

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.

[0006] 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.

[0007] 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

[0008] Provided herein are anti-KLK5 antibodies and methods of using the same.

[0009] In one [aspectexample](#), the present disclosure refers to an isolated antibody that binds to KLK5, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:28; (b) HVR-H2 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:38, SEQ ID NO:45, and SEQ ID NO:54; (c) HVR-H3 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:65, SEQ ID NO:69, and SEQ ID NO:72; (d)

HVR-L1 comprising the amino acid sequence of SEQ ID NO:96; € HVR-L2 comprising the amino acid sequence of SEQ ID NO:109; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:127.

[0009a] In one aspect, the present disclosure refers to an isolated antibody that binds to kallikrein-related peptidase 5 (KLK5), wherein the antibody comprises:

(i) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:17; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:35, 36, or 37; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:65; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:82; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:101; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:115; or

(ii) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:22; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:42; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:69; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:87; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:105; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:119.

[0010] In some examples, the antibody comprises (a) HVR-H1 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:17, SEQ ID NO:22, and SEQ ID NO:24; (b) HVR-H2 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, and SEQ ID NO:53; (c) HVR-H3 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:65, SEQ ID NO:69, and SEQ ID NO:72; (d) HVR-L1 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:82, SEQ ID NO:87, and SEQ ID NO:91; (e) HVR-L2 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:99, SEQ ID NO:101, and SEQ ID NO:105; and (f) HVR-L3 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:115, SEQ ID NO:119, and SEQ ID NO:122.

[0011] In some examples of any of the antibodies, the antibody comprises (i) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:17; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:35; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:65; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:82; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:101; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:115; (ii) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:22; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:42; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:69; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:87; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:105; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:119; or (iii) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:24; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:52; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:72; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:91; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:99; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:122.

[0012] In some examples of any of the antibodies, the antibody comprises a) a VH sequence of SEQ ID NO:202 and a VL sequence of SEQ ID NO:140; b) a VH sequence of SEQ ID NO:225 and a VL sequence of SEQ ID NO:151; or c) a VH sequence of SEQ ID NO:257 and a VL sequence of SEQ ID NO:162.

[0013] In some examples of any of the antibodies, the antibody comprises a) a VH sequence of SEQ ID NO:201 and a VL sequence of SEQ ID NO:139; b) a VH sequence of SEQ ID NO:221 and a VL sequence of SEQ ID NO:149; or c) a VH sequence of SEQ ID NO:248 or SEQ ID NO:254, and a VL sequence of SEQ ID NO:160.

[0014] In another [aspectexample](#), the present disclosure refers to an isolated antibody that binds to KLK5, wherein the antibody comprises a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:201 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:139; b) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:221 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:149; or c) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:248 or SEQ ID NO:254, and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:160.

[0015] In yet another [aspectexample](#), the present disclosure refers to an isolated antibody that binds to KLK5, wherein the antibody comprises (i) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:14; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:32; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:62; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:79; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:99; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:112; (ii) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:15; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:33; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:63; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:80; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:100; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:113; (iii) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:16; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:34; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:64; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:81; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:99; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:114; (iv) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:18; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:39; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:66; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:83; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:102; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:116; (v) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:19; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:40; (c)

[0017] In some examples, the antibody comprises (a) a VH sequence of SEQ ID NO:170 and a VL sequence of SEQ ID NO:131; (b) a VH sequence of SEQ ID NO:171 and a VL sequence of SEQ ID NO:132; (c) a VH sequence of SEQ ID NO:172 and a VL sequence of SEQ ID NO:133; (d) a VH sequence of SEQ ID NO:203 and a VL sequence of SEQ ID NO:141; (e) a VH sequence of SEQ ID NO:204 and a VL sequence of SEQ ID NO:142; (f) a VH sequence of SEQ ID NO:205 and a VL sequence of SEQ ID NO:143; (g) a VH sequence of SEQ ID NO:206 and a VL sequence of SEQ ID NO:144; (h) a VH sequence of SEQ ID NO:226 and a VL sequence of SEQ ID NO:152; (i) a VH sequence of SEQ ID NO:227 and a VL sequence of SEQ ID NO:153; or (j) a VH sequence of SEQ ID NO:228 and a VL sequence of SEQ ID NO:154.

[0018] In a further [aspectexample](#), the present disclosure refers to an isolated antibody that binds to KLK5, wherein the antibody comprises (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:170 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:131; (b) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:171 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:132; (c) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:172 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:133; (d) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:203 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:141; (e) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:204 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:142; (f) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:205 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:143; (g) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:206 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:144; (h) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:226 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:152; (i) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:227 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:153; or (j) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:228 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:154.

[0019] In some examples of any of the antibodies, the antibody is an IgG1 or IgG4.

[0020] In some examples of any of the antibodies, the antibody inhibits the biological activity of KLK5 by at least 50% as measured by one or more methods as described in the Examples herein below. In some examples, the one or more methods is selected from the group consisting of 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 $K_{i(app)}$ assay. In some examples, the biological activity is the serine protease activity of KLK5.

[0021] In some examples of any of the antibodies, the antibody is a monoclonal antibody.

[0022] In some examples of any of the antibodies, the antibody is a human, humanized, or chimeric antibody.

[0023] In some examples of any of the antibodies, the antibody is an antibody fragment that binds KLK5.

[0024] In one [aspectexample](#), the present disclosure refers to an antibody that forms a thermodynamic epitope when bound to KLK5 comprising one or more of the sequences selected from the group consisting of SEQ ID NO:316, SEQ ID NO:317, SEQ ID NO:318, and SEQ ID NO:319 as measured by hydrogen exchange mass spectrometry.

[0025] In another [exampleaspect](#), the present disclosure refers to an antibody that competes for binding with any of the antibodies described herein.

[0026] In yet another [exampleaspect](#), the present disclosure refers to an antibody that binds to the same epitope as any of the antibodies described herein.

[0027] In one aspect, the present disclosure refers to an isolated nucleic acid encoding any of the antibodies described herein.

[0028] In one aspect, the present disclosure refers to a host cell comprising the nucleic acid described herein.

[0029] In one aspect, the present disclosure refers to a method of producing an antibody comprising culturing the host cell described herein so that the antibody is produced.

[0030] In one aspect, the present disclosure refers to an immunoconjugate comprising the antibody described herein.

[0031] In one aspect, the present disclosure refers to a pharmaceutical formulation comprising the antibody described herein and a pharmaceutically acceptable carrier.

[0032] In one aspect, the present disclosure refers to the antibody as described herein for use as a medicament.

[0033] In one aspect, the present disclosure refers to the antibody as described herein for use in treating a disease selected from the group consisting of Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis and rosacea. Further provided herein is the antibody as described herein for use in treating a disease selected from the group consisting of Netherton Syndrome, asthma, atopic dermatitis, psoriasis, and rosacea. In some examples, the disease is selected from the group consisting

of Netherton Syndrome, asthma, atopic dermatitis, psoriasis, rosacea and eosinophilic esophagitis. In some examples, the asthma is selected from the group consisting of 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. In some examples, the asthma is TH2-low asthma.

[0034] In one aspect, the present disclosure refers to the antibody as described herein for use in inhibiting the biological activity of KLK5.

[0035] In one [aspectexample](#), the present disclosure refers to the use of the antibody as described herein in the manufacture of a medicament. In some examples, the medicament is for treating a disease selected from the group consisting of Netherton Syndrome, asthma, atopic dermatitis, psoriasis, and rosacea. In some examples, the disease is selected from the group consisting of Netherton Syndrome, asthma, atopic dermatitis, psoriasis, rosacea and eosinophilic esophagitis. In some examples, the asthma is selected from the group consisting of 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. In some examples, the asthma is TH2-low asthma. [In one aspect, the present disclosure refers to use of the antibody as described herein in the manufacture of a medicament for treating a disease selected from the group consisting of Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis and rosacea.](#)

[0036] In one [aspectexample](#), the present disclosure refers to the use of the antibody described herein in the manufacture of a medicament for inhibiting the biological activity of KLK5.

[0037] Further provided is a method of treating an individual having a disease, wherein the disease is selected from the group consisting of Netherton Syndrome, asthma, atopic dermatitis, psoriasis, and rosacea comprising administering to the individual an effective amount of the antibody described herein. In some examples, the disease is selected from the group consisting of Netherton Syndrome, asthma, atopic dermatitis, psoriasis, rosacea and eosinophilic esophagitis. In some examples, the asthma is selected from the group

consisting of 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. In some examples, the asthma is Th2-low asthma.

[0038] Further provided is a method of inhibiting the biological activity of KLK5 in an individual comprising administering to the individual an effective amount of the antibody described herein to inhibit the biological activity of KLK5.

[0039] In one [aspectexample](#), the present disclosure refers to an antibody that specifically binds to human KLK5, 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, 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. In some examples, 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. In some examples, 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, 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 examples, the antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from the group consisting of 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.

[0040] In one [aspectexample](#), the present disclosure refers to an 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.

WHAT IS CLAIMED IS:

~~1. — An isolated antibody that binds to KLK5, wherein the antibody comprises:~~

~~(a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:28; (b) HVR-H2 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:38, SEQ ID NO:45, and SEQ ID NO:54; (c) HVR-H3 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:65, SEQ ID NO:69, and SEQ ID NO:72; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:96; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:109; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:127.~~

~~2. — The antibody of claim 1, wherein the antibody comprises:~~

~~(a) HVR-H1 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:17, SEQ ID NO:22, and SEQ ID NO:24; (b) HVR-H2 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, and SEQ ID NO:53; (c) HVR-H3 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:65, SEQ ID NO:69, and SEQ ID NO:72; (d) HVR-L1 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:82, SEQ ID NO:87, and SEQ ID NO:91; (e) HVR-L2 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:99, SEQ ID NO:101, and SEQ ID NO:105; and (f) HVR-L3 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:115, SEQ ID NO:119, and SEQ ID NO:122.~~

~~3.1. — An isolated antibody that binds to kallikrein-related peptidase 5 (KLK5) The antibody of any one of claims 1 or 2, wherein the antibody comprises:~~

~~(i) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:17; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:35, 36, or 37; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:65; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:82; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:101; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:115; or~~

~~(ii) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:22; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:42; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:69; (d) HVR-L1 comprising the amino acid sequence of SEQ ID~~

NO:87; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:105; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:119;~~or~~

~~(iii) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:24; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:52; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:72; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:91; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:99; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:122.~~

2. The antibody of claim 1, wherein the antibody comprises:

(a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:17; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:35, 36, or 37; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:65; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:82; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:101; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:115.

3. The antibody of claim 1, wherein the antibody comprises:

(a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:22; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:42; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:69; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:87; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:105; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:119.

4. The antibody of ~~any one of claims 1-3~~claim 1, wherein the antibody comprises a) a VH sequence of SEQ ID NO:202 and a VL sequence of SEQ ID NO:140;or b) a VH sequence of SEQ ID NO:225 and a VL sequence of SEQ ID NO:151;~~or c) a VH sequence of SEQ ID NO:257 and a VL sequence of SEQ ID NO:162.~~

5. The antibody of claim 4, wherein the antibody comprises a VH sequence of SEQ ID NO:202 and a VL sequence of SEQ ID NO:140.

6. The antibody of claim 4, wherein the antibody comprises a VH sequence of SEQ ID NO:225 and a VL sequence of SEQ ID NO:151.

7. The antibody of claim 1 or 4, wherein the antibody comprises a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:201 and a VL

sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:139; or b) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:221 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:149.

8. The antibody of any one of claims 1, 2, 4, and 5, wherein the antibody comprises a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:201 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:139.

9. The antibody of any one of claims 1, 3, 4, and 6, wherein the antibody comprises a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:221 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:149.

~~5-10.~~ The antibody of any one of claims ~~1-4~~ 1, 4, and 7, wherein the antibody comprises a) a VH sequence of SEQ ID NO:201 and a VL sequence of SEQ ID NO:139; or b) a VH sequence of SEQ ID NO:221 and a VL sequence of SEQ ID NO:149; ~~or c) a VH sequence of SEQ ID NO:248 or SEQ ID NO:254, and a VL sequence of SEQ ID NO:160.~~

11. The antibody of any one of claims 1, 2, 4, 5, 7, and 8, wherein the antibody comprises a VH sequence of SEQ ID NO:201 and a VL sequence of SEQ ID NO:139.

12. The antibody of any one of claims 1, 3, 4, 6, 7, and 9, wherein the antibody comprises a VH sequence of SEQ ID NO:221 and a VL sequence of SEQ ID NO:149.

~~6. An isolated antibody that binds to KLK5, wherein the antibody comprises a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:201 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:139; b) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:221 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:149; or c) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:248 or SEQ ID NO:254, and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:160.~~

~~7. An isolated antibody that binds to KLK5, wherein the antibody comprises:~~

~~(i) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:14; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:32; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:62; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:79; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:99; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:112;~~

~~(ii) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:15; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:33; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:63; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:80; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:100; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:113;~~

~~(iii) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:16; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:34; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:64; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:81; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:99; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:114;~~

~~(iv) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:18; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:39; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:66; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:83; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:102; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:116;~~

~~(v) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:19; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:40; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:67; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:84; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:103; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:117;~~

~~(vi) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:20; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:33; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:68; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:85; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:103; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:118;~~

~~(vii) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:21; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:41; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:69; (d) HVR-L1 comprising the amino acid sequence of SEQ ID~~

NO:86; (e) HVR L2 comprising the amino acid sequence of SEQ ID NO:104; and (f) HVR L3 comprising the amino acid sequence of SEQ ID NO:118;

(viii) (a) HVR H1 comprising the amino acid sequence of SEQ ID NO:22; (b) HVR H2 comprising the amino acid sequence of SEQ ID NO:46; (c) HVR H3 comprising the amino acid sequence of SEQ ID NO:69; (d) HVR L1 comprising the amino acid sequence of SEQ ID NO:88; (e) HVR L2 comprising the amino acid sequence of SEQ ID NO:105; and (f) HVR L3 comprising the amino acid sequence of SEQ ID NO:120;

(ix) (a) HVR H1 comprising the amino acid sequence of SEQ ID NO:22; (b) HVR H2 comprising the amino acid sequence of SEQ ID NO:42; (c) HVR H3 comprising the amino acid sequence of SEQ ID NO:70; (d) HVR L1 comprising the amino acid sequence of SEQ ID NO:89; (e) HVR L2 comprising the amino acid sequence of SEQ ID NO:105; and (f) HVR L3 comprising the amino acid sequence of SEQ ID NO:118; or

(x) (a) HVR H1 comprising the amino acid sequence of SEQ ID NO:23; (b) HVR H2 comprising the amino acid sequence of SEQ ID NO:47; (c) HVR H3 comprising the amino acid sequence of SEQ ID NO:71; (d) HVR L1 comprising the amino acid sequence of SEQ ID NO:90; (e) HVR L2 comprising the amino acid sequence of SEQ ID NO:106; and (f) HVR L3 comprising the amino acid sequence of SEQ ID NO:121.

8. —The antibody of claim 7, wherein the antibody comprises a VH sequence selected from the group consisting of SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, SEQ ID NO:226, SEQ ID NO:227, and SEQ ID NO:228, and a VL sequence selected from the group consisting of SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:152, SEQ ID NO:153, and SEQ ID NO:154.

9. —The antibody of any one of claims 7 or 8, wherein the antibody comprises (a) a VH sequence of SEQ ID NO:170 and a VL sequence of SEQ ID NO:131; (b) a VH sequence of SEQ ID NO:171 and a VL sequence of SEQ ID NO:132; (c) a VH sequence of SEQ ID NO:172 and a VL sequence of SEQ ID NO:133; (d) a VH sequence of SEQ ID NO:203 and a VL sequence of SEQ ID NO:141; (e) a VH sequence of SEQ ID NO:204 and a VL sequence of SEQ ID NO:142; (f) a VH sequence of SEQ ID NO:205 and a VL sequence of SEQ ID NO:143; (g) a VH sequence of SEQ ID NO:206 and a VL sequence of SEQ ID NO:144; (h) a VH sequence of SEQ ID NO:226 and a VL sequence of SEQ ID NO:152; (i) a VH sequence of

SEQ ID NO:227 and a VL sequence of SEQ ID NO:153; or (j) a VH sequence of SEQ ID NO:228 and a VL sequence of SEQ ID NO:154.

10. —An isolated antibody that binds to KLK5, wherein the antibody comprises (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:170 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:131; (b) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:171 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:132; (c) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:172 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:133; (d) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:203 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:141; (e) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:204 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:142; (f) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:205 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:143; (g) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:206 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:144; (h) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:226 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:152; (i) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:227 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:153; or (j) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:228 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:154.

44.13. The antibody of any one of claims 1-4012, wherein the antibody is an IgG1 or IgG4.

42.14. The antibody of any one of claims 1-4413, wherein the antibody inhibits the biological activity of KLK5 by at least 50% as measured by one or more methods selected from the group consisting of 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 $K_{i(app)}$ assay.

~~13.15.~~ The antibody of ~~any one of claims 1-12~~claim 14, wherein the biological activity is the serine protease activity of KLK5.

~~14.16.~~ The antibody of any one of claims 1-~~13~~15, wherein the antibody is a monoclonal antibody.

~~15.17.~~ The antibody of any one of claims 1-~~14~~16, wherein the antibody is a human, humanized, or chimeric antibody.

~~16.18.~~ The antibody of any one of claims 1-~~15~~17, wherein the antibody is an antibody fragment that binds KLK5.

~~17.—An antibody that forms a thermodynamic epitope when bound to KLK5 comprising one or more of the sequences selected from the group consisting of SEQ ID NO:316, SEQ ID NO:317, SEQ ID NO:318, and SEQ ID NO:319 as measured by hydrogen exchange mass spectrometry.~~

~~18.—An antibody that competes for binding with the antibody of any one of claims 1-16.~~

~~19.—An antibody that binds to the same epitope as the antibody of any one of claims 1-16.~~

~~20.19.~~ An isolated nucleic acid encoding the antibody of any one of claims 1-~~16~~18.

~~21.20.~~ A host cell comprising the nucleic acid of claim ~~20~~19.

~~22.21.~~ A method of producing an antibody comprising culturing the host cell of claim ~~21~~20 so that the antibody is produced.

~~23.22.~~ An immunoconjugate comprising the antibody of any one of claims 1-~~16~~18.

~~24.23.~~ A pharmaceutical formulation comprising the antibody of any one of claims 1-~~16-18~~ and a pharmaceutically acceptable carrier.

~~25.24.~~ The antibody of any one of claims 1-~~16-18~~ for use as a medicament.

~~26.25.~~ The antibody of any one of claims 1-~~16-18~~ for use in treating a disease selected from the group consisting of Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis and rosacea.

~~27.26.~~ The antibody for use of claim ~~26.25~~, wherein the asthma is selected from the group consisting of 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.

~~28.27.~~ The antibody for use of claim ~~27.26~~, wherein the asthma is TH2-low asthma.

~~29.28.~~ The antibody of any one of claims 1-~~16-18~~ for use in inhibiting the biological activity of KLK5.

~~30. — Use of the antibody of any one of claims 1-16 in the manufacture of a medicament.~~

~~31.29.~~ Use of the antibody of any one of claims 1-18 in the manufacture of a medicament~~The use of claim 30, wherein the medicament is~~ for treating a disease selected from the group consisting of Netherton Syndrome, asthma, atopic dermatitis, psoriasis, eosinophilic esophagitis and rosacea.

~~32.30.~~ The use of claim ~~31.29~~, wherein the asthma is selected from the group consisting of 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.

~~33.31.~~ The use of claim ~~3230~~, wherein the asthma is TH2-low asthma.

~~34.—Use of the antibody of any one of claims 1–16 in the manufacture of a medicament for inhibiting the biological activity of KLK5.~~

~~35.—An antibody that specifically binds to human KLK5, 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, 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.~~

~~36.—The antibody of claim 35, 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.~~

~~37.—The antibody of claim 35, 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, Gly133, Val162, Leu163, Ser164, Gln165, Lys166, Arg167, Glu169, Asp170, Ala171, Tyr172, Pro173, Arg174, Gln174A, Ile176, Asp177, and Lys233 according to standard protease numbering.~~

~~38.—The antibody of claim 35, wherein the antibody binds to an epitope on human KLK5 comprising one or more amino acid residues selected from the group consisting of 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.~~

39. — An 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.