SUMMARY

The present disclosure provides anti-HtrA1 antibodies and methods of using the same for therapeutic and diagnostic purposes. The anti-HtrA1 antibodies of the disclosure are highly potent and have a high binding affinity for HtrA1. The improved properties of the antibodies of the disclosure make them suitable for use in therapy.

In one example, there is provided an isolated antibody that specifically binds to an HtrA1 epitope, where the HtrA1 epitope comprises at least one amino acid of the HtrA1 protein selected from the group consisting of Arg190, Leu192, Pro193, Phe194, and Arg197, where the amino acid numbering refers to the numbering for the human HtrA1 precursor protein. In one example, there is provided an isolated antibody that specifically binds to an HtrA1 epitope, wherein the HtrA1 epitope comprises at least one amino acid of the HtrA1 protein selected from the group consisting of Arg190, Leu192, Pro193, Phe194, and Arg197.

In a further example, the HtrA1 epitope comprises at least one amino acid of the HtrA1 protein selected from the group consisting of Leu192, Pro193, and Arg197.

In another example, the HtrA1 epitope comprises at least two amino acids of the HtrA1 protein selected from the group consisting of Leu192, Pro193, and Arg197.

In a particular example, the HtrA1 epitope comprises the HtrA1 amino acids Leu192, Pro193, and Arg197.

In another example, the HtrA1 epitope comprises the HtrA1 amino acids Arg190, Leu192, Pro193, and Arg197.

In an additional example, the HtrA1 epitope comprises the HtrA1 amino acids Arg190, Leu192, Pro193, Phe194, and Arg197.

In one example, there is provided an isolated antibody that specifically binds human HtrA serine peptidase 1 (HtrA1) with a KD of about 550 pM or lower. In some examples, the antibody specifically binds human HtrA1 with a KD between about 40 pM and about 550 pM. In some examples, the antibody specifically binds human HtrA1 with a KD between about 40 pM and about 250 pM. In some examples, the antibody specifically binds human HtrA1 with a KD between about 50 pM and about 125 pM. In some examples, the antibody specifically binds human HtrA1 with a KD of about 110 pM. In some examples, the antibody specifically binds human HtrA1 with a KD of about 60 pM. In some examples, the KD is measured by surface plasmon resonance (SPR) (e.g., BIACORE® SPR). In some examples, the SPR is performed as described herein (e.g., in the Examples section).

In some examples, any one of the preceding antibodies is capable of inhibiting the activity of HtrA1. In some examples, the antibody inhibits the activity of the protease domain of human HtrA1(huHtrA1-PD) with a 50% inhibitory concentration (IC50) of 1.5 nM or lower. In some examples, the antibody inhibits the activity of huHtrA1-PD with an IC50 of 0.25 nM to about 0.5 nM. In some examples, the antibody inhibits the activity of huHtrA1-PD with an IC50 of about 0.3 nM. In some examples, the inhibitory activity is an in vitro FRET-based blocking assay measurement. In some examples, the in vitro FRET-based blocking assay comprises cleavage of an H2-Opt probe (e.g., SEQ ID NO: 152). In some examples, the in vitro FRET-based blocking assay is performed as described herein (e.g., in the Examples).

In some examples of the above aspect, the antibody comprises a binding domain comprising: (a) an HVR-H1 comprising the amino acid sequence of $DSEX_1H$ (SEQ ID NO: 1), wherein X_1 is Met or

Leu; (b) an HVR-H2 comprising the amino acid sequence of GVDPETX$_2$GAAYNQKFKG (SEQ ID NO: 2), wherein X$_2$ is Glu or Asp; and (c) an HVR-H3 comprising the amino acid sequence of GYDYDYALDY (SEQ ID NO: 3). In some examples, the antibody comprises a binding domain comprising: (a) an HVR-H1 comprising the amino acid sequence of DSEMH (SEQ ID NO: 7); (b) an HVR-H2 comprising the amino acid sequence of GVDPETEGAAYNQKFKG (SEQ ID NO: 8); and (c) an HVR-H3 comprising the amino acid sequence of GYDYDYALDY (SEQ ID NO: 3). In some examples, the antibody further comprises: (a) an FR-H1 comprising the amino acid sequence of EVQLVQSGAEVKKPGASVKVSCKASGYX$_1$FX$_2$ (SEQ ID NO: 12), wherein X$_1$ is Lys or Thr and X$_2$ is Thr, Lys, or Arg; (b) an FR-H2 comprising the amino acid sequence of WVRQAPGQGLEWIG (SEQ ID NO: 13); (c) an FR-H3 comprising the amino acid sequence of RATITRDTSTSTAYLELSSLRSEDTAVYYCTR (SEQ ID NO: 14); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLVTVSS (SEQ ID NO: 15). In some examples, the antibody further comprises: (a) an FR-H1 comprising the amino acid sequence of EVQLVQSGAEVKKPGASVKVSCKASGYKFT (SEQ ID NO: 16); (b) an FR-H2 comprising the amino acid sequence of WVRQAPGQGLEWIG (SEQ ID NO: 13); (c) an FR-H3 comprising the amino acid sequence of RATITRDTSTSTAYLELSSLRSEDTAVYYCTR (SEQ ID NO: 14); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLVTVSS (SEQ ID NO: 15).

In some examples of the above aspect, the binding domain further comprises: (a) an HVR-L1 comprising the amino acid sequence of RASSSVX$_3$FIH (SEQ ID NO: 4), wherein X$_3$ is Glu or Asn; (b) an HVR-L2 comprising the amino acid sequence of ATSX$_4$LAS (SEQ ID NO: 5), wherein X$_4$ is Asn, His or Glu; and (c) an HVR-L3 comprising the amino acid sequence of QQWX$_5$SX$_6$PWT (SEQ ID NO: 6), wherein X$_5$ is Ser or Tyr and X$_6$ is Ala or Asn. In some examples, the binding domain further comprises: (a) an HVR-L1 comprising the amino acid sequence of RASSSVEFIH (SEQ ID NO: 9); (b) an HVR-L2 comprising the amino acid sequence of ATSNLAS (SEQ ID NO: 10); and (c) an HVR-L3 comprising the amino acid sequence of QQWSSAPWT (SEQ ID NO: 11). In some examples, the antibody further comprises: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 17); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGKAPKPLIS (SEQ ID NO: 18); (c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO: 19); and (d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 20).

In another example, there is provided an isolated antibody that specifically binds HtrA1, wherein the antibody comprises a binding domain comprising (a) a heavy chain variable (VH) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 21; (b) a light chain variable (VL) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 22; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the VH domain further comprises: (a) an FR-H1 comprising the amino acid sequence of EVQLVQSGAEVKKPGASVKVSCKASGYKFT (SEQ ID NO: 16); (b) an FR-H2 comprising the amino acid sequence of WVRQAPGQGLEWIG (SEQ ID NO: 13); (c) an FR-H3 comprising the amino acid sequence of RATITRDTSTSTAYLELSSLRSEDTAVYYCTR (SEQ ID NO: 14); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLVTVSS (SEQ ID NO: 15). In some

examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 21. In some examples, the VL domain further comprises: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 17); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGKAPKPLIS (SEQ ID NO: 18); (c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO: 19); and (d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 20). In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 22.

In another aspect, there is provided an isolated antibody that specifically binds HtrA1, wherein the antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of $DSEX_1H$ (SEQ ID NO: 1), wherein X_1 is Met or Leu; (b) an HVR-H2 comprising the amino acid sequence of $GVDPETX_2GAAYNQKFKG$ (SEQ ID NO: 2), wherein X_2 is Glu or Asp; (c) an HVR-H3 comprising the amino acid sequence of GYDYDYALDY (SEQ ID NO: 3); (d) an HVR-L1 comprising the amino acid sequence of $RASSSVX_3FIH$ (SEQ ID NO: 4), wherein X_3 is Glu or Asn; (e) an HVR-L2 comprising the amino acid sequence of $ATSX_4LAS$ (SEQ ID NO: 5), wherein X_4 is Asn, His or Glu; and (f) an HVR-L3 comprising the amino acid sequence of $QQWX_5SX_6PWT$ (SEQ ID NO: 6), wherein X_5 is Ser or Tyr and X_6 is Ala or Asn. In some examples, the binding domain comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of DSEMH (SEQ ID NO: 7); (b) an HVR-H2 comprising the amino acid sequence of GVDPETEGAAYNQKFKG (SEQ ID NO: 8); (c) an HVR-H3 comprising the amino acid sequence of GYDYDYALDY (SEQ ID NO: 3); (d) an HVR-L1 comprising the amino acid sequence of RASSSVEFIH (SEQ ID NO: 9); (e) an HVR-L2 comprising the amino acid sequence of ATSNLAS (SEQ ID NO: 10); and (f) an HVR-L3 comprising the amino acid sequence of QQWSSAPWT (SEQ ID NO: 11).

In another example, there is provided an isolated antibody that specifically binds HtrA1, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 21; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 22; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the VH domain further comprises: (a) an FR-H1 comprising the amino acid sequence of EVQLVQSGAEVKKPGASVKVSCKASGYKFT (SEQ ID NO: 16); (b) an FR-H2 comprising the amino acid sequence of WVRQAPGQGLEWIG (SEQ ID NO: 13); (c) an FR-H3 comprising the amino acid sequence of RATITRDTSTSTAYLELSSLRSEDTAVYYCTR (SEQ ID NO: 14); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLVTVSS (SEQ ID NO: 15). In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 21. In some examples, the VL domain further comprises: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 17); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGKAPKPLIS (SEQ ID NO: 18); (c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO: 19); and (d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 20). In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 22.

In another example, there is provided an isolated antibody that specifically binds HtrA1, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 21 and (b) a VL domain comprising an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 22.

In another example, there is provided an isolated antibody that specifically binds HtrA1, wherein the antibody comprises a binding domain comprising (a) a heavy chain variable (VH) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 23; (b) a light chain variable (VL) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 24; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the VH domain further comprises: (a) an FR-H1 comprising the amino acid sequence of QVQLQQSGAELVRPGASVTLSCKASGYTFT (SEQ ID NO: 24); (b) an FR-H2 comprising the amino acid sequence of WVKQTPVHGLEWIG (SEQ ID NO: 25); (c) an FR-H3 comprising the amino acid sequence of KATLTADKSSSTAYMELRSLTSEDSAVYYCTR (SEQ ID NO: 26); and (d) an FR-H4 comprising the amino acid sequence of WGQGTSVTVSS (SEQ ID NO: 27). In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 23. In some examples, the VL domain further comprises: (a) an FR-L1 comprising the amino acid sequence of NIVVTQSPASLAVSLGQRATISC (SEQ ID NO: 29); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGQPPKLLIY (SEQ ID NO: 30); (c) an FR-L3 comprising the amino acid sequence of GVPARFSGSGSRTDFTLTIDPVEADDAATYYC (SEQ ID NO: 31); and (d) an FR-L4 comprising the amino acid sequence of FGGGTKLEIK (SEQ ID NO: 32). In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 24.

In another example, there is provided an isolated antibody that specifically binds HtrA1, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 23 and (b) a VL domain comprising an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 24.

In another example, there is provided an isolated antibody that specifically binds HtrA1, wherein the antibody comprises a binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SYIMS (SEQ ID NO: 39); (b) an HVR-H2 comprising the amino acid sequence of YISNGGGTTYYSDTIKG (SEQ ID NO: 40); (c) an HVR-H3 comprising the amino acid sequence of QNFRSDGSSMDY (SEQ ID NO: 41); (d) an HVR-L1 comprising the amino acid sequence of RASESVDSYGKSFMH (SEQ ID NO: 42); (e) an HVR-L2 comprising the amino acid sequence of LASKLES (SEQ ID NO: 43); and (f) an HVR-L3 comprising the amino acid sequence of QQNNEDPYT (SEQ ID NO: 44).

In another example, there is provided an isolated antibody that specifically binds HtrA1, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 45; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid

sequence of SEQ ID NO: 46; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the VH domain further comprises: (a) an FR-H1 comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFS (SEQ ID NO: 47); (b) an FR-H2 comprising the amino acid sequence of WVRQAPGKGLEWVA (SEQ ID NO: 48); (c) an FR-H3 comprising the amino acid sequence of RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR (SEQ ID NO: 49); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLVTVSS (SEQ ID NO: 50). In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 45. In some examples, the VL domain further comprises: (a) an FR-L1 comprising the amino acid sequence of DIVMTQSPDSLAVSLGERATINC (SEQ ID NO: 51); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGQPPKLLIY (SEQ ID NO: 52); (c) an FR-L3 comprising the amino acid sequence of GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC (SEQ ID NO: 53); and (d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 54). In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 46.

In another example, there is provided an isolated antibody that specifically binds HtrA1, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 45 and (b) a VL domain comprising an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 46.

In another example, there is provided an isolated antibody that specifically binds HtrA1, wherein the antibody comprises a binding domain comprising (a) a heavy chain variable (VH) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 55; (b) a light chain variable (VL) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 56; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the VH domain further comprises: (a) an FR-H1 comprising the amino acid sequence of EVKLVESGGGLVEPGGSLKLACVASGFTFS (SEQ ID NO: 57); (b) an FR-H2 comprising the amino acid sequence of WVRQTPEKRLEWVA (SEQ ID NO: 58); (c) an FR-H3 comprising the amino acid sequence of RFTISRDNAKNTLYLQMSTLKSEDTAIYFCAR (SEQ ID NO: 59); and (d) an FR-H4 comprising the amino acid sequence of WGQGTAVTVSS (SEQ ID NO: 60). In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 55. In some examples, the VL domain further comprises: (a) an FR-L1 comprising the amino acid sequence of NIVVTQSPASLAVSLGQRATISC (SEQ ID NO: 61); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGQPPKLLIY (SEQ ID NO: 62); (c) an FR-L3 comprising the amino acid sequence of GVPARFSGSGSRTDFTLTIDPVEADDAATYYC (SEQ ID NO: 63); and (d) an FR-L4 comprising the amino acid sequence of FGGGTKLEIK (SEQ ID NO: 64). In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 56.

In another example, there is provided an isolated antibody that specifically binds HtrA1, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 55 and (b) a VL domain comprising an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 56.

In another example, there is provided an isolated antibody that specifically binds HtrA1, wherein the antibody comprises a binding domain comprising (a) a heavy chain variable (VH) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 65; (b) a light chain variable (VL) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 66; or (c) a VH domain as in (a) and a VL domain as in (b).

In another example, there is provided an isolated antibody that specifically binds HtrA1, wherein the antibody comprises a binding domain comprising (a) a heavy chain variable (VH) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 67; (b) a light chain variable (VL) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 68; or (c) a VH domain as in (a) and a VL domain as in (b).

In another example, there is provided an isolated antibody that specifically binds HtrA1, wherein the antibody comprises a binding domain comprising (a) a heavy chain variable (VH) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 69; (b) a light chain variable (VL) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 70; or (c) a VH domain as in (a) and a VL domain as in (b).

In some examples of any of the preceding aspects, the antibody is monoclonal, human, humanized, or chimeric. In particular examples, the antibody is monoclonal, humanized, or chimeric.

In some examples of any of the preceding aspects, the antibody is an antibody fragment that binds to HtrA1. In some examples, the antibody fragment is selected from the group consisting of Fab, Fab'-SH, Fv, scFV, and $(Fab')_2$ fragments. In some examples, the antibody fragment is an Fab. In some examples, the Fab comprises a truncation in the hinge region of the heavy chain constant region. In some examples, the Fab comprises a truncation in the upper hinge of the heavy chain constant region. In some examples, the heavy chain constant region terminates at position 221 (EU numbering). In some examples, the amino acid residue at position 221 is an aspartic acid (Asp) residue. In some examples, the heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 156. In some examples, the antibody comprises the heavy chain amino acid sequence of SEQ ID NO: 160. In some examples, the antibody comprises the light chain amino acid sequence of SEQ ID NO: 159. In some examples, the antibody comprises the heavy chain amino acid sequence of SEQ ID NO: 160 and the light chain amino acid sequence of SEQ ID NO: 159.

In some examples, the Fab is an IgG1 Fab.

In some examples of any of the preceding aspects, the antibody is a full-length antibody. In some examples, the antibody is an IgG antibody. In some examples, the antibody is a monospecific antibody.

In some examples of any of the preceding aspects, the antibody is a bispecific antibody. In some examples, the bispecific antibody comprises a second binding domain that binds to Factor D. In some examples, the second binding domain comprises the following six HVRs: (a) an HVR-H1

comprising the amino acid sequence of GYTFTNYGMN (SEQ ID NO: 109); (b) an HVR-H2 comprising the amino acid sequence of WINTYTGETTYAX$_1$DFKG (SEQ ID NO: 110), wherein X$_1$ is Asp or Glu; (c) an HVR-H3 comprising the amino acid sequence of EGGVX$_1$N (SEQ ID NO: 111), wherein X$_1$ is Asn or Ser; (d) an HVR-L1 comprising the amino acid sequence of ITSTX$_1$IX$_2$X$_3$DMN (SEQ ID NO: 112), wherein X$_1$ is Asp or Ser, X$_2$ is Asp or Glu, and X$_3$ is Asp or Ser; (e) an HVR-L2 comprising the amino acid sequence of GGNTLRP (SEQ ID NO: 113); and (f) an HVR-L3 comprising the amino acid sequence of LQSX$_1$SLPYT (SEQ ID NO: 114), wherein X$_1$ is Asp or Glu. In some examples, the second binding domain comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of GYTFTNYGMN (SEQ ID NO: 109); (b) an HVR-H2 comprising the amino acid sequence of WINTYTGETTYADDFKG (SEQ ID NO: 115); (c) an HVR-H3 comprising the amino acid sequence of EGGVNN (SEQ ID NO: 116); (d) an HVR-L1 comprising the amino acid sequence of ITSTDIDDDMN (SEQ ID NO: 117); (e) an HVR-L2 comprising the amino acid sequence of GGNTLRP (SEQ ID NO: 113); and (f) an HVR-L3 comprising the amino acid sequence of LQSDSLPYT (SEQ ID NO: 118). In some examples, the second binding domain comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 119; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 120; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 119. In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 120.

In another example, there is provided an isolated antibody that specifically binds both HtrA1 and Factor D, wherein the antibody comprises a first binding domain that specifically binds HtrA1 comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of DSEMH (SEQ ID NO: 7); (b) an HVR-H2 comprising the amino acid sequence of GVDPETEGAAYNQKFKG (SEQ ID NO: 8); (c) an HVR-H3 comprising the amino acid sequence of GYDYDYALDY (SEQ ID NO: 3), (d) an HVR-L1 comprising the amino acid sequence of RASSSVEFIH (SEQ ID NO: 9); (e) an HVR-L2 comprising the amino acid sequence of ATSNLAS (SEQ ID NO: 10); and (f) an HVR-L3 comprising the amino acid sequence of QQWSSAPWT (SEQ ID NO: 11); and a second binding domain that specifically binds Factor D comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of GYTFTNYGMN (SEQ ID NO: 109); (b) an HVR-H2 comprising the amino acid sequence of WINTYTGETTYADDFKG (SEQ ID NO: 115); (c) an HVR-H3 comprising the amino acid sequence of EGGVNN (SEQ ID NO: 116); (d) an HVR-L1 comprising the amino acid sequence of ITSTDIDDDMN (SEQ ID NO: 117); (e) an HVR-L2 comprising the amino acid sequence of GGNTLRP (SEQ ID NO: 113); and (f) an HVR-L3 comprising the amino acid sequence of LQSDSLPYT (SEQ ID NO: 118).

In another example, there is provided an isolated antibody that specifically binds both HtrA1 and Factor D, wherein the antibody comprises a first binding domain that specifically binds HtrA1 comprising (a) a VH domain comprising an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 21 and (b) a VL domain comprising an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 22, and a second binding domain that specifically binds Factor D comprising (a) a VH domain comprising an amino acid

sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 119 and (b) a VL domain comprising an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 120.

In some examples of the above aspects, there is provided an isolated antibody that specifically binds to an HtrA1 epitope, where the HtrA1 epitope comprises at least one amino acid of the HtrA1 protein selected from the group consisting of Arg190, Leu192, Pro193, Phe194, and Arg197, where the amino acid numbering refers to the numbering for the human HtrA1 precursor protein.

In one example, the HtrA1 epitope comprises at least one amino acid of the HtrA1 protein selected from the group consisting of Leu192, Pro193, and Arg197.

In a particular example, the HtrA1 epitope comprises the HtrA1 amino acids Leu192, Pro193, and Arg197.

In another example, the HtrA1 epitope comprises the HtrA1 amino acids Arg190, Leu192, Pro193, and Arg197.

In an additional example, the HtrA1 epitope comprises the HtrA1 amino acids Arg190, Leu192, Pro193, Phe194, and Arg197.

In another aspect, there is provided an isolated nucleic acid encoding any of the antibodies disclosed herein. In another example, there is provided a vector (e.g., an expression vector) comprising the isolated nucleic acid for expressing the antibody. In another example, there are provided host cells comprising the preceding nucleic acids and/or vectors. In some examples, the host cell is a mammalian cell. In some examples, the mammalian cell is a Chinese hamster ovary (CHO) cell or a 293 cell. In some examples, the host cell is a prokaryotic cell. In some examples, the prokaryotic cell is *E. coli*.

In another example, there is provided a method of producing any of the antibodies disclosed herein, the method comprising culturing a host cell that comprises any of the preceding vectors (e.g., expression vectors) in a culture medium. In some examples, the method further comprises recovering the antibody from the host cell or the culture medium. In another aspect, there is provided a method of producing an antibody, the method comprising culturing a host cell comprising a vector comprising an isolated nucleic acid disclosed herein and recovering the antibody from the host cell or the host cell culture medium.

In another example, there is provided a composition comprising any one of the preceding antibodies. In some examples, the composition further comprises a pharmaceutically acceptable carrier, excipient, or diluent. In some examples, the composition is a pharmaceutical composition. In another aspect, there is provided a pharmaceutical composition comprising any one of the disclosed antibodies and further comprising at least one pharmaceutically acceptable carrier, excipient, or diluent. In some examples, the pharmaceutical composition is lyophilized. In some examples, the composition further comprises a Factor D binding antagonist. In some examples, the Factor D binding antagonist is an anti-Factor D antibody or an antigen-binding fragment thereof. In some examples, the antigen-binding fragment is an Fab or an $(Fab')_2$. In some examples, the anti-Factor D antibody or antigen-binding fragment thereof comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of GYTFTNYGMN (SEQ ID NO: 109); (b) an HVR-H2 comprising the amino acid sequence of WINTYTGETTYAX_1DFKG (SEQ ID NO: 110), wherein X_1 is Asp or Glu; (c) an HVR-H3 comprising the amino acid sequence of EGGVX_1N (SEQ ID NO: 111), wherein X_1 is Asn or Ser; (d) an HVR-L1 comprising the amino acid sequence of ITSTX_1IX_2X_3DMN (SEQ ID NO: 112), wherein X_1 is Asp or Ser, X_2 is Asp or Glu, and X_3 is Asp or Ser; (e) an HVR-L2 comprising the amino acid

sequence of GGNTLRP (SEQ ID NO: 113); and (f) an HVR-L3 comprising the amino acid sequence of LQSX$_1$SLPYT (SEQ ID NO: 114), wherein X$_1$ is Asp or Glu. In some examples, the anti-Factor D antibody or antigen-binding fragment thereof comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of GYTFTNYGMN (SEQ ID NO: 109); (b) an HVR-H2 comprising the amino acid sequence of WINTYTGETTYADDFKG (SEQ ID NO: 115); (c) an HVR-H3 comprising the amino acid sequence of EGGVNN (SEQ ID NO: 116); (d) an HVR-L1 comprising the amino acid sequence of ITSTDIDDDMN (SEQ ID NO: 117); (e) an HVR-L2 comprising the amino acid sequence of GGNTLRP (SEQ ID NO: 113); and (f) an HVR-L3 comprising the amino acid sequence of LQSDSLPYT (SEQ ID NO: 118). In some examples, the anti-Factor D antibody or antigen-binding fragment thereof comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 119; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 120; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 119. In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 120. In some examples, the anti-Factor D antigen-binding antibody fragment is lampalizumab.

In another example, there is provided a combination therapy comprising any of the preceding anti-HtrA1 antibodies and a Factor D antagonist. In a particular example, the Factor D antagonist is an anti-Factor D antibody. In another example, there is provided a combination therapy comprising any of the antibodies disclosed herein and a Factor D antagonist, wherein the Factor D antagonist is an anti-Factor D antibody. In a particular example, the Factor D antagonist is lampalizumab. In a particular example, the anti-Factor D antagonist is administered sequentially.

In some examples, any one of the preceding antibodies can be used as a medicament.

In some examples, any one of the preceding antibodies can be used in treating an HtrA1-associated disorder or an ocular disorder. In another aspect, there is provided any of the disclosed antibodies for use as a medicament. In another aspect, there is provided any of the disclosed antibodies for use in treating an HtrA1-associated disorder or an ocular disorder in a subject in need thereof, wherein the HtrA1-associated disorder or the ocular disorder is age-related macular degeneration (AMD), diabetic retinopathy, retinopathy of prematurity, or polypoidal choroidal vasculopathy, wherein optionally the HtrA1-associated disorder or the ocular disorder is early dry AMD, intermediate dry AMD, or advanced dry AMD, wherein optionally the advanced dry AMD is geographic atrophy. In another aspect, there is provided use of any of the disclosed antibodies in the manufacture of a medicament for treating an HtrA1-associated disorder or an ocular disorder in a subject in need thereof, wherein the HtrA1-associated disorder or the ocular disorder is AMD, diabetic retinopathy, retinopathy of prematurity, or polypoidal choroidal vasculopathy, wherein optionally the HtrA1-associated disorder or the ocular disorder is early dry AMD, intermediate dry AMD, or advanced dry AMD, wherein optionally the advanced dry AMD is geographic atrophy; wherein optionally the medicament is to be administered with a Factor D antagonist, wherein the Factor D antagonist is an anti-Factor D antibody, and wherein optionally the anti-Factor D antibody is lampalizumab. In some examples, the HtrA1-associated disorder or the ocular disorder is age-related macular degeneration (AMD), diabetic retinopathy, retinopathy of prematurity, or polypoidal choroidal vasculopathy. In some examples, the HtrA1-associated disorder or the ocular disorder is AMD. In some examples, the AMD is early dry AMD, intermediate dry AMD, or advanced dry AMD. In some examples, the advanced dry AMD is geographic atrophy.

In some examples, any one of the preceding antibodies can be used in the manufacture of a medicament for treating an HtrA1-associated disorder or an ocular disorder. In some examples, the HtrA1-associated disorder or the ocular disorder is AMD, diabetic retinopathy, retinopathy of prematurity, or polypoidal choroidal vasculopathy. In some examples, the HtrA1-associated disorder or the ocular disorder is AMD. In some examples, the AMD is early dry AMD, intermediate dry AMD, or advanced dry AMD. In some examples, the advanced dry AMD is geographic atrophy. In some examples, the medicament is formulated for use in combination with a Factor D binding antagonist. In some examples, the Factor D binding antagonist is an anti-Factor D antibody or an antigen-binding fragment thereof. In some examples, the antigen-binding fragment is an Fab or an (Fab')$_2$. In some examples, the the anti-Factor D antibody or antigen-binding fragment thereof comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of GYTFTNYGMN (SEQ ID NO: 109); (b) an HVR-H2 comprising the amino acid sequence of WINTYTGETTYAX$_1$DFKG (SEQ ID NO: 110),

wherein X_1 is Asp or Glu; (c) an HVR-H3 comprising the amino acid sequence of $EGGVX_1N$ (SEQ ID NO: 111), wherein X_1 is Asn or Ser; (d) an HVR-L1 comprising the amino acid sequence of $ITSTX_1IX_2X_3DMN$ (SEQ ID NO: 112), wherein X_1 is Asp or Ser, X_2 is Asp or Glu, and X_3 is Asp or Ser; (e) an HVR-L2 comprising the amino acid sequence of GGNTLRP (SEQ ID NO: 113); and (f) an HVR-L3 comprising the amino acid sequence of $LQSX_1SLPYT$ (SEQ ID NO: 114), wherein X_1 is Asp or Glu. In some examples, the anti-Factor D antibody or antigen-binding fragment thereof comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of GYTFTNYGMN (SEQ ID NO: 109); (b) an HVR-H2 comprising the amino acid sequence of WINTYTGETTYADDFKG (SEQ ID NO: 115); (c) an HVR-H3 comprising the amino acid sequence of EGGVNN (SEQ ID NO: 116); (d) an HVR-L1 comprising the amino acid sequence of ITSTDIDDDMN (SEQ ID NO: 117); (e) an HVR-L2 comprising the amino acid sequence of GGNTLRP (SEQ ID NO: 113); and (f) an HVR-L3 comprising the amino acid sequence of LQSDSLPYT (SEQ ID NO: 118). In some examples, the anti-Factor D antibody or antigen-binding fragment thereof comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 119; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 120; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 119. In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 120. In some examples, the anti-Factor D antigen-binding fragment is lampalizumab.

In another example, there is provided a method of treating an HtrA1-associated disorder or an ocular disorder in a subject in need thereof, the method comprising administering a therapeutically effective amount of the antibody of any one of the preceding antibodies. In some examples, the HtrA1-associated disorder or the ocular disorder is AMD, diabetic retinopathy, retinopathy of prematurity, or polypoidal choroidal vasculopathy. In some examples, the HtrA1-associated disorder or the ocular disorder is AMD. In some examples, the AMD is early dry AMD, intermediate dry AMD, or advanced dry AMD. In some examples, the advanced dry AMD is geographic atrophy. In some examples, the method further comprises administering a Factor D binding antagonist.

In another example, there is provided a method for inhibiting retinal or photoreceptor cell degeneration in a subject, the method comprising administering to the subject an effective amount of any one of the preceding antibodies, thereby inhibiting retinal or photoreceptor cell degeneration.

In another example, there is provided a method for inhibiting HtrA1 serine protease activity in an eye of a subject, the method comprising administering to the subject an effective amount of any one of the preceding antibodies, thereby inhibiting HtrA1 serine protease activity in the eye. In some examples, the method further comprises administering a Factor D binding antagonist.

In another example, there is provided a method of treating an HtrA1-associated disorder or a complement-associated disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an HtrA1 binding antagonist and a Factor D binding antagonist. In some examples, the HtrA1-associated disorder or the complement-associated disorder is an ocular disorder. In some examples, the ocular disorder is selected from the group consisting of

AMD, diabetic retinopathy, choroidal neovascularization (CNV), uveitis, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, central retinal vein occlusion, corneal vascularization, and retinal neovascularization. In some examples, the ocular disorder is AMD. In some examples, the AMD is early dry AMD, intermediate dry AMD, or advanced dry AMD. In some examples, the advanced dry AMD is geographic atrophy. In some examples, the HtrA1 binding antagonist is an anti-HtrA1 antibody or an antigen-binding fragment thereof. In some examples, the antigen-binding fragment is selected from the group consisting of Fab, Fab'-SH, Fv, scFV, and $(Fab')_2$ fragments. In some examples, the antigen-binding fragment is an Fab. In some examples, the Fab comprises a truncation in the upper hinge of the heavy chain constant region. In some examples, the heavy chain constant region terminates at position 221 (EU numbering). In some examples, the amino acid residue at position 221 is an aspartic acid (Asp) residue. In some examples, the heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 156. In some examples, the antibody comprises the heavy chain amino acid sequence of SEQ ID NO: 160. In some examples, the antibody comprises the light chain amino acid sequence of SEQ ID NO: 159. In some examples, the antibody comprises the heavy chain amino acid sequence of SEQ ID NO: 160 and the light chain amino acid sequence of SEQ ID NO: 159. In some examples, the Fab is an IgG1 Fab.

In another example, there is provided a method of treating an HtrA1-associated disorder or a complement-associated disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of any one of the preceding antibodies and a therapeutically effective amount of a Factor D binding antagonist.

In some examples of any of the preceding aspects, the Factor D binding antagonist is an anti-Factor D antibody or an antigen-binding fragment thereof. In some examples, the antigen-binding fragment is an Fab or an $(Fab')_2$. In some examples, the anti-Factor D antibody or antigen-binding fragment thereof comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of GYTFTNYGMN (SEQ ID NO: 109); (b) an HVR-H2 comprising the amino acid sequence of WINTYTGETTYAX_1DFKG (SEQ ID NO: 110), wherein X_1 is Asp or Glu; (c) an HVR-H3 comprising the amino acid sequence of EGGVX_1N (SEQ ID NO: 111), wherein X_1 is Asn or Ser; (d) an HVR-L1 comprising the amino acid sequence of ITSTX_1IX_2X_3DMN (SEQ ID NO: 112), wherein X_1 is Asp or Ser, X_2 is Asp or Glu, and X_3 is Asp or Ser; (e) an HVR-L2 comprising the amino acid sequence of GGNTLRP (SEQ ID NO: 113); and (f) an HVR-L3 comprising the amino acid sequence of LQSX_1SLPYT (SEQ ID NO: 114), wherein X_1 is Asp or Glu. In some examples, the anti-Factor D antibody or antigen-binding fragment thereof comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of GYTFTNYGMN (SEQ ID NO: 109); (b) an HVR-H2 comprising the amino acid sequence of WINTYTGETTYADDFKG (SEQ ID NO: 115); (c) an HVR-H3 comprising the amino acid sequence of EGGVNN (SEQ ID NO: 116); (d) an HVR-L1 comprising the amino acid sequence of ITSTDIDDDMN (SEQ ID NO: 117); (e) an HVR-L2 comprising the amino acid sequence of GGNTLRP (SEQ ID NO: 113); and (f) an HVR-L3 comprising the amino acid sequence of LQSDSLPYT (SEQ ID NO: 118). In some examples, the anti-Factor D antibody or antigen-binding fragment thereof comprises (a) a VH domain

comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 119; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 120; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 119. In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 120. In some examples, the anti-Factor D antigen-binding fragment is lampalizumab.

In some examples of any of the preceding aspects, the HtrA1-associated disorder or the complement-associated disorder is an ocular disorder. In some examples, the ocular disorder is selected from the group consisting of AMD, diabetic retinopathy, choroidal neovascularization (CNV), uveitis, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, central retinal vein occlusion, corneal vascularization, and retinal neovascularization. In some examples, the ocular disorder is AMD. In some examples, the AMD is early dry AMD, intermediate dry AMD, or advanced dry AMD. In some examples, the advanced dry AMD is geographic atrophy.

In some examples of any of the preceding aspects, the antibody is administered intravitreally, ocularly, intraocularly, juxtasclerally, subtenonly, superchoroidally, topically, intravenously, intramuscularly, intradermally, percutaneously, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intrathecally, intranasally, intravaginally, intrarectally, topically, intraperitoneally, peritoneally, intraventricularly, subcutaneously, subconjunctivally, intravesicularly, mucosally, intrapericardially, intraumbilically, intraorbitally, orally, transdermally, by inhalation, by injection, by eye drop, by implantation, by infusion, by continuous infusion, by localized perfusion bathing target cells directly, by catheter, by lavage, in cremes, or in lipid compositions. In some examples, the antibody is administered intravitreally, ocularly, intraocularly, juxtasclerally, subtenonly, superchoroidally, or topically. In some examples, the antibody is administered intravitreally by injection. In some examples, the antibody is administered topically by eye drop or ointment. In some examples, the antibody is administered by a long-acting delivery system. In particular examples, the long-acting delivery system is a PLGA-based solid implant or an implantable port delivery system.

In some examples of any of the preceding aspects, the subject is a human.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1A-1B are graphs showing that the majority of enzyme-linked immunosorbent assay (ELISA)-positive hybridoma clones showed similar reactivity profiles to both human (hu) and murine (mu) HtrA1 protease domain (PD). The graphs show the optical density at 650 nm (OD_{650nm}) for each of the indicated 75 clones. Background signal in this assay was < 0.05 OD_{650nm}. The human and murine HtrA1 protease domains share 91% homology.

FIG. 2A is a schematic diagram of a blocking assay used to determine the ability of the indicated anti-HtrA1 hybridoma clone supernatants to inhibit HtrA1-PD-mediated cleavage of a BODIPY® FL-labeled fluorescent substrate.

CLAIMS

What is claimed is:

1. An isolated antibody that specifically binds HtrA1, wherein the antibody comprises a binding domain comprising the following six HVRs:

(a) an HVR-H1 comprising the amino acid sequence of DSEX_1H (SEQ ID NO: 1), wherein X_1 is Met or Leu;

(b) an HVR-H2 comprising the amino acid sequence of GVDPETX_2GAAYNQKFKG (SEQ ID NO: 2), wherein X_2 is Glu or Asp;

(c) an HVR-H3 comprising the amino acid sequence of GYDYDYALDY (SEQ ID NO: 3);

(d) an HVR-L1 comprising the amino acid sequence of RASSSVX_3FIH (SEQ ID NO: 4), wherein X_3 is Glu or Asn;

(e) an HVR-L2 comprising the amino acid sequence of ATSX_4LAS (SEQ ID NO: 5), wherein X_4 is Asn, His or Glu; and

(f) an HVR-L3 comprising the amino acid sequence of QQWX_5SX_6PWT (SEQ ID NO: 6), wherein X_5 is Ser or Tyr and X_6 is Ala or Asn.

2. The antibody of claim 1, wherein:

(a) HVR-H1 comprises the amino acid sequence of DSEMH (SEQ ID NO: 7);

(b) HVR-H2 comprises the amino acid sequence of GVDPETEGAAYNQKFKG (SEQ ID NO: 8);

(c) HVR-H3 comprises the amino acid sequence of GYDYDYALDY (SEQ ID NO: 3);

(d) HVR-L1 comprises the amino acid sequence of RASSSVEFIH (SEQ ID NO: 9);

(e) HVR-L2 comprises the amino acid sequence of ATSNLAS (SEQ ID NO: 10); and

(f) HVR-L3 comprises the amino acid sequence of QQWSSAPWT (SEQ ID NO: 11).

3. The antibody of claim 2, wherein the antibody comprises a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 21 and/or a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 22.

4. The antibody of claim 3, wherein the antibody comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 21 and/or a VL domain comprising the amino acid sequence of SEQ ID NO: 22.

5. The antibody of any one of claims 1-4, wherein:

(i) the antibody is monoclonal, humanized, or chimeric; wherein optionally

(ii) the antibody is an antibody fragment that binds to HtrA1; wherein optionally

(iii) the antibody fragment is selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and $(Fab')_2$ fragments; wherein optionally

(iv) the antibody fragment is a Fab; wherein optionally

(v) the Fab comprises a truncation in the upper hinge of the heavy chain constant region; and wherein optionally

(vi) the heavy chain constant region terminates at position 221 (EU numbering).

6. The antibody of any one of claims 5(ii)-5(vi), wherein the antibody comprises the heavy chain amino acid sequence of SEQ ID NO: 160 and the light chain amino acid sequence of SEQ ID NO: 159.

7. The antibody of any one of claims 1-6, wherein said antibody specifically binds to an HtrA1 epitope, wherein the HtrA1 epitope comprises at least one amino acid of the HtrA1 protein selected from the group consisting of Arg190, Leu192, Pro193, Phe194, and Arg197.

8. The antibody of claim 7, wherein the HtrA1 epitope comprises at least one amino acid of the HtrA1 protein selected from the group consisting of Leu192, Pro193, and Arg197; wherein optionally the HtrA1 epitope comprises the HtrA1 amino acids Leu192, Pro193, and Arg197; and wherein optionally the HtrA1 epitope comprises the HtrA1 amino acids Arg190, Leu192, Pro193, Phe194, and Arg197.

9. The antibody of any one of claims 1-8, wherein the antibody is a bispecific antibody.

10. An isolated nucleic acid encoding the antibody of any one of claims 1-9.

11. A method of producing an antibody, the method comprising culturing a host cell comprising a vector comprising an isolated nucleic according to claim 10 and recovering the antibody from the host cell or the host cell culture medium.

12. A pharmaceutical composition comprising an antibody of any one of claims 1-9 and further comprising at least one pharmaceutically acceptable carrier, excipient, or diluent.

13. The pharmaceutical composition of claim 12, wherein the composition is lyophilized.

14. The antibody of any one of claims 1-9 for use as a medicament.

15. The antibody of any one of claims 1-9 for use in treating an HtrA1-associated disorder or an ocular disorder in a subject in need thereof, wherein the HtrA1-associated disorder or the ocular disorder is age-related macular degeneration (AMD), diabetic retinopathy, retinopathy of prematurity,

or polypoidal choroidal vasculopathy, wherein optionally the HtrA1-associated disorder or the ocular disorder is early dry AMD, intermediate dry AMD, or advanced dry AMD, wherein optionally the advanced dry AMD is geographic atrophy.

16. The antibody for use of claim 15, wherein the antibody is to be administered to the subject with a Factor D antagonist.

17. The antibody for use of claim 16, wherein the Factor D antagonist is an anti-Factor D antibody.

18. The antibody for use of claim 17, wherein the anti-Factor D antibody is lampalizumab.

19. The antibody for use of any one of claims 16-18, wherein the anti-Factor D antagonist is to be administered sequentially.

20. Use of the antibody of any one of claims 1-9 in the manufacture of a medicament for treating an HtrA1-associated disorder or an ocular disorder in a subject in need thereof, wherein the HtrA1-associated disorder or the ocular disorder is AMD, diabetic retinopathy, retinopathy of prematurity, or polypoidal choroidal vasculopathy, wherein optionally the HtrA1-associated disorder or the ocular disorder is early dry AMD, intermediate dry AMD, or advanced dry AMD, wherein optionally the advanced dry AMD is geographic atrophy; wherein optionally the medicament is to be administered with a Factor D antagonist, wherein the Factor D antagonist is an anti-Factor D antibody, and wherein optionally the anti-Factor D antibody is lampalizumab.

21. The use of claim 20, wherein the medicament is to be administered intravitreally, ocularly, intraocularly, juxtasclerally, subtenonly, superchoroidally, or topically, wherein optionally the medicament is to be administered intravitreally by injection; or wherein the medicament is to be administered by a long-acting delivery system, wherein optionally the long-acting delivery system is a PLGA-based solid implant or an implantable port delivery system.