We Claim

1. An isolated Fn14-binding protein comprising an antigen binding domain, wherein the antigen binding domain binds specifically to Fn14 and wherein, when the protein is an antibody it reduces Tweak-induced NFκB-signaling in a cell expressing Fn14, and ~~wherein the protein~~ does not detectably induce NFκB-signaling when contacted to a cell expressing Fn14 in the absence of Tweak.

2. An isolated Fn14-binding protein comprising an antigen binding domain of an anti-Fn14 antibody, wherein the antigen binding domain binds specifically to Fn14 and wherein when the protein is an antibody it reduces Tweak-induced NFκB-signaling in a cell expressing Fn14, and ~~wherein the protein~~ does not detectably induce NFκB-signaling when contacted to a cell expressing Fn14 in the absence of Tweak.

3. The Fn14-binding protein of claim 1 or 2, ~~which~~ wherein the Fn14-binding protein:

(i) binds specifically to an epitope in Fn14 comprising residues contained within the sequence set forth in SEQ ID NO: 34;~~.~~

~~4. The Fn14-binding protein of any one of claims 1 to 3, which has one or more of the following characteristics:~~

~~(i)~~(ii) does not detectably bind to a polypeptide comprising a region of Fn14, the region consisting of a sequence set forth in SEQ ID NO: 31 or 44;

~~(ii)~~(iii) binds to an extracellular domain of Fn14 comprising a proline or alanine substituted for the arginine at position 56 of SEQ ID NO: 1 at a similar or substantially the same level as it binds to an extracellular domain of Fn14;

~~(iii)~~(iv) protein binds to an extracellular domain of Fn14 comprising an alanine substituted for the arginine at position 58 of SEQ ID NO: 1 at a similar or substantially the same level as it binds to an extracellular domain of Fn14;

(~~iv~~) binds to an extracellular domain of Fn14 comprising an alanine substituted for the histidine at position 60 of SEQ ID NO: 1 at a similar or substantially the same level as it binds to an extracellular domain of Fn14;

(vi) binds to a peptide consisting of the sequence set forth in SEQ ID NO: 48 (optionally with an additional six histidine residues at a terminus) at a similar or substantially the same level as it binds to an extracellular domain of Fn14;

(vii) binds to an extracellular domain of Fn14 comprising an alanine substituted for the tryptophan at position 42 of SEQ ID NO: 1 at a similar or substantially the same level as it binds to an extracellular domain of Fn14;

(viii) binds to an extracellular domain of Fn14 comprising one of the following amino acid substitutions (numbering relative to SEQ ID NO: 1) T33N, A34S, R38S, R56P, L77M, R56A, R56K, R58A, W42A, , L46A, D51A, S54A, A57G, P59A, H60A, S61A, D62A, F63A, L65A or H60K. In one example, the level of binding is similar or substantially the same level as the Fn14-binding protein binds to an extracellular domain of Fn14; ~~and/or~~

~~(viii)~~(ix) binds to a peptide consisting of a sequence set forth in SEQ ID NO: 35 in an amount within 75% of the amount of bound by an antibody comprising a V_H comprising a sequence set forth in SEQ ID NO: 19 and a V_L comprising a sequence set forth in SEQ ID NO: 26 when measured by enzyme linked immunosorbent assay and the Fn14-binding protein is assayed at a concentration of about 2μg/ml; and/or~~.~~

~~5.~~(x) ~~The Fn14-binding protein of any one of claims 1 to 4, which~~ binds to a conformational epitope in Fn14; and/or~~.~~

(xi) ~~6. The Fn14-binding protein of any one of claims 1 to 5, which~~ does not detectably bind to a polypeptide comprising an extracellular domain of Fn14 fused to an Fc region of an antibody, wherein the polypeptide is reduced or reduced and alkylated.

~~7~~4. The Fn14-binding protein of any one of claims 1 to ~~9~~3, which competitively inhibits binding of any one of the following antibodies to Fn14 and/or a polypeptide comprising a sequence set forth in SEQ ID NO: 2 or 34 or which binds to the same epitope in Fn14 as any one or more of the following antibodies:

(i) an antibody comprising a heavy chain variable region (V_H) comprising a sequence set forth in SEQ ID NO: 15 and a light chain variable region (V_L) comprising a sequence set forth in SEQ ID NO: 22;

(ii) an antibody comprising a V_H comprising a sequence set forth in SEQ ID NO: 16 and a V_L comprising a sequence set forth in SEQ ID NO: 23;

(iii) an antibody comprising a V_H comprising a sequence set forth in SEQ ID NO: 17 and a V_L comprising a sequence set forth in SEQ ID NO: 24;

(iv) an antibody comprising a V_H comprising a sequence set forth in SEQ ID NO: 18 and a V_L comprising a sequence set forth in SEQ ID NO: 25;

(v) an antibody comprising a V_H comprising a sequence set forth in SEQ ID NO: 19 and a V_L comprising a sequence set forth in SEQ ID NO: 26;

(vi) an antibody comprising a V_H comprising a sequence set forth in SEQ ID NO: 20 and a V_L comprising a sequence set forth in SEQ ID NO: 27;and

(vii) an antibody comprising a V_H comprising a sequence set forth in SEQ ID NO: 21 and a V_L comprising a sequence set forth in SEQ ID NO: 28.

~~8~~5. The Fn14-binding protein of any one of claims 1 to ~~7~~4, wherein the antigen binding domain comprises:

(i) a heavy chain variable region (V_H) comprising a sequence set forth in any one of SEQ ID NOs: 13 or 15 to 21 or a humanized, chimeric, synhumanized or deimmunized version thereof or an affinity matured form of any of the foregoing; and/or

(ii) a light chain variable region (V_L) comprising a sequence set forth in any one of SEQ ID NOs: 14 or 22 to 28 or a humanized, chimeric, synhumanized or deimmunized version thereof or an affinity matured form of any of the foregoing.

~~9~~6. The Fn14-binding protein of any one of claims 1 to ~~13~~5 comprising at least a heavy chain variable region (V_H) and a light chain variable region (V_L), wherein the V_H and V_L bind to form a Fv comprising the antigen binding domain, and wherein the Fv comprises any one of the following:

(i) a V_H comprising CDRs 1, 2, and 3 of a V_H comprising a sequence set forth in SEQ ID NO: 15 and a V_L comprising CDRs 1, 2, and 3 of a V_L comprising a sequence set forth in SEQ ID NO: 22;

(ii) a V_H comprising CDRs 1, 2, and 3 of a V_H comprising a sequence set forth in SEQ ID NO: 16 and a V_L comprising CDRs 1, 2, and 3 of a V_L comprising a sequence set forth in SEQ ID NO: 23;

(iii) a V_H comprising CDRs 1, 2, and 3 of a V_H comprising a sequence set forth in SEQ ID NO: 17 and a V_L comprising CDRs 1, 2, and 3 of a V_L comprising a sequence set forth in SEQ ID NO: 24;

(iv) a V_H comprising CDRs 1, 2, and 3 of a V_H comprising a sequence set forth in SEQ ID NO: 18 and a V_L comprising CDRs 1, 2, and 3 of a V_L comprising a sequence set forth in SEQ ID NO: 25;

(v) a V_H comprising CDRs 1, 2, and 3 of a V_H comprising a sequence set forth in SEQ ID NO: 19 and a V_L comprising CDRs 1, 2, and 3 of a V_L comprising a sequence set forth in SEQ ID NO: 25;

(vi) a V_H comprising CDRs 1, 2, and 3 of a V_H comprising a sequence set forth in SEQ ID NO: 20 and a V_L comprising CDRs 1, 2, and 3 of a V_L comprising a sequence set forth in SEQ ID NO: 25; and

(vii) a V_H comprising CDRs 1, 2, and 3 of a V_H comprising a sequence set forth in SEQ ID NO: 21 and a V_L comprising CDRs 1, 2, and 3 of a V_L comprising a sequence set forth in SEQ ID NO: 26.

~~107~~. The Fn14-binding protein of any one of claims ~~144~~ to ~~166~~, wherein the V_H and the V_L are in a single polypeptide chain and the Fn14-binding protein is:

(i) a single chain Fv fragment (scFv);

(ii) a dimeric scFv (di-scFv);

(iii) at least one of (i) and/or (ii) linked to a heavy chain constant region or an Fc or a heavy chain constant domain (C_H) 2 and/or C_H3; or

(iv) at least one of (i) and/or (ii) linked to a protein that binds to an immune effector cell; or

wherein the V_L and V_H are in separate polypeptide chains and the Fn14-binding protein is:

(i) a diabody;

(ii) a triabody;

(iii) a tetrabody;

(iv) a Fab;

(v) a $F(ab')_2$;

(vi) a Fv;

(vii) at least one of (i) to (vi) linked to a heavy chain constant region or an Fc or a heavy chain constant domain (C_H) 2 and/or C_H3;

(viii) at least one of (i) to (vi) linked to a protein that binds to an immune effector cell; or

(ix) an antibody.

~~118~~. The Fn14-binding protein of claim 1, wherein the Fn14-binding protein is selected from the group consisting of a non-antibody antigen binding domain, an adnectin, an affibody, an atrimer, an evasin, a designed ankyrin-repeat protein (DARPin) or an anticalin.

~~129~~. An isolated anti-Fn14 antibody, the antibody comprising any one of the following:

(i) a V_H comprising a sequence set forth in SEQ ID NO: 13 or a humanized, synhumanized or deimmunized version thereof or an affinity matured form of any of the foregoing and a V_L comprising a sequence set forth in SEQ ID NO: 14 or a humanized, synhumanized or deimmunized version thereof or an affinity matured form of any of the foregoing;

(ii) a V_H comprising a sequence set forth in SEQ ID NO: 15 or a humanized, synhumanized or deimmunized version thereof or an affinity matured form of any of the foregoing and a V_L comprising a sequence set forth in SEQ ID NO: 22 or a humanized, synhumanized or deimmunized version thereof or an affinity matured form of any of the foregoing;

(iii) a V_H comprising a sequence set forth in SEQ ID NO: 16 or a humanized, synhumanized or deimmunized version thereof or an affinity matured form of any of the foregoing and a V_L comprising a sequence set forth in SEQ ID NO: 23 or a humanized, synhumanized or deimmunized version thereof or an affinity matured form of any of the foregoing;

(iv) a V_H comprising a sequence set forth in SEQ ID NO: 17 or a humanized, synhumanized or deimmunized version thereof or an affinity matured form of any of the foregoing and a V_L comprising a sequence set forth in SEQ ID NO: 24 or a humanized, synhumanized or deimmunized version thereof or an affinity matured form of any of the foregoing;

(v) a V_H comprising a sequence set forth in SEQ ID NO: 18 or a humanized, synhumanized or deimmunized version thereof or an affinity matured form of any of the foregoing and a V_L comprising a sequence set forth in SEQ ID NO: 25 or a humanized, synhumanized or deimmunized version thereof or an affinity matured form of any of the foregoing;

(vi) a V_H comprising a sequence set forth in SEQ ID NO: 19 or a humanized, synhumanized or deimmunized version thereof or an affinity matured form of any of the foregoing and a V_L comprising a sequence set forth in SEQ ID NO: 26 or a humanized, synhumanized or deimmunized version thereof or an affinity matured form of any of the foregoing;

(vii) a V_H comprising a sequence set forth in SEQ ID NO: 20 or a humanized, synhumanized or deimmunized version thereof or an affinity matured form of any of the foregoing and a V_L comprising a sequence set forth in SEQ ID NO: 27 or a

humanized, synhumanized or deimmunized version thereof or an affinity matured form of any of the foregoing; or

(viii) a V_H comprising a sequence set forth in SEQ ID NO: 21 or a humanized, synhumanized or deimmunized version thereof or an affinity matured form of any of the foregoing and a V_L comprising a sequence set forth in SEQ ID NO: 28 or a humanized, synhumanized or deimmunized version thereof or an affinity matured form of any of the foregoing.

~~13~~10. A composition comprising the protein of any one of claims 1 to ~~11~~8 or the antibody of claim ~~12~~9 and a suitable carrier.

~~14~~11. Use of the protein of any one of claims 1 to 8 or the antibody of claim 9 or the composition of claim 10 in the manufacture of a medicament for ~~A method for~~ treating or preventing an Fn14-mediated condition in a subject~~, the method comprising administering the protein of any one of claims 1 to 11 or the antibody of claim 12 or the composition of claim 13 to the subject~~.

~~15~~12. The ~~method~~ use of claim ~~14~~11, wherein the Fn14-mediated condition is cancer, metastasis, excessive vascularization or angiogenesis, an autoimmune disease, an inflammatory disease, a neurodegenerative disease, a wasting disorder,a cardiovascular disease or ischemia.

~~16~~13. The ~~method~~ use of claim ~~15~~12, wherein the condition is cancer and the method reduces or prevents invasiveness of the cancer into tissue of a subject or reduces or prevents metastasis of the cancer.

~~17~~14. Use of the protein of any one of claims 1 to 8 or the antibody of claim 9 or the composition of claim 10 to the subject in the manufacture of a medicament for ~~A method of~~ treating or preventing a wasting disorder which is associated with a condition.~~, the method comprising administering to a subject an Fn14 binding protein comprising an antigen binding domain of an anti-Fn14 antibody~~.

~~18~~15. The ~~method~~ use of claim ~~17~~14, wherein the wasting disorder is cachexia.

~~19~~16. The ~~method~~ use of claim ~~18~~15, wherein the wasting disorder is cachexia associated with cancer or diabetes.

~~20~~17. The ~~method~~ use of claim ~~17~~16, wherein the condition is cancer cachexia and the method additionally comprises selecting a subject suffering from cancer cachexia, wherein the subject suffers from a cancer expressing Fn14.

~~21. The method of any one of claims 14 to 20, wherein the Fn14-binding protein is the Fn14-binding protein of any one of claims 1 to 11 or the antibody of claim 12 or the composition of claim 13.~~

~~22~~18. The ~~method~~ use of any one of claims 14 to ~~21~~17, wherein the Fn14-binding protein has one or more of the following ~~g~~characteristics:

(i) binds to recombinant human Fn14 with a K_D of 1nM or less;

(ii) binds to recombinant human Fn14 with a Kd of about $8x10^{-4}s^{-1}$ or less;

(iii) binds to an extracellular domain of Fn14 comprising a proline or alanine substituted for the arginine at position 56 of SEQ ID NO: 1 at a similar or substantially the same level as it binds to an extracellular domain of Fn14;

(iv) binds to an extracellular domain of Fn14 comprising an alanine substituted for the arginine at position 58 of SEQ ID NO: 1 at a similar or substantially the same level as it binds to an extracellular domain of Fn14; and/or

(v) binds to an extracellular domain of Fn14 comprising an alanine substituted for the histidine at position 60 of SEQ ID NO: 1 at a similar or substantially the same level as it binds to an extracellular domain of Fn14.

~~23~~19. The ~~method~~ use of any one of claims 14 to ~~22~~18, wherein the Fn14-binding protein is an antibody comprising one or more of the following:

(i) a V_H comprising a sequence set forth in SEQ ID NO: 15 or a humanized, synhumanized or deimmunized version thereof and a V_L comprising a sequence set forth in SEQ ID NO: 22 or a humanized, synhumanized or deimmunized version thereof; or

(ii) a V_H comprising a sequence set forth in SEQ ID NO: 16 or a humanized, synhumanized or deimmunized version thereof and a V_L comprising a sequence set forth in SEQ ID NO: 23 or a humanized, synhumanized or deimmunized version thereof.