CLAIMS

1. An isolated antibody, capable of binding to the VHL ligand degron of a PROTAC.

2. The antibody of claim 1 which is a monospecific antibody.

3. The antibody of claim 1 or 2, which is a full-length antibody of the IgG type, or a fragment thereof, or a single domain antibody, or a single chain antibody.

4. The antibody of claim 3, wherein the full-length antibody is of the IgG1 or IgG4 type.

5. The antibody of claim 3, wherein the single domain antibody is a VHH antibody.

6. The antibody of claim 3, wherein the single chain antibody is a monospecific monovalent single chain antibody (scFv).

7. The antibody of any of claims 1, or 3-6, which is a bi-specific antibody, wherein the second binding capability is for a target protein.

8. The antibody of claim 7, comprising
   a) a monospecific bivalent antibody consisting of two full length antibody heavy chains and two full length antibody light chains, wherein each chain comprises only one variable domain,
   b) two monospecific monovalent single chain antibodies (scFv's), each consisting of an antibody heavy chain variable domain, an antibody light chain variable domain, and a single-chain-linker between said antibody heavy chain variable domain and said antibody light chain variable domain, and, optionally,
   c) peptide-linkers, connecting the C-termini of part (a) and the N-termini of part (b).

9. The antibody of claim 7, comprising
   a) a monospecific bivalent antibody consisting of two full length antibody heavy chains and two full length antibody light chains whereby each chain comprises only one variable domain,
   b) two variable two heavy chain single domain (VHH) antibodies, each consisting of one antibody variable domain, and, optionally,

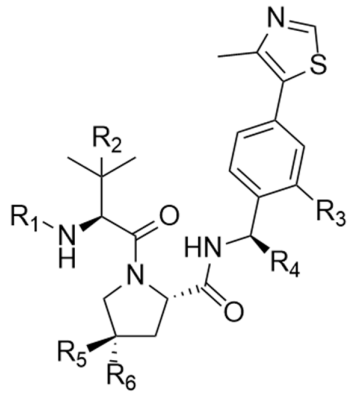
c) peptide-linkers, connecting the C-termini of part (a) and the N-termini of part (b).

10. The antibody of claim 9, wherein the N-termini of the two heavy chain single domain (VHH) antibodies of part (b) and the C-termini of the monospecific bivalent antibody of part (a) are connected via peptide linkers.

11. The antibody of any of claims 8 - 10, wherein the variable domains of part (a) are capable of binding the target protein, and the variable domains of part (b) are capable of binding the VHL ligand degron of the PROTAC.

12. The antibody of any of claims 8 - 10, wherein the variable domains of part (b) are capable of binding the target protein, and the variable domains of part (a) are capable of binding the degron of the PROTAC.

13. The antibody of claim 11 or 12, wherein the degron of the PROTAC is a VH032 derivative of Formula I:



(I)

wherein

one of R_1 or R_2 is a linker connected to a warhead, with the proviso that

if R_2 is the linker, R_1 is acetyl, and

if R_1 is the linker, R_2 is methyl;

R_3 is H, OH, cyano, F, Cl, amino or methyl;

R_4 is H or methyl;

R_5, R_6 are H or OH, with the proviso that

if R_6 is H, R_5 is OH, and

if R_5 is H, R_6 is OH.

14. The antibody of claim 13, wherein

R_1 is PB-Q-$(CH_2$-CH_2-$O)_n$-$(CH_2$-CH_2-CH_2-$O)_m$-$(CH_2)_p$-(C=O)-,

wherein

PB is a protein binding warhead,

Q is NH, C=O, or absent,

n, m are, independently, 0, 1, 2, 3 or 4,

p is 0 - 10;

R_2 is methyl;

and R_3, R_4, R_5, and R_6 are as described in claim 13.

15. The antibody of claim 14, wherein

R_1 is PB-Q-$(CH_2$-CH_2-$O)_n$-$(CH_2$-CH_2-CH_2-$O)_m$-$(CH_2)_p$-(C=O)-,

wherein

PB is a protein binding warhead;

Q is NH, C=O, or absent;

(i) n, m, p are 1; or

(ii) n is 3 or 4, m is 0, p is 1; or

(iii) n is 1, m is 0, p is 2; or

(iv) n is 2, m is 0, p is 2; or

(v) n, m are 0, p is 6, 7, 8, 9 or 10;

R_2 is methyl;

and R_3, R_4, R_5, and R_6 are as described in claim 13.

16. The antibody of claim 13, wherein

R_1 is acetyl;

R_2 is PB-NH-$(CH_2)_p$-S-, wherein PB is a protein binding warhead,

and p is 1, 2, 3, 4, 5, or 6;

and R_3, R_4, R_5, and R_6 are as described in claim 13.

17. The antibody of claim 13, wherein the PROTAC is chosen from the PROTACs shown in Figure 8 (a) and 8 (b).

18. The antibody of any of claims 1, 3-17, wherein the target protein is a cell surface protein.

19. The antibody of claim 18, wherein the cell surface protein is a tumor antigen.

20. The antibody of claim 19, wherein the cell surface protein is Her2, CD33, CLL1, TROP2, NAPI2B, B7H3 or EGFR.

21. The antibody of any of claims 1-20, wherein the variable domains capable of binding the degron of the PROTAC are those of a full-length antibody, and comprise the following CDR sequences:
HC CDR1: G Y S X_1 T X_2 X_3 Y (SEQ ID NO: 1);
HC CDR2: I T Y S G X_4 T (SEQ ID NO: 2);
HC CDR3: X_5 X_6 Y X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} (SEQ ID NO: 3);
LC CDR1: Q X_{16} X_{17} X_{18} X_{19} X_{20} X_{21} X_{22} X_{23} X_{24} Y (SEQ ID NO: 4);
LC CDR2: X_{25} X_{26} X_{27} (SEQ ID NO: 5);
LC CDR3: X_{28} Q X_{29} X_{30} X_{31} X_{32} P Y T (SEQ ID NO: 6);
wherein: X_1 is I or A; X_2 is G or N; X_3 is D or N; X_4 is G or A; X_5 is A or G; X_6 is K or Y; X_7 is G or Y; X_8 is absent or A; X_9 is absent or V; X_{10} is absent or P; X_{11} is D or Y; X_{12} is G or Y; X_{13} is G or F; X_{14} is R or A; X_{15} is D or H; X_{16} is S or G; X_{17} is L or I; X_{18} is S or absent; X_{19} is Y or absent; X_{20} is S or absent; X_{21} is D or absent, X_{22} is G or absent; X_{23} is N or G; X_{24} is T or N; X_{25} is L or Y; X_{26} is V or A; X_{27} is S or T, X_{28} is V or L; X_{29} is S or Y; X_{30} is I or D; X_{31} is H or E; and X_{32} is V or Y.

22. The antibody of any of claims 1-20, wherein the variable domains capable of binding the degron of the PROTAC are those of a VHH antibody, and comprise the following CDR sequences:
CDR1: G X_1 X_2 X_3 X_4 X_5 X_6 X_7 (SEQ ID NO: 17);
CDR2: X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} (SEQ ID NO: 18);
CDR3: X_{16} X_{17} X_{18} X_{19} X_{20} X_{21} X_{22} X_{23} X_{24} X_{25} X_{26} X_{27} X_{28} X_{29} X_{30} X_{31} X_{32} X_{33} X_{34} X_{35} X_{36} (SEQ ID NO: 19);
wherein: X_1 is F or R; X_2 is T, A, S or R; X_3 is L or F; X_4 is D or N; X_5 is D or T; X_6 is Y or L; X7 is A or T; X_8 is I, N or L; X_9 is S or T; X_{10} is S or W; X_{11} is S or N; X_{12} is D or G; X_{13} is G or D; X_{14} is S or N; X_{15} is A, or T; X_{16} is A, S or T; X_{17} is A, V or I; X_{18} is S, A, I or D; X_{19} is T, Y, R or A; X_{20} is R, Y or G; X_{21} is V, S, L or T; X_{22} is L, G, S or C; X_{23} is S, A, C or P; X_{24} is T, A, S or N; X_{25} is P, I, V or D; X_{26} is absent, V or A; X_{27} is D, S, R, or absent; X_{28} is V, G or P; X_{29} is D, T, G or R; X_{30} is Q, I, T or R; X_{31} is V, K or R; X_{32} is R, I or Y; X_{33} is Y, Q, F or A; X_{34} is V or L; X_{35} is E, P or D; X_{36} V, Y or A.

23. The antibody of claim 22, wherein
X_1 is F; X_2 is T or S; X_3 is L or F; X_4 is D; X_5 is D; X_6 is Y; X_7 is AT; X_8 is I; X_9 is S or T; X_{10} is S; X_{11} is S; X_{12} is D; X_{13} is G; X_{14} is S; X_{15} is A, or T; X_{16} is A or S; X_{17} is V or

A; X_{18} is A or I; X_{19} is T or Y; X_{20} is G or R; X_{21} is L or S; X_{22} is C or S; X_{23} is P or C; X_{24} is A or S; X_{25} is V or D; X_{26} is absent or V; X_{27} is R, or absent; X_{28} is G or P; X_{29} is T or G; X_{30} is Q, or I; X_{31} is K or R; X_{32} is R, I or Y; X_{33} is F or A; X_{34} is L; X_{35} is E,or D; X_{36} V or Y.

24. The antibody of claim 23, wherein
CDR1 is GFSFDDYA (SEQ ID NO: 21)
CDR2 is ISSSDGST (SEQ ID NO: 22)
CDR3 is SAIYRLSCSVVRPTIRYALDY (SEQ ID NO: 23).

25. The antibody of claim 23, wherein
CDR1 is GFTFDDYA (SEQ ID NO: 25)
CDR2 is ISSSDGSA (SEQ ID NO: 26)
CDR3 is AVATGSCPADGGQKIFLEV (SEQ ID NO: 27).

26. In vitro use of a mono-specific antibody of any preceding claim for detecting, quantifying or purifying a PROTAC.

27. A complex (PAX) of a bi-specific antibody of any of claims 1, 3-25 and a PROTAC, wherein the bi-specific antibody binds to the degron of the PROTAC.

28. The complex (PAX) of claim 26, wherein the degron and the linker of the PROTAC are as described in any of claims 13-17.

29. Pharmaceutical composition, comprising the complex of claims 27 or 28, and one or more further pharmaceutically acceptable ingredients.

30. Use of the complex of claims 27 or 28 to deliver a PROTAC to a target cell, which expresses the degradation target protein.

31. Use of the complex of claims 27 or 28 in the manufacture of a medicament for treating a disease, wherein said medicament is to be administered to a patient in need thereof, and wherein the disease benefits from the degradation of the degradation target protein of the PROTAC.

32. The complex (PAX) of claims 27 or 28 for use in treating a disease which benefits from the degradation of the degradation target protein of the PROTAC.

33. The complex (PAX) of claims 27 or 28 for use in treating a disease which benefits from the degradation of the degradation target protein of the PROTAC, wherein the PAX, is to be administered first, followed by a subsequent administration of the PROTAC component of the PAX alone.

34. The complex (PAX) of claims 27 or 28 for use in treating a disease which benefits from the degradation of the degradation target protein of the PROTAC, wherein the antibody component of the PAX, is to be administered first, and the PROTAC component of the PAX, is to be administered subsequently.