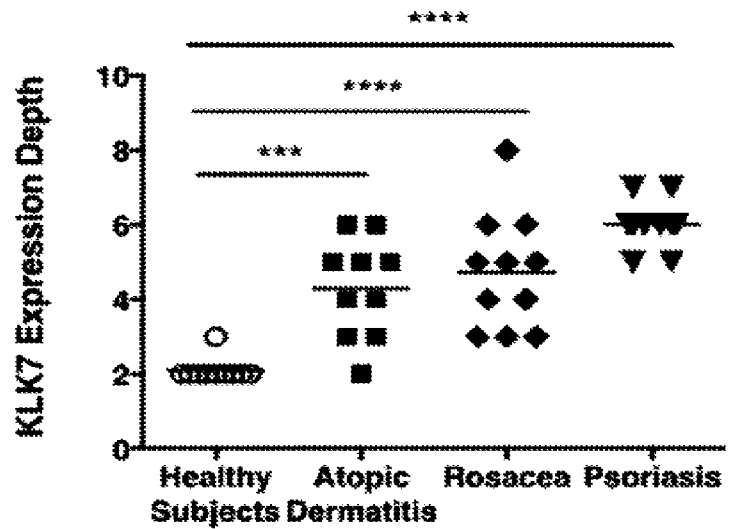
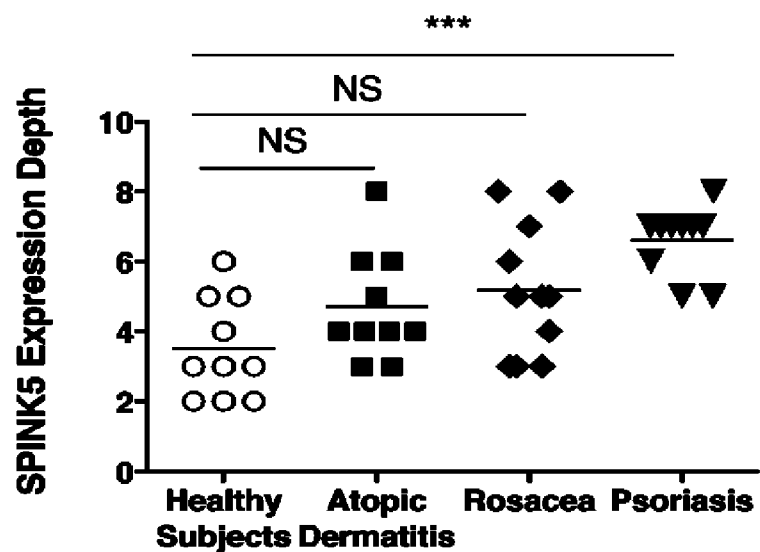
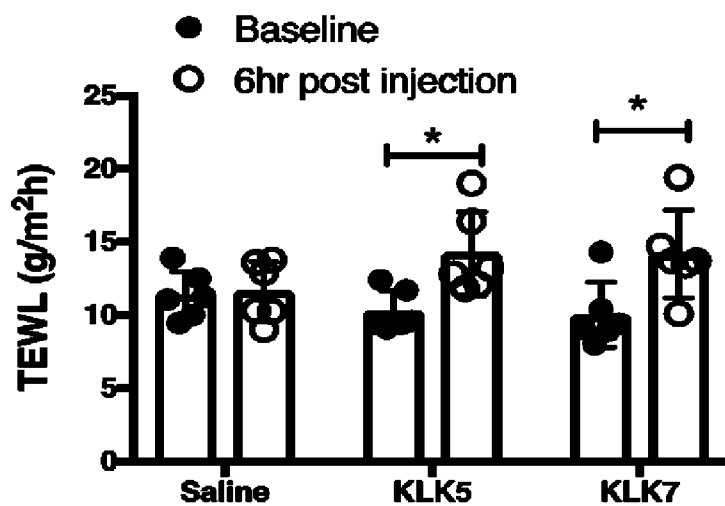
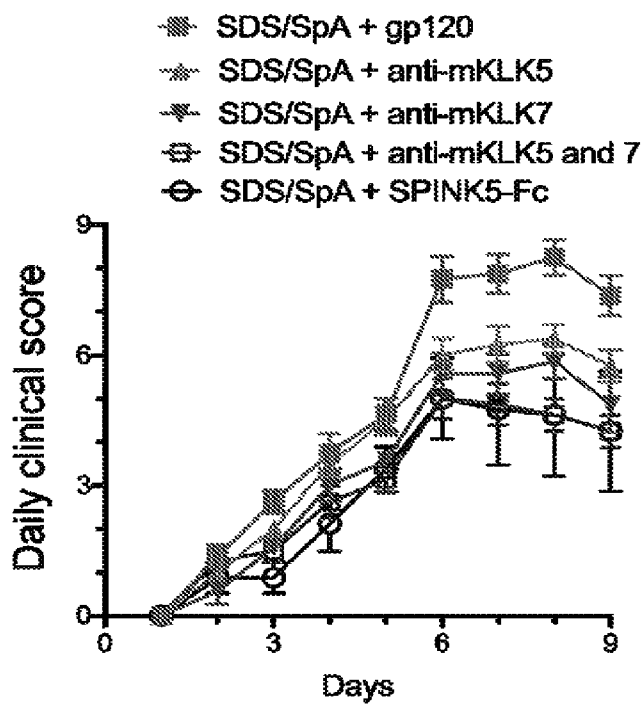
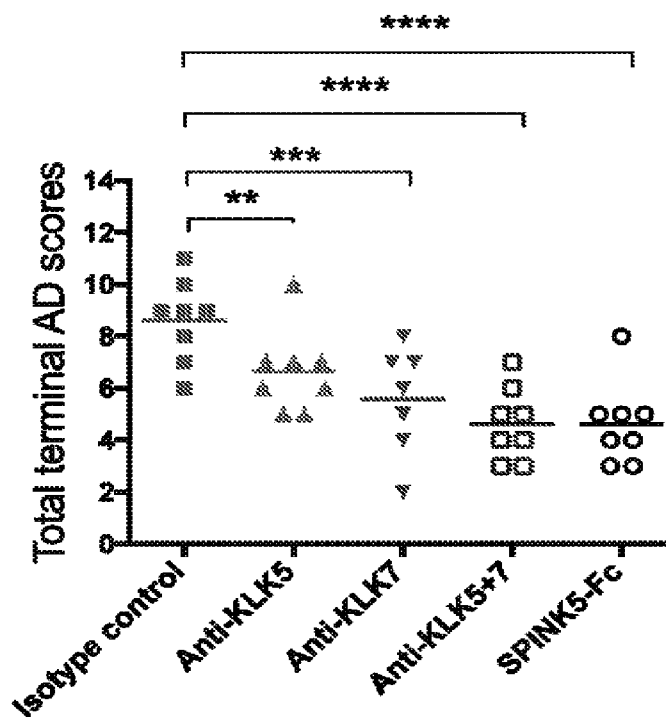
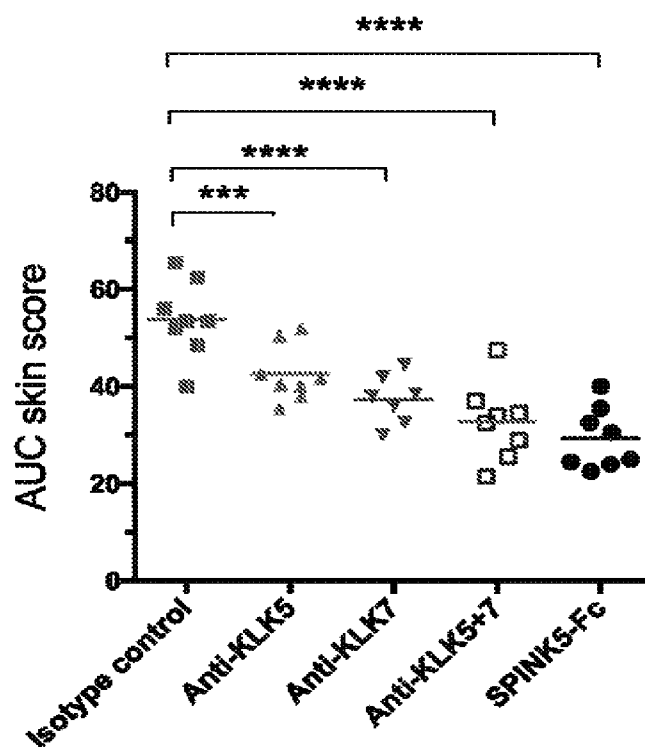
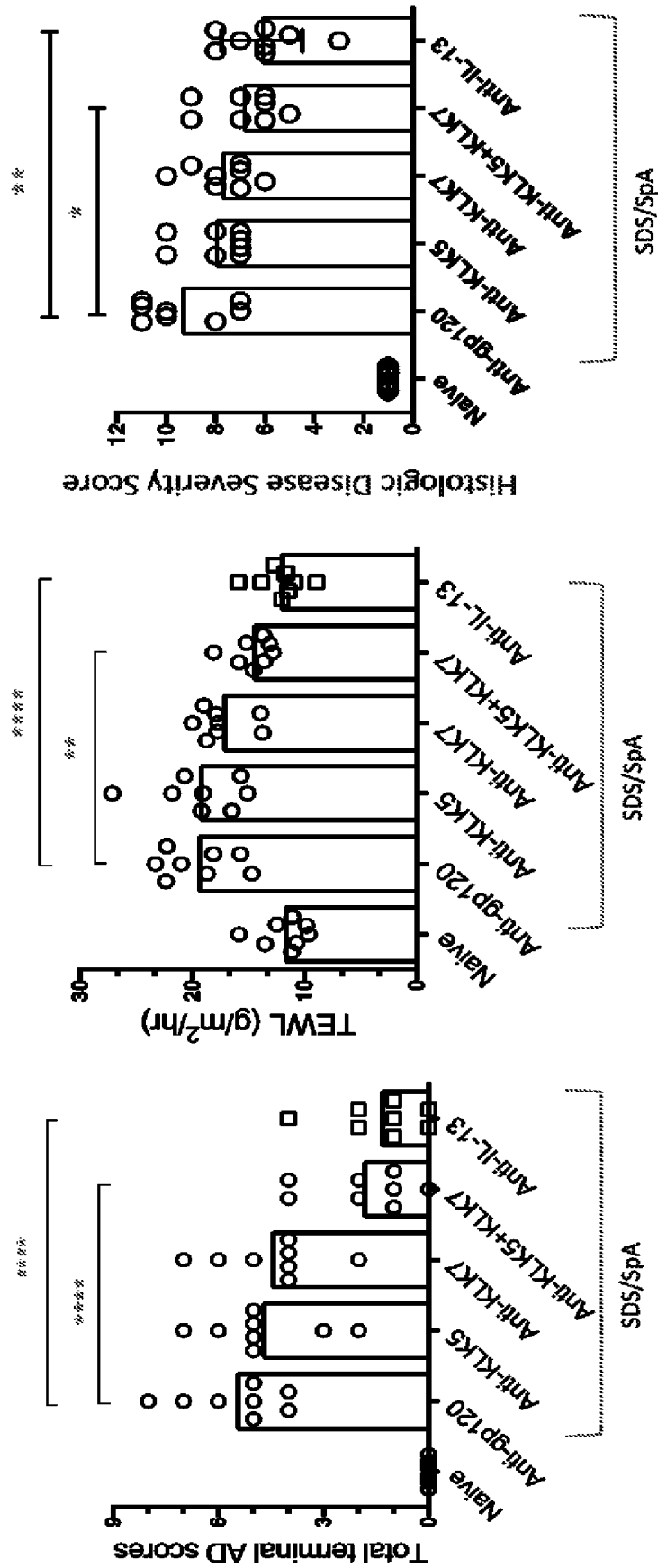
FIG. 10A**FIG. 10B****FIG. 10C**

FIG. 11**FIG. 12A**

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FIG. 12B**FIG. 12C**



*p:0.05, * p<0.01, *** p<0.001, **** p<0.0001

* Blinded clinical score of skin edema, erythema, scaling.

FIG. 13

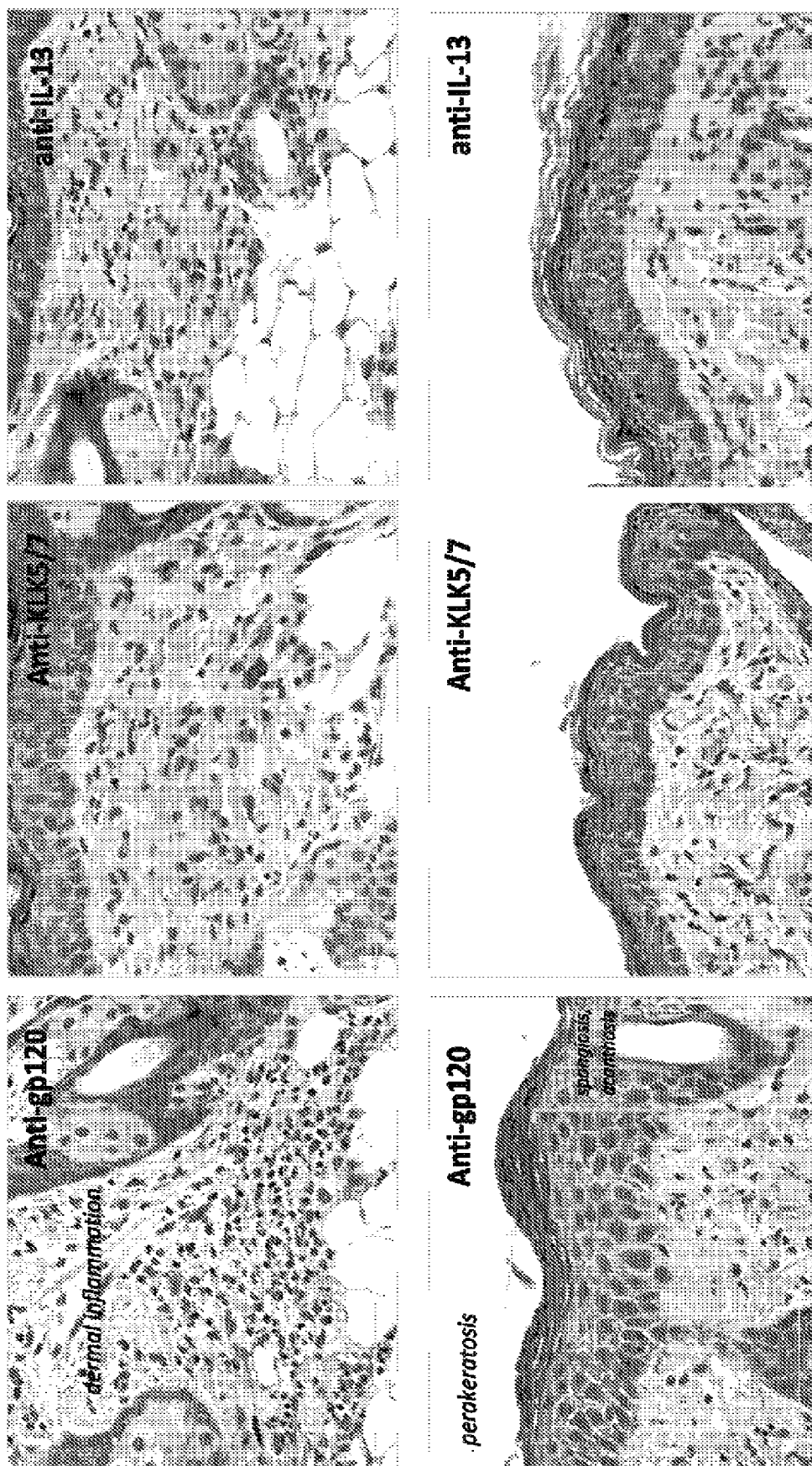


FIG. 14

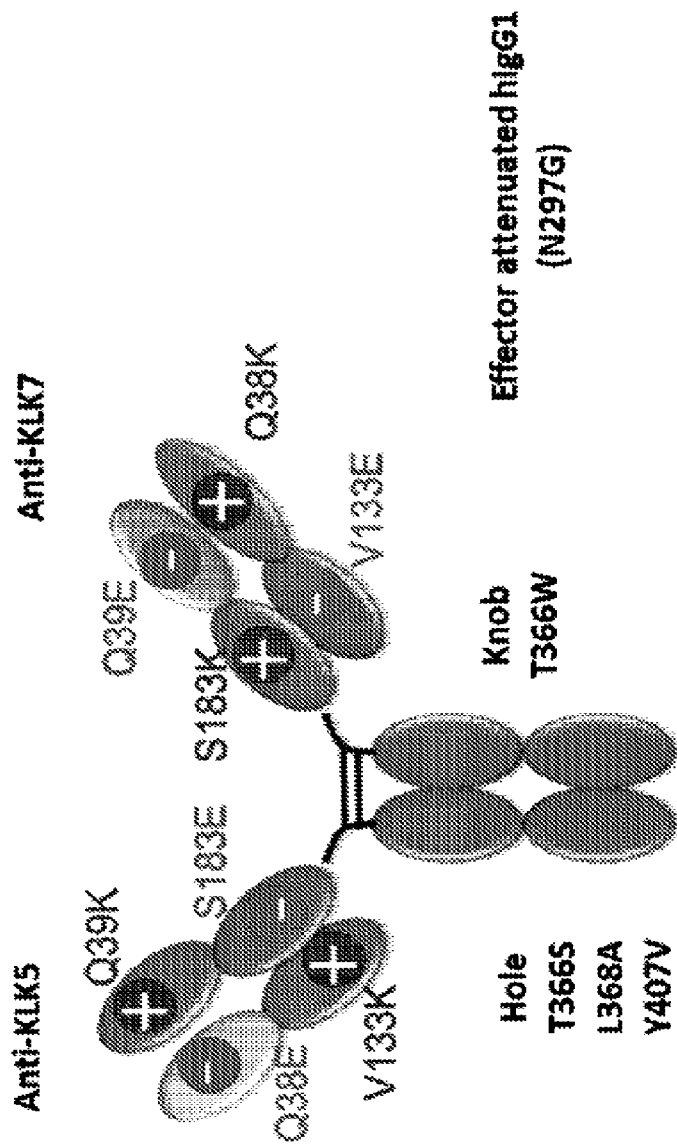


FIG. 15



FIG. 16B

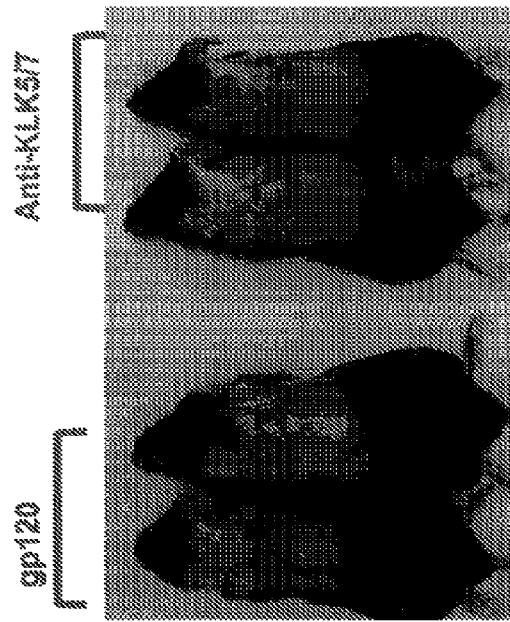


FIG. 16D



FIG. 16A

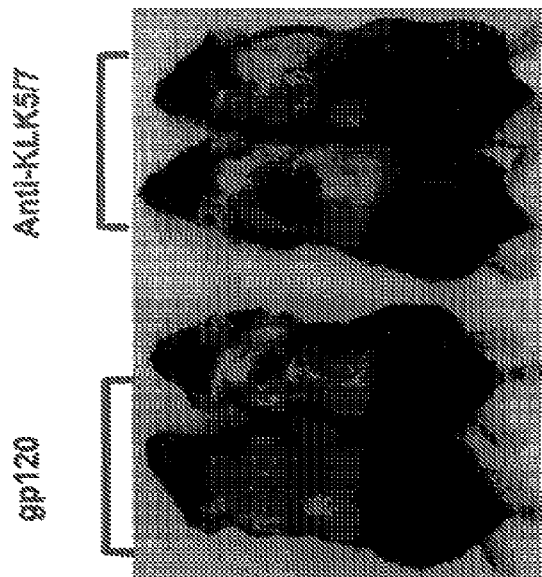
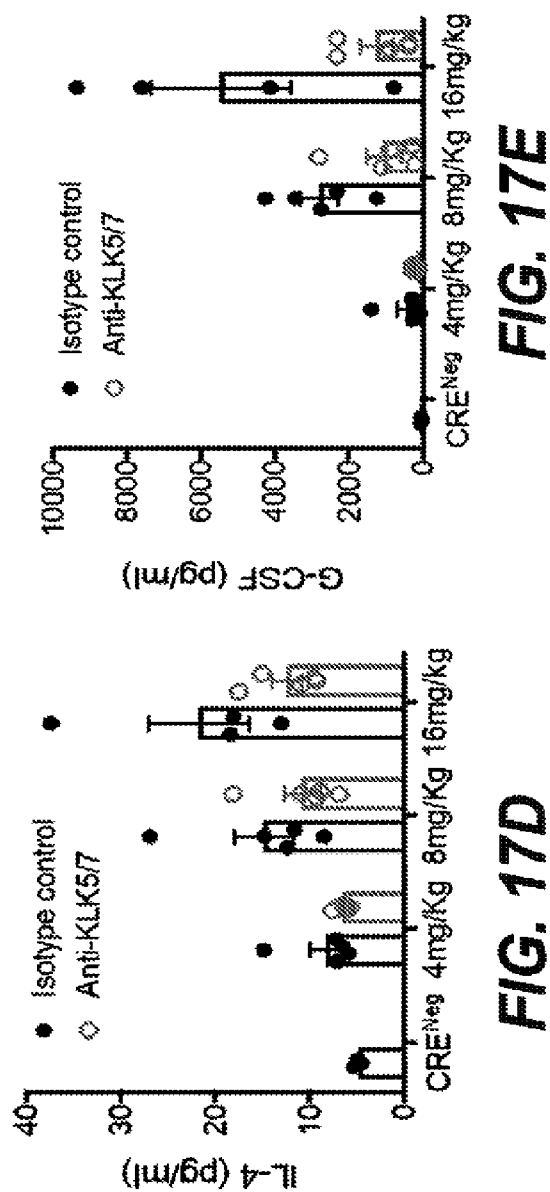
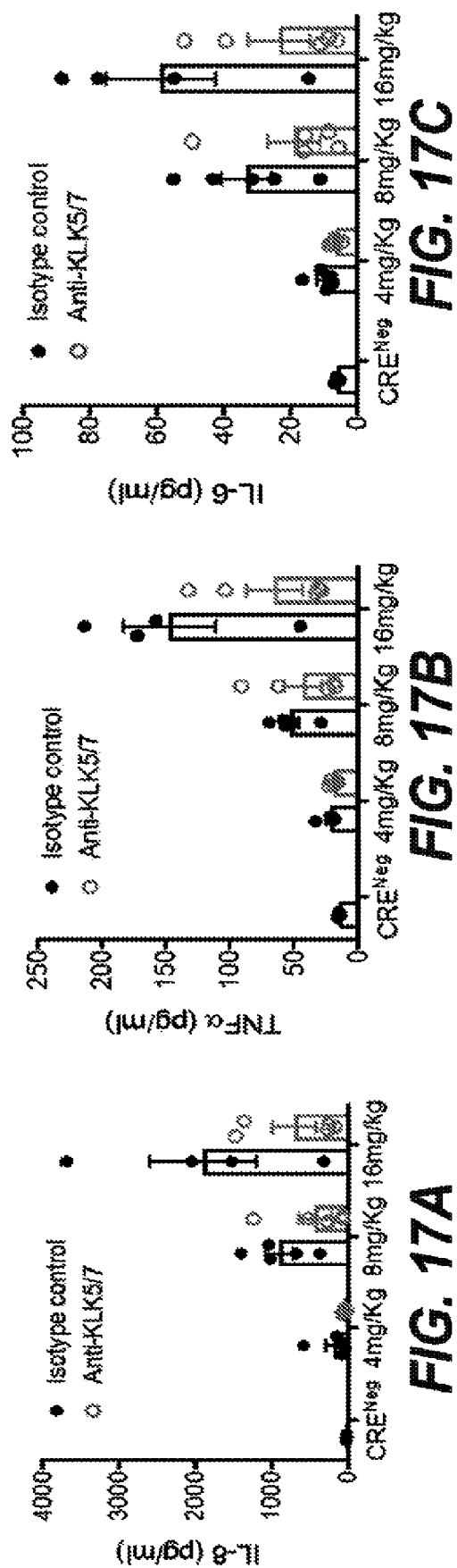


FIG. 16C



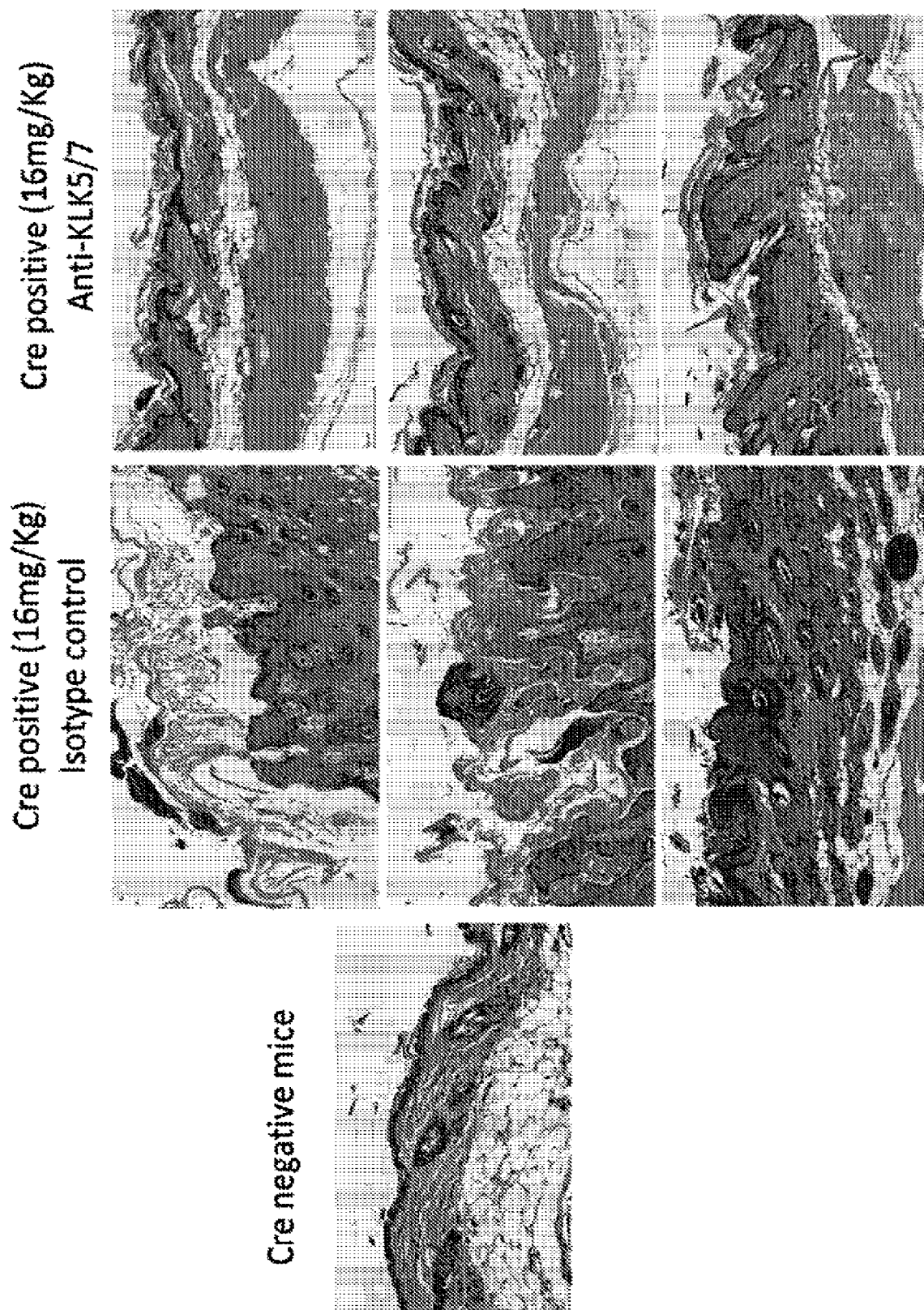
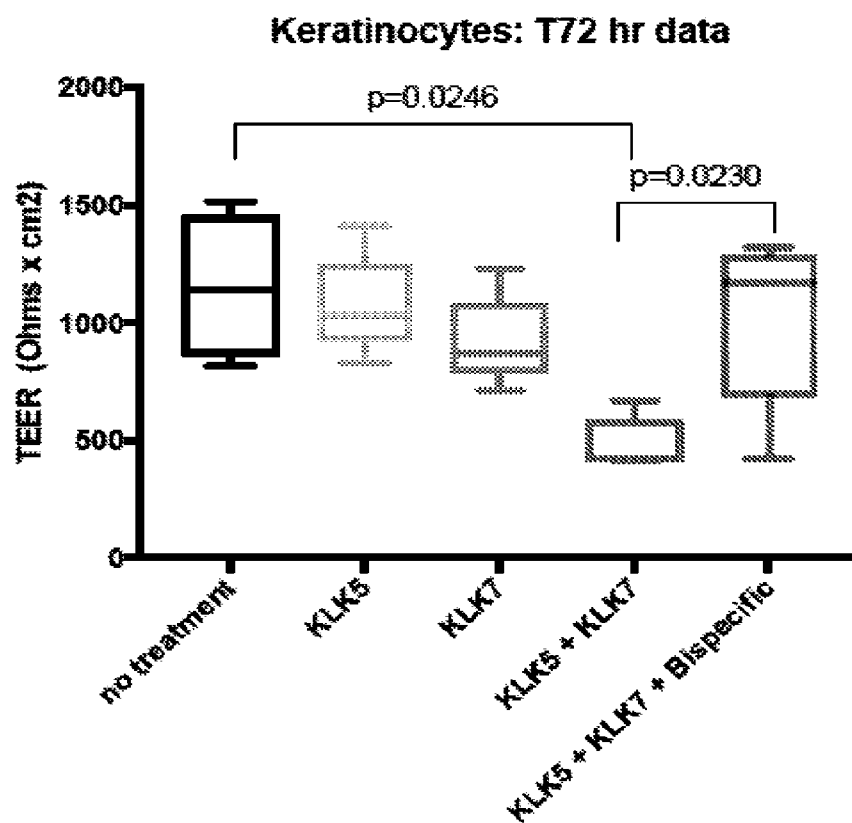
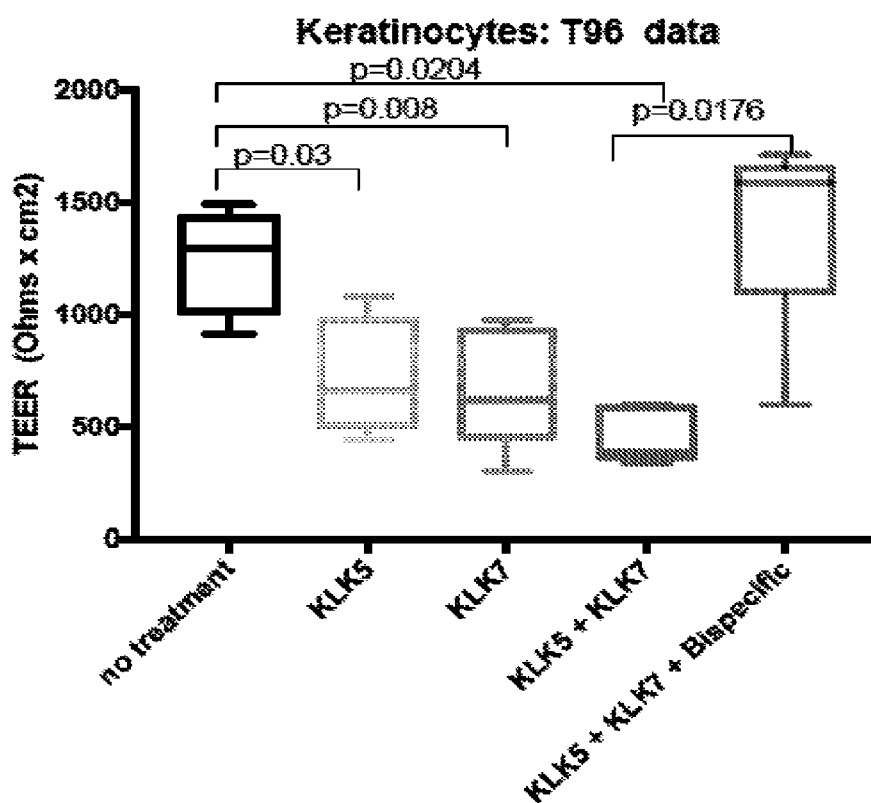


FIG. 19A**FIG. 19B**

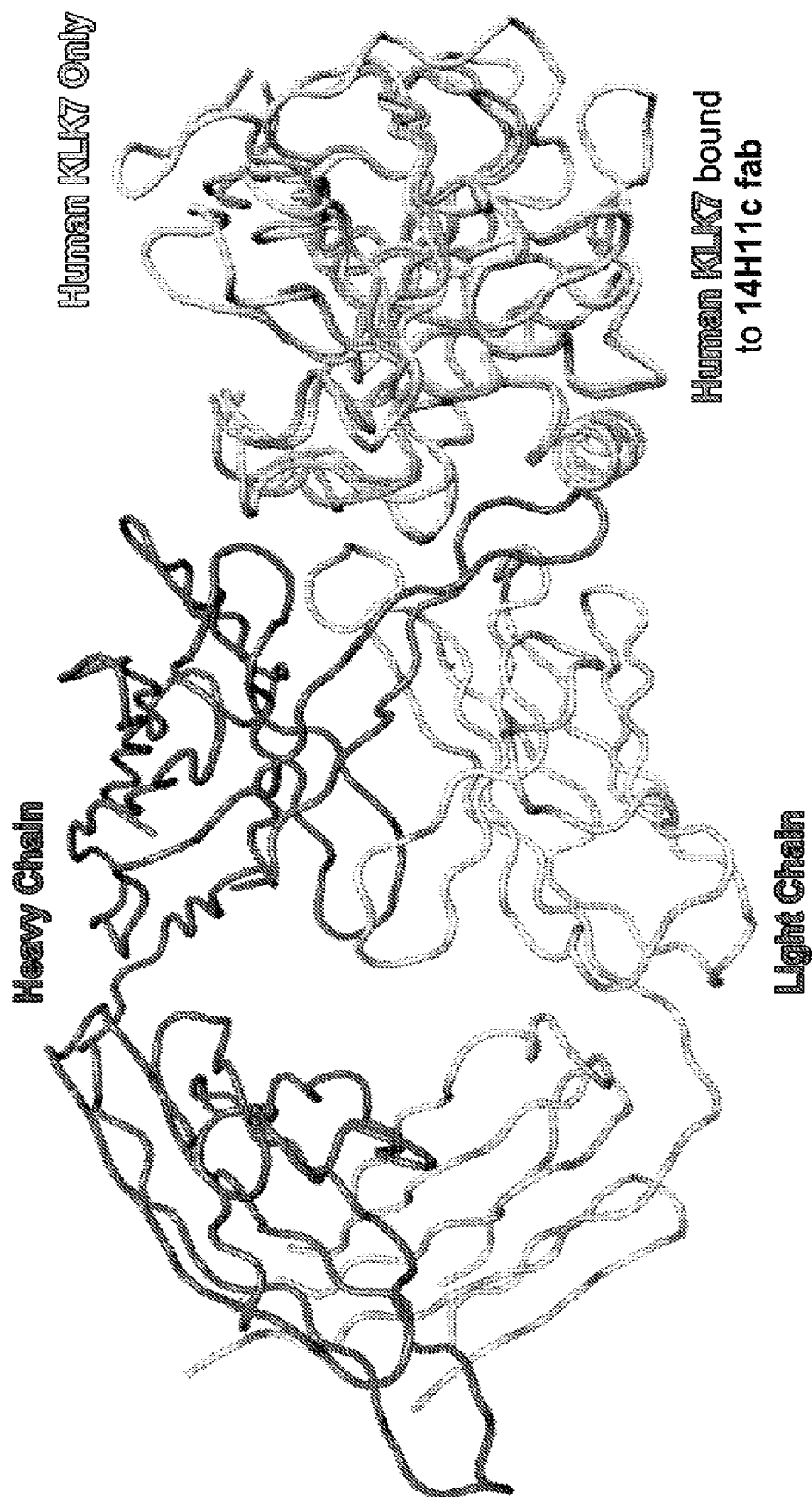


FIG. 20A

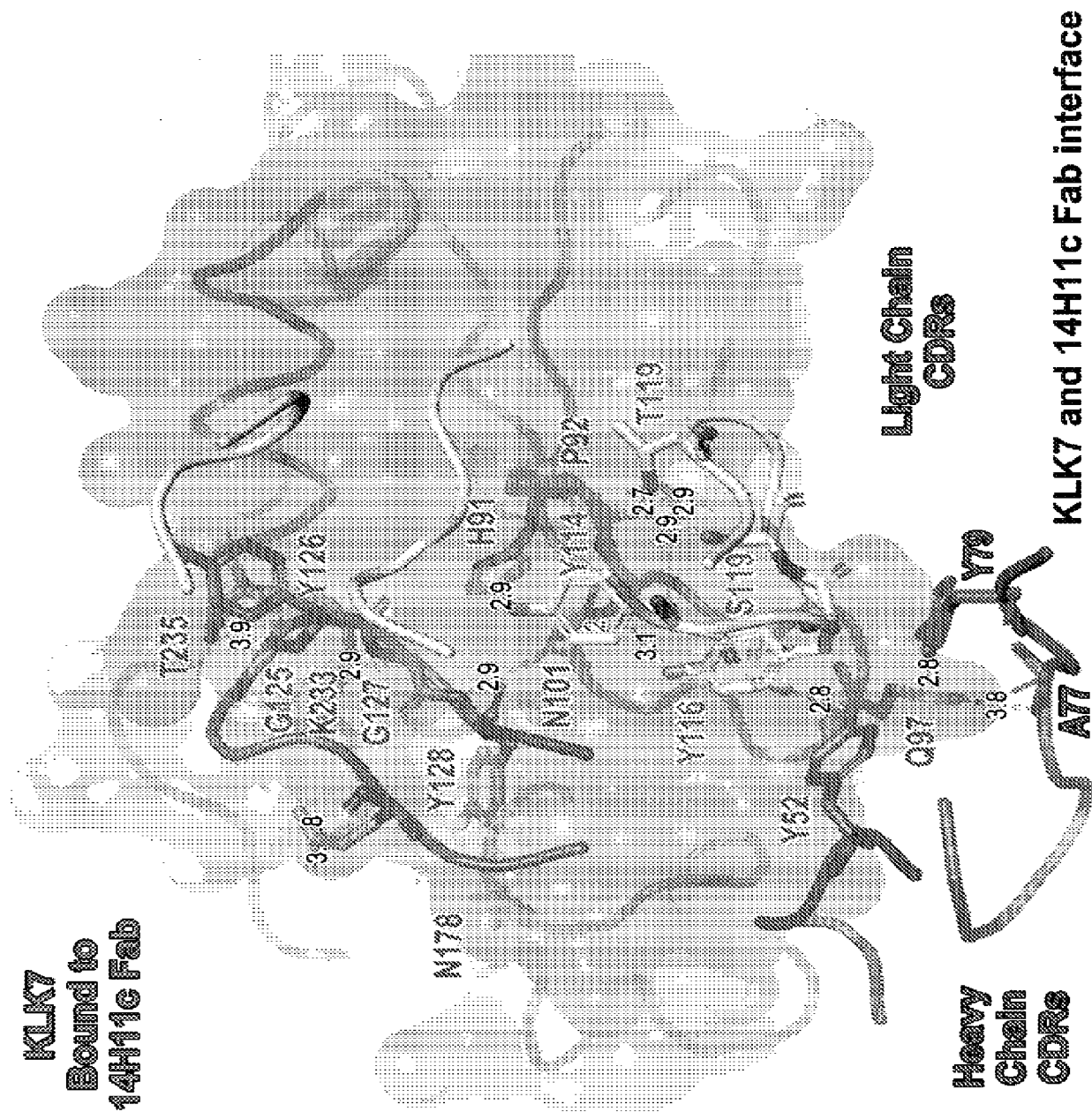


FIG. 20B

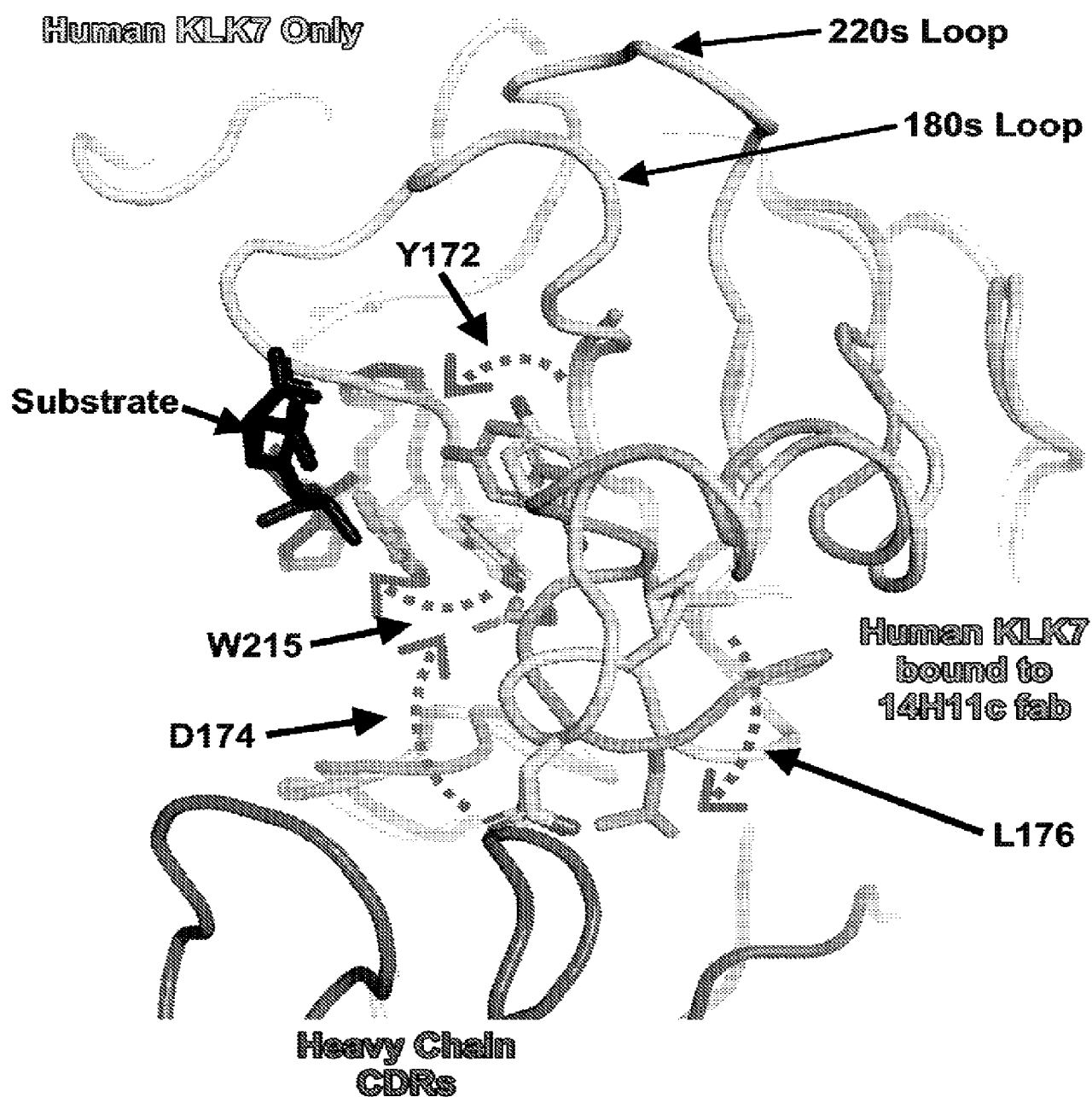
**FIG. 20C**

FIG. 19B

