

Claims

1. An isolated protein comprising a tenth fibronectin type III (¹⁰F_n3) domain that specifically binds to Proprotein Convertase Subtilisin Kexin type 9 (PCSK9), wherein
 - (i) the amino acid of the ¹⁰F_n3 domain corresponding to position 94 of the wild-type ¹⁰F_n3 domain set forth in SEQ ID NO: 1 is directly linked to a moiety consisting of the amino acid sequence PmX_n, wherein P is proline, X is any amino acid, m is an integer that is at least 1 and n is 0 or an integer that is at least 1, and
 - (ii) the PmX_n moiety provides enhanced stability to the protein relative to the protein that is not linked to the PmX_n moiety.
2. The isolated protein of claim 1, wherein the moiety linked to the ¹⁰F_n3 domain consists of P (m is 1 and n is 0).
3. The isolated protein of claim 1, wherein the moiety linked to the ¹⁰F_n3 domain consists of PP (m is 2 and n is 0).
4. The isolated protein of claim 1, wherein the moiety linked to the ¹⁰F_n3 domain consists of PmX_n, wherein n is 1-150.
5. The isolated protein of claim 1, wherein the moiety linked to the ¹⁰F_n3 domain consists of PmX_n, wherein n is 1-10.
6. The isolated protein of claim 1, wherein the moiety linked to the ¹⁰F_n3 domain consists of PmX_n, wherein n is 1-5.
7. The isolated protein of claim 1, wherein the moiety linked to the ¹⁰F_n3 domain consists of PI, PC, PID, PIE, PIDK (SEQ ID NO: 61), PIEK (SEQ ID NO: 63), PIDKP (SEQ ID NO: 65), PIEKP (SEQ ID NO: 67), PIDKPS (SEQ ID NO: 69), PIEKPS (SEQ ID NO: 71), PIDKPC (SEQ ID NO: 73), PIEKPC (SEQ ID NO: 75), PIDKPSQ (SEQ ID NO: 77), PIEKPSQ (SEQ ID NO: 79), PIDKPCQ (SEQ ID NO: 81), PIEKPCQ (SEQ ID NO: 83), PHHHHHH (SEQ ID NO: 87) or PCHHHHHH (SEQ ID NO: 86).

8. The isolated protein of any one of claims 1-7, wherein the ¹⁰F_n3 domain binds specifically to Proprotein Convertase Subtilisin Kexin type 9 (PCSK9) with a K_d of less than 500 nM.
9. The isolated protein of any one of claims 1-8, wherein the ¹⁰F_n3 domain comprises the amino acid sequence set forth in SEQ ID NO: 96 or SEQ ID NO: 99, wherein the amino acids following the threonine corresponding to position 94 of the wild-type ¹⁰F_n3 domain (SEQ ID NO: 1) have been replaced by the PmX_n moiety.
10. The isolated protein of any one of claims 1-8, wherein the ¹⁰F_n3 domain comprises the amino acid sequence set forth in SEQ ID NO: 100.
11. The isolated protein of claim 9 or 10, wherein the N-terminal methionine (M) residue is removed.
12. The isolated protein of any of claims 1-11, wherein at least one X of PmX_n moiety linked to the ¹⁰F_n3 domain is a cysteine.
13. The isolated protein of claim 12, wherein the PmX_n moiety is PmCX_n or PmX_n₁CX_n₂, wherein C is cysteine and n₁ and n₂ are independently 0 or an integer that is at least 1.
14. The isolated protein of claim 13, wherein the cysteine in the PmX_n moiety is conjugated to a heterologous molecule.
15. The isolated protein of claim 14, wherein the heterologous molecule is a PKE moiety selected from human serum albumin, a protein that binds to human serum albumin, an Fc or PEG.
16. The isolated protein of claim 14, wherein the heterologous molecule is a detectable moiety.

17. The isolated protein of claim 14, wherein the heterologous molecule is a drug moiety and the drug moiety and the protein form a protein-drug conjugate.
18. The isolated protein of any one of claims 1-17, wherein enhanced stability is an increase in T_m of at least 1°C, 2°C, 3°C, 4°C, 5°C or more.