HtrA1 promoter region, which results in increased HtrA1 transcript levels (Dewan, A., et al., *Science* 314:989-92 (2006); Yang, Z., et al., *Science* 314:992-3 (2006)). Therefore, inhibition of HtrA1 enzymatic function is an attractive therapeutic approach, e.g. in age-related macular degeneration and in arthritic disease.

SUMMARY

The disclosure provides anti-HtrA1 antibodies and methods of using the same for diagnostic and therapeutic purposes.

In one aspect, the invention provides an isolated monoclonal antibody that binds to HtrA1 competitively with an antibody comprising a VH sequence of SEQ ID NO:8 and a VL sequence of SEQ ID NO:7. Competitive binding may be determined, for example, using an ELISA assay.

In one embodiment, the disclosure provides an isolated antibody that bind to HtrA1 having one or more of the following properties: (i) an IC_{50} of less than 50 nM, 30 nM, 25 nM, 20 nM, 15 nM, 10 nM, 5 nM, 3 nM, 2.5 nM, 2 nM, 1 nM, or less for one or more HtrA1 substrates; (ii) binds to HtrA1 with a ratio of 1 variable domain to one subunit of an HtrA1 trimer (e.g., a Fab binds to an HtrA1 trimer with a ratio of 3 Fab to 1 HtrA1 trimer, and an IgG binds to an HtrA1 trimer with a ratio of 3 IgG to 2 HtrA1 trimers), (iii) for antibodies comprising two variable domains, binds to HtrA1 in a manner that results in the forming a "cage" similar to that shown in Fig. 9, (iv) does not prevent trimer formation of HtrA1, (v) binds to one or more residues in Loop C of the HtrA1 protein, (vi) binds to the protease domain of HtrA1, (vii) binds to an epitope comprising one or both of amino acids N224 or K248 of SEQ ID NO:13, or amino acids equivalent thereto in a different HtrA1 sequence (e.g., amino acids N224 and K248 of SEQ ID NO:14, see Figs. 10A and B); (viii) binds to an epitope comprising one or more of the following residues of N224, K248, V201, T223, K243, K225, E247 and H220 of SEQ ID NO:13, or amino acids equivalent thereto in a different HtrA1 sequence; (ix) cross-reacts with murine HtrA1; (x) does not cross-react with HtrA2, HtrA3 and/or HtrA4; (xi) binds to HtrA1 competitively with an antibody comprising a VH sequence of SEQ ID NO:8 and a VL sequence of SEQ ID NO:7, (xii) binds to HtrA1 with a dissociation constant of $\leq$500 nM, or (xiii) inhibits complex formation between HtrA1 and α1-antitrypsin (A1AT).

~~In another aspect, the invention~~ Also provided is an isolated antibody that binds to HtrA1, wherein the antibody (i) binds to an epitope that includes N224, K248, or both of HtrA1, and (ii) inhibits HtrA1 with an IC_{50} of $\leq$ 30 nM. In one aspect, the invention provides an isolated monoclonal antibody that binds to HtrA1, wherein the antibody (i) binds to an epitope that includes N224, K248, or both of HtrA1, and (ii) inhibits HtrA1 with a dissociation constant of $\leq$500 nM. In certain embodiments, the epitope further includes one or more of the following residues of HtrA1: V201, T223, K243, K225, E247 and H220. In certain embodiments, the antibody may further comprise one or more of the

In certain embodiments, an antibody described herein comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:18; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19.

In certain embodiments, an antibody described herein comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:21; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:22.

In certain embodiments, an antibody described herein further comprises a heavy chain variable domain framework (FR2) sequence of SEQ ID NO:17.

In one ~~aspect~~embodiment, there is provided an antibody that binds to HtrA1 comprising (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:8; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:7; or (c) a VH sequence as in (a) and a VL sequence as in (b).

In certain embodiments, an antibody described herein comprises (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:29; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:7; or (c) a VH sequence as in (a) and a VL sequence as in (b).

In certain embodiments, an antibody described herein comprises (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:29; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:28; or (c) a VH sequence as in (a) and a VL sequence as in (b).

In certain embodiments, an antibody described herein comprises (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:29; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:30; or (c) a VH sequence as in (a) and a VL sequence as in (b).

In one ~~aspect~~embodiment, there is provided an antibody that binds to HtrA1 comprising (a) a VH sequence comprising SEQ ID NO: 32; (b) a VL sequence comprising SEQ ID NO: 31; or (c) a VH sequence comprising SEQ ID NO: 32 and a VL sequence comprising SEQ ID NO: 31.

In certain embodiments, an antibody described herein comprises a VH sequence of SEQ ID NO:8.

In certain embodiments, an antibody described herein comprises a VL sequence of SEQ ID NO:7.

In certain embodiments, an antibody described herein comprises a VH sequence of SEQ ID NO:30.

In certain embodiments, an antibody described herein comprises a VL sequence of SEQ ID NO:28.

In certain embodiments, an antibody described herein comprises a VL sequence of SEQ ID NO:29.

In one aspect, an antibody described herein comprises a VH sequence of SEQ ID NO:8 and a VL sequence of SEQ ID NO:7.

In one aspect, there is provided an antibody comprising a VH sequence of SEQ ID NO:29 and a VL sequence of SEQ ID NO:28.

In certain embodiments, an antibody described herein comprises a VH sequence of SEQ ID NO:30 and a VL sequence of SEQ ID NO:28.

In one aspect, an antibody described herein comprises a VH sequence of SEQ ID NO:30 and a VL sequence of SEQ ID NO:29.

In one ~~aspect~~embodiment, there is provided an antibody comprising (a) HVR-H1 comprising the amino acid sequence $GFX_lIX_mX_nYYIH$, wherein X_l is N, S or T; X_m is S, D, Y or A; and X_n is G or D (SEQ ID NO: 25); (b) HVR-H2 comprising the amino acid sequence $WIDPYGGDTX_oYADSVKG$, wherein X_o is N or D (SEQ ID NO:26); (c) HVR-H3 comprising the amino acid sequence $GTFLTX_pWGHYFDY$, wherein X_p is S or T (SEQ ID NO: 27); (d) HVR-L1 comprising the amino acid sequence $RASQX_aX_bX_cX_dX_eX_fA$, wherein X_a is D, S or V; X_b is V or I; X_c is S, N or G; X_d is T or N; X_e is A or Y; and X_f is V or L (SEQ ID NO: 23); (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (f) HVR-L3 comprising the amino acid sequence $QQX_gX_hX_iX_jPX_kT$, wherein X_g is S, V or D; X_h is Y, D or S; X_i is T, S, A, D or N; X_j is T, H, N, S, A, L or R; and X_k is P, T, A or S (SEQ ID NO: 24).

In certain embodiments, an antibody described herein comprises (a) HVR-H1 comprising an amino acid sequence selected from: SEQ ID NO:4, 20,and 47-51; (b) HVR-H2 comprising an amino acid sequence selected from: SEQ ID NO:5 and 52; (c) HVR-H3 comprising an amino acid sequence selected from: SEQ ID NO:6 and 53; (d) HVR-L1 comprising an amino acid sequence selected from: SEQ ID NO:1, 18, 21 and 33; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (f) HVR-L3 comprising an amino acid sequence selected from: SEQ ID NO:3, 19, 22, and 34-46.

In certain embodiments, an antibody described herein comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:4; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:5; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:1; (e) HVR-L2 comprising

the amino acid sequence of SEQ ID NO:2; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:3.

In certain embodiments, an antibody described herein comprises (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:5; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:18; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19.

In certain embodiments, an antibody described herein comprises (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:5; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:21; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:22.

In certain embodiments, an antibody described herein comprises (a) HVR-H3 comprising the amino acid sequence GTFLTX$_p$WGHY, wherein X$_p$ is S or T (SEQ ID NO: 89); (b) HVR-L3 comprising the amino acid sequence X$_g$X$_h$X$_i$X$_j$PX$_k$, wherein X$_g$ is S, V or D; X$_h$ is Y, D or S; X$_i$ is T, S, A, D or N; X$_j$ is T, H, N, S, A, L or R; and X$_k$ is P, T, A or S (SEQ ID NO: 86); and (c) HVR-H2 comprising the amino acid sequence WIDPYGGDTX$_o$, wherein X$_o$ is N or D (SEQ ID NO:88).

In one ~~aspect~~embodiment, there is provided an antibody comprising (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 87; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:88; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:89; (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:58; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 86.

In certain embodiments, an antibody described herein comprises (a) HVR-H1 comprising the amino acid sequence GFX$_i$IX$_m$X$_n$YY, wherein X$_i$ is N, S or T; X$_m$ is S, D, Y or A; and X$_n$ is G or D (SEQ ID NO:87); (b) HVR-H2 comprising the amino acid sequence WIDPYGGDTX$_o$, wherein X$_o$ is N or D (SEQ ID NO:88); and (c) HVR-H3 comprising the amino acid sequence GTFLTX$_p$WGHY, wherein X$_p$ is S or T (SEQ ID NO: 89).

In certain embodiments, an antibody described herein further comprises (a) HVR-L1 comprising the amino acid sequence X$_a$X$_b$X$_c$X$_d$X$_e$X$_f$, wherein X$_a$ is D, S or V; X$_b$ is V or I; X$_c$ is S, N or G; X$_d$ is T or N; X$_e$ is A or Y; and X$_f$ is V or L (SEQ ID NO: 85); (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:58; and (c) HVR-L3 comprising the amino acid sequence X$_g$X$_h$X$_i$X$_j$PX$_k$, wherein X$_g$ is S, V or D; X$_h$ is Y, D or S; X$_i$ is T, S, A, D or N; X$_j$ is T, H, N, S, A, L or R; and X$_k$ is P, T, A or S (SEQ ID NO: 86).

In certain embodiments, an antibody described herein comprises (a) HVR-H1 comprising the amino acid sequence GFX$_i$IX$_m$X$_n$YY, wherein X$_i$ is N, S or T; X$_m$ is S, D, Y or A; and X$_n$ is G or D (SEQ ID NO:87); (b) HVR-H2 comprising the amino acid sequence

WHAT IS CLAIMED IS:

1. An isolated antibody that binds to HtrA1 competitively with an antibody comprising a VH sequence of SEQ ID NO:8 and a VL sequence of SEQ ID NO:7.

2. The antibody of claim 1, wherein competitive binding is determined using an ELISA assay.

3. An isolated antibody that binds to HtrA1, wherein the antibody (i) binds to an epitope that includes N224, K248, or both of HtrA1, and (ii) inhibits HtrA1 with an IC_{50} of ≤ 30 nM.

4. The antibody of claim 3, wherein the antibody further comprises one or more of the following properties: (i) binds to HtrA1 with a ratio of 1 variable domain to one subunit of an HtrA1 trimer, or (ii) does not prevent trimer formation of HtrA1.

5. The antibody of claim 3, wherein the IC_{50} is determined using a serine protease assay with a substrate having SEQ ID NO:12.

6. The antibody of any one of claims 1-5, wherein the antibody does not cross-react with one or more of HtrA2, HtrA3 and HtrA4.

7. The antibody of any one of claims 1-6, wherein the antibody has a dissociation constant of ≤500 nM.

8. The antibody of claim 6, wherein the dissociation constant is determined by BIAcore using a Fab at 25 °C.

9. The antibody of any one of claims 1-8, selected from a group consisting of:

i) an antibody which is a monoclonal antibody,

ii) an antibody which is a human, humanized, or chimeric antibody, and

iii) an antibody which is an antibody fragment that binds HtrA1.

10. The antibody of any one of claims 1-9, wherein the antibody comprises (a) HVR-H3 comprising the amino acid sequence GTFLTX$_p$WGHYFDY, wherein X_p is S or T (SEQ ID NO: 27); (b) HVR-L3 comprising the amino acid sequence QQX$_g$X$_h$X$_i$X$_j$PX$_k$T, wherein X_g is S, V or D; X_h is Y, D or S; X_i is T, S, A, D or N; X_j is T, H, N, S, A, L or R; and X_k is P, T, A or S (SEQ ID NO: 24); and (c) HVR-H2 comprising the amino acid sequence WIDPYGGDTX$_o$YADSVKG, wherein X_o is N or D (SEQ ID NO: 26).

11. The antibody of any one of claims 1-10, selected from a group consisting of:

(i) an antibody which comprises (a) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6; (b) HVR-L3 comprising the amino acid sequence of SEQ ID NO:3; and (c) HVR-H2 comprising the amino acid sequence of SEQ ID NO:5,

(ii) an antibody which comprises (a) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6; (b) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19; and (c) HVR-H2 comprising the amino acid sequence of SEQ ID NO:5,

(iii) an antibody which comprises (a) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6; (b) HVR-L3 comprising the amino acid sequence of SEQ ID NO:22; and (c) HVR-H2 comprising the amino acid sequence of SEQ ID NO:5, and

(iv) an antibody which comprises (a) HVR-H1 comprising the amino acid sequence $GFX_lIX_mX_nYYIH$, wherein X_l is N, S or T; X_m is S, D, Y or A; and X_n is G or D (SEQ ID NO: 25); (b) HVR-H2 comprising the amino acid sequence $WIDPYGGDTX_oYADSVKG$, wherein X_o is N or D (SEQ ID NO:26); and (c) HVR-H3 comprising the amino acid sequence $GTFLTX_pWGHYFDY$, wherein X_p is S or T (SEQ ID NO: 27).

12. The antibody of any one of claims 1-10 or 11(iv), further comprising (a) HVR-L1 comprising the amino acid sequence $RASQX_aX_bX_cX_dX_eX_fA$, wherein X_a is D, S or V; X_b is V or I; X_c is S, N or G; X_d is T or N; X_e is A or Y; and X_f is V or L (SEQ ID NO: 23); (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (c) HVR-L3 comprising the amino acid sequence $QQX_gX_hX_iX_jPX_kT$, wherein X_g is S, V or D; X_h is Y, D or S; X_i is T, S, A, D or N; X_j is T, H, N, S, A, L or R; and X_k is P, T, A or S (SEQ ID NO: 24).

13. The antibody of any one of claims 1-10, 11(iv) or 12, selected from a group consisting of:

(i) an antibody which comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:4; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:5; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6,

(ii) an antibody which comprises (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:5; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6,

(iii) an antibody which comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:1; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:3,

(iv) an antibody which comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:18; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19, and

(v) an antibody which comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:21; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:22.

14. The antibody of claim 13(i), further comprising (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:1; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:3.

15. The antibody of claim 13(ii), selected from a group consisting of:

an antibody that further comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:18; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19; and

an antibody that further comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:21; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:22.

16. The antibody of any one of claims 1-15, further comprising a heavy chain variable domain framework (FR2) sequence of SEQ ID NO:17.

17. The antibody of any one of claims 1-16 comprising (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:8; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:7; or (c) a VH sequence as in (a) and a VL sequence as in (b).

18. The antibody of any one of claims 1-17, comprising (a) a VH sequence comprising SEQ ID NO: 32; (b) a VL sequence comprising SEQ ID NO: 31; or (c) a VH sequence comprising SEQ ID NO: 32 and a VL sequence comprising SEQ ID NO: 31.

19. The antibody of claim 17 or 18, selected from a group consisting of:

(i) an antibody comprising a VH sequence of SEQ ID NO:8,

(ii) an antibody comprising a VL sequence of SEQ ID NO:7,

(iii) an antibody comprising a VL sequence of SEQ ID NO:30,

(iv) an antibody comprising a VL sequence of SEQ ID NO:28; and

(v) an antibody comprising a VH sequence of SEQ ID NO:29.

20. An antibody comprising a VH sequence of SEQ ID NO:8 and a VL sequence of SEQ ID NO:7.

21. An antibody comprising a VH sequence of SEQ ID NO:29 and a VL sequence of SEQ ID NO:28.

22. An antibody comprising a VL sequence of SEQ ID NO:30 and a VH sequence of SEQ ID NO:29.

23. An antibody that binds to HtrA1 comprising (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:8; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:7; or (c) a VH sequence as in (a) and a VL sequence as in (b).

24. An antibody that binds to HtrA1 comprising (a) a VH sequence comprising SEQ ID NO: 32; (b) a VL sequence comprising SEQ ID NO: 31; or (c) a VH sequence comprising SEQ ID NO: 32 and a VL sequence comprising SEQ ID NO: 31.

25. An antibody comprising (a) HVR-H1 comprising the amino acid sequence $GFX_lIX_mX_nYYIH$, wherein X_l is N, S or T; X_m is S, D, Y or A; and X_n is G or D (SEQ ID NO: 25); (b) HVR-H2 comprising the amino acid sequence $WIDPYGGDTX_oYADSVKG$, wherein X_o is N or D (SEQ ID NO:26); (c) HVR-H3 comprising the amino acid sequence $GTFLTX_pWGHYFDY$, wherein X_p is S or T (SEQ ID NO: 27); (d) HVR-L1 comprising the amino acid sequence $RASQX_aX_bX_cX_dX_eX_fA$, wherein X_a is D, S or V; X_b is V or I; X_c is S, N or G; X_d is T or N; X_e is A or Y; and X_f is V or L (SEQ ID NO: 23); (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (f) HVR-L3 comprising the amino acid sequence $QQX_gX_hX_iX_jPX_kT$, wherein X_g is S, V or D; X_h is Y, D or S; X_i is T, S, A, D or N; X_j is T, H, N, S, A, L or R; and X_k is P, T, A or S (SEQ ID NO: 24).

26. The antibody of claim 25, wherein the antibody comprises (a) HVR-H1 comprising an amino acid sequence selected from: SEQ ID NO:4, 20,and 47-51; (b) HVR-H2 comprising an amino acid sequence selected from: SEQ ID NO:5 and 52; (c) HVR-H3 comprising an amino acid sequence selected from: SEQ ID NO:6 and 53; (d) HVR-L1 comprising an amino acid sequence selected from: SEQ ID NO:1, 18, 21 and 33; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (f) HVR-L3 comprising an amino acid sequence selected from: SEQ ID NO:3, 19, 22, and 34-46.

27. The antibody of claim 26, selected from a group consisting of:

(i)an antibody which comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:4; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:5; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:1; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:3,

(ii) an antibody which comprises (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:5; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:18; (e) HVR-L2 comprising the

amino acid sequence of SEQ ID NO:2; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19, and

(iii)an antibody which comprises (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:5; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:21; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:22.

28. The antibody of any one of claims 1-27, which is a full length IgG1 or IgG4 antibody.

29. An isolated nucleic acid encoding the antibody of any one of claims 1-28.

30. A host cell comprising the nucleic acid of claim 29.

31. A method of producing an antibody comprising culturing the host cell of claim 30 under conditions suitable for expression of the nucleic acid encoding the anti-HtrA1 antibody.

32. The method of claim 31, further comprising recovering the anti-HtrA1 antibody from the host cell culture.

33. An immunoconjugate comprising the antibody of any one of claims 1-28 and a cytotoxic agent.

34. A pharmaceutical formulation comprising the antibody of any one of claims 1-28 and a pharmaceutically acceptable carrier.

35. The antibody of any one of claims 1-28 for use as a medicament.

36. Use of the antibody of any one of claims 1-28 in the manufacture of a medicament.

37. The use of claim 36, selected from a group consisting of:

(i) a use wherein the medicament is for treatment of treating age-related macular degeneration, geographic atrophy, diabetic retinopathy, retinopathy of prematurity, or polypoidal choroidal vasculopathy,

(ii) a use wherein the medicament is for inhibiting degeneration of retinal or photoreceptor cells, and

(iii) a use wherein the medicament is for inhibiting HtrA1 protease activity in an eye.

38. The use of claim 37(i), wherein the age-related macular degeneration is dry age-related macular degeneration.

39. The antibody of any one of claims 1-10, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 87; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:88; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 89.

40. The antibody of any one of claims 1-10 or 39, further comprising (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 85; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:58; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 86.

41. An antibody comprising (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 87; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:88; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:89; (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:58; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 86.

42. The antibody of claim 41, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 25; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:26; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:27; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:23; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:24.

43. The antibody of claim 41 or 42, wherein the antibody comprises (a) HVR-H1 comprising an amino acid sequence selected from: SEQ ID NO:4, 20, 47-51 and 75-80; (b) HVR-H2 comprising an amino acid sequence selected from: SEQ ID NO:5, 52 and 81-82; (c) HVR-H3 comprising an amino acid sequence selected from: SEQ ID NO:6, 53 and 83-84; (d) HVR-L1 comprising an amino acid sequence selected from: SEQ ID NO:1, 18, 21, 33 and 54-57; (e) HVR-L2 comprising an amino acid sequence selected from: SEQ ID NO:2 and 58; and (f) HVR-L3 comprising an amino acid sequence selected from: SEQ ID NO:3, 19, 22, 34-46 and 59-74.

44. The antibody of any one of claims 39-43, which is a full length IgG1 or IgG4 antibody.

45. An isolated nucleic acid encoding the antibody of any one of claims 39-44.

46. A host cell comprising the nucleic acid of claim 45.

47. A method of producing an antibody comprising culturing the host cell of claim 46 under conditions suitable for expression of the nucleic acid encoding the anti-HtrA1 antibody.

48. The method of claim 47, further comprising recovering the anti-HtrA1 antibody from the host cell culture.

49. An immunoconjugate comprising the antibody of any one of claims 39-44 and a cytotoxic agent.

50. A pharmaceutical formulation comprising the antibody of any one of claims 39-44 and a pharmaceutically acceptable carrier.

51. The antibody of any one of claims 39-44 for use as a medicament.

52. Use of the antibody of any one of claims 39-44 in the manufacture of a medicament.

53. The use of claim 52, selected from a group consisting of:

(i) a use wherein the medicament is for treatment of treating age-related macular degeneration, geographic atrophy, diabetic retinopathy, retinopathy of prematurity, or polypoidal choroidal vasculopathy,

(ii) a use wherein the medicament is for inhibiting degeneration of retinal or photoreceptor cells, and

(iii) a use wherein the medicament is for inhibiting HtrA1 protease activity in an eye.

54. The use of claim 53(i), wherein the age-related macular degeneration is dry age-related macular degeneration.

55. An isolated antibody that binds to HtrA1 and inhibits its serine protease activity for one or more HtrA1 substrates.

56. The antibody of claim 55, wherein the antibody inhibits HtrA1 with an IC_{50} of less than 50 nM.

WHAT IS CLAIMED IS:

1. An isolated monoclonal antibody that binds to HtrA1, wherein the antibody (i) binds to an epitope that includes N224, K248, or both of HtrA1, and (ii) inhibits HtrA1 with a dissociation constant of ≤500 nM.

2. The antibody of claim 1, wherein the antibody further comprises one or more of the following properties: (i) binds to HtrA1 with a ratio of one variable domain to one subunit of an HtrA1 trimer, or (ii) does not prevent trimer formation of HtrA1.

3. The antibody of claim 1 or 2, wherein the antibody does not cross-react with one or more of HtrA2, HtrA3 and HtrA4.

4. The antibody of claim 1, wherein the dissociation constant is determined by BIAcore using a Fab at 25 °C.

5. An isolated monoclonal antibody that binds to HtrA1 competitively with an antibody comprising a VH sequence of SEQ ID NO: 8 and a VL sequence of SEQ ID NO: 7.

6. The antibody of claim 5, wherein competitive binding is determined using an ELISA assay.

7. The antibody of any one of claims 1-6, selected from a group consisting of:

i) an antibody which is a monoclonal antibody,

ii) an antibody which is a human, humanized, or chimeric antibody, and

iii) an antibody which is an antibody fragment that binds HtrA1.

8. The antibody of any one of claims 1-7, wherein the antibody comprises (a) HVR-H3 comprising the amino acid sequence GTFLTX$_p$WGHYFDY, wherein X$_p$ is S or T (SEQ ID NO: 27); (b) HVR-L3 comprising the amino acid sequence QQX$_g$X$_h$X$_i$X$_j$PX$_k$T, wherein X$_g$ is S, V or D; X$_h$ is Y, D or S; X$_i$ is T, S, A, D or N; X$_j$ is T, H, N, S, A, L or R; and X$_k$ is P, T, A or S (SEQ ID NO: 24); and (c) HVR-H2 comprising the amino acid sequence WIDPYGGDTX$_0$YADSVKG, wherein X$_0$ is N or D (SEQ ID NO: 26).

9. The antibody of any one of claims 1-8, selected from a group consisting of:

(i) an antibody which comprises (a) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6; (b) HVR-L3 comprising the amino acid sequence of SEQ ID NO:3; and
(c) HVR-H2 comprising the amino acid sequence of SEQ ID NO:5,

(ii) an antibody which comprises (a) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6; (b) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19; and (c) HVR-H2 comprising the amino acid sequence of SEQ ID NO:5,

(iii) an antibody which comprises (a) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6; (b) HVR-L3 comprising the amino acid sequence of SEQ ID NO:22; and (c) HVR-H2 comprising the amino acid sequence of SEQ ID NO:5, and

(iv) an antibody which comprises (a) HVR-H1 comprising the amino acid sequence $GFX_iIX_mX_nYYIH$, wherein X_i is N, S or T; X_m is S, D, Y or A; and X_n is G or D (SEQ ID NO: 25); (b) HVR-H2 comprising the amino acid sequence $WIDPYGGDTX_0YADSVKG$, wherein X_0 is N or D (SEQ ID NO:26); and (c) HVR-H3 comprising the amino acid sequence $GTFLTX_pWGHYFDY$, wherein X_p is S or T (SEQ ID NO: 27).

10. The antibody of any one of claims 1-8 or 9(iv), further comprising (a) HVR-L1 comprising the amino acid sequence $RASQX_aX_bX_cX_dX_eX_fA$, wherein X_a is D, S or V; X_b is V or I; X_c is S, N or G; X_d is T or N; X_e is A or Y; and X_f is V or L (SEQ ID NO: 23); (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (c) HVR-L3 comprising the amino acid sequence $QQX_gX_hX_iX_jPX_kT$, wherein X_g is S, V or D; X_h is Y, D or S; X_i is T, S, A, D or N; X_j is T, H, N, S, A, L or R; and X_k is P, T, A or S (SEQ ID NO: 24).

11. The antibody of any one of claims 1-8, 9(iv) or 10, selected from a group consisting of:

(i) an antibody which comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:4; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:5; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6,

(ii) an antibody which comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID N0:20; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:5; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6,

(iii) an antibody which comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID N0:1; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:3,

(iv) an antibody which comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID N0:18; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19, and

(v) an antibody which comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:21; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:22.

12. The antibody of claim 11(i), further comprising (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:1; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:3.

13. The antibody of claim 11(ii), selected from a group consisting of:

an antibody that further comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:18; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19; and

an antibody that further comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:21; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:22.

14. The antibody of any one of claims 1-13, further comprising a heavy chain variable domain framework (FR2) sequence of SEQ ID NO:17.

15. The antibody of any one of claims 1-14 comprising (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:8; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:7; or (c) a VH sequence as in (a) and a VL sequence as in (b).

16. The antibody of any one of claims 1-15, comprising (a) a VH sequence comprising SEQ ID NO: 32; (b) a VL sequence comprising SEQ ID NO: 31; or (c) a VH sequence comprising SEQ ID NO: 32 and a VL sequence comprising SEQ ID NO: 31.

17. The antibody of claim 15 or 16, selected from a group consisting of:

(i) an antibody comprising a VH sequence of SEQ ID NO:8,
(ii) an antibody comprising a VL sequence of SEQ ID NO:7,
(iii) an antibody comprising a VL sequence of SEQ ID NO:30,
(iv) an antibody comprising a VL sequence of SEQ ID NO:28; and
(v) an antibody comprising a VH sequence of SEQ ID NO:29.

18. An antibody comprising a VH sequence of SEQ ID NO:8 and a VL sequence of SEQ ID NO:7.

19. An antibody comprising a VH sequence of SEQ ID NO:29 and a VL sequence of SEQ ID NO:28.

20. An antibody comprising a VL sequence of SEQ ID NO:30 and a VH sequence of SEQ ID NO:29.

21. The antibody of any one of claims 1-7, wherein the antibody binds to HtrA1 comprising (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:8; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:7; or (c) a VH sequence as in (a) and a VL sequence as in (b).

22. The antibody of any one of claims 1-7, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence $GFX_lIX_mX_nYYIH$, wherein X_l is N, S or T; X_m is S, D, Y or A; and X_n is G or D (SEQ ID NO: 25); (b) HVR-H2 comprising the amino acid sequence $WIDPYGGDTX_0YADSVKG$, wherein X_0 is N or D (SEQ ID NO:26); (c) HVR-H3 comprising the amino acid sequence $GTFLTX_pWGHYFDY$, wherein X_p is S or T (SEQ ID NO: 27); (d) HVR-L1 comprising the amino acid sequence $RASQX_aX_bX_cX_dX_eX_fA$, wherein X_a is D, S or V; X_b is V or I; X_c is S, N or G; X_d is T or N; X_e is A or Y; and X_f is V or L (SEQ ID NO: 23); (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (f) HVR-L3 comprising the amino acid sequence $QQX_gX_hX_iX_jPX_kT$, wherein X_g is S, V or D; X_h is Y, D or S; X_i is T, S, A, D or N; X_j is T, H, N, S, A, L or R; and X_k is P, T, A or S (SEQ ID NO: 24).

23. The antibody of claim 22, wherein the antibody comprises (a) HVR-H1 comprising an amino acid sequence selected from: SEQ ID NO: 4, 20, and 47-51; (b) HVR-H2 comprising an amino acid sequence selected from: SEQ ID NO: 5 and 52; (c) HVR-H3 comprising an amino acid sequence selected from: SEQ ID NO: 6 and 53; (d) HVR-L1 comprising an amino acid sequence selected from: SEQ ID NO: 1, 18, 21 and 33; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 2; and (f) HVR-L3 comprising an amino acid sequence selected from: SEQ ID NO: 3, 19, 22, and 34-46.

24. The antibody of claim 23, selected from a group consisting of:

(i) an antibody which comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:4; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:5; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:1; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:3,

(ii) an antibody which comprises (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:5; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:18; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (f) HVR-13 comprising the amino acid sequence of SEQ ID NO:19, and

(iii) an antibody which comprises (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:5; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:6; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:21; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:2; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:22.

25. The antibody of any one of claims 1-24, which is a full length IgG1 or IgG4 antibody.

26. An isolated nucleic acid encoding the antibody of any one of claims 1-25.

27. A host cell comprising the nucleic acid of claim 26.

28. A method of producing an antibody comprising culturing the host cell of claim 27 under conditions suitable for expression of the nucleic acid encoding the anti-HtrA1 antibody.

29. The method of claim 28, further comprising recovering the anti-HtrA1 antibody from the host cell culture.

30. An immunoconjugate comprising the antibody of any one of claims 1-25 and a cytotoxic agent.

31. A pharmaceutical formulation comprising the antibody of any one of claims 1-25 and a pharmaceutically acceptable carrier.

32. The antibody of any one of claims 1-25 for use as a medicament.

33. Use of the antibody of any one of claims 1-25 in the manufacture of a medicament.

34. The use of claim 33, selected from a group consisting of:

(i) a use wherein the medicament is for treatment of treating age-related macular degeneration, geographic atrophy, diabetic retinopathy, retinopathy of prematurity, or polypoidal choroidal vasculopathy,

(ii) a use wherein the medicament is for inhibiting degeneration of retinal or photoreceptor cells, and

(iii) a use wherein the medicament is for inhibiting HtrA1 protease activity in an eye.

35. The use of claim 34(i), wherein the age-related macular degeneration is dry age-related macular degeneration.

36. The antibody of any one of claims 1-24, wherein the antibody binds to HtrA1 and inhibits its serine protease activity for one or more HtrA1 substrates.