

What is claimed is:

1. A composition comprising
 - a. an IL-12 protein comprising a first IL-12 subunit and a second IL-12 protein subunit;
 - b. a peptide or protein comprising an EDB binding domain; and
 - c. a linker between the IL-12 protein and the peptide or protein comprising the EDB binding domain.
2. The composition according to claim 1, wherein the linker between the IL-12 protein and the peptide or protein comprising the EDB binding domain comprises GSADGGSSAGGSDAG (SEQ ID NO: 4).
3. The composition according to claims 1 or 2, wherein the peptide or protein comprising the EDB binding domain comprises an scFv.
4. The composition according to claims 1 or 2, wherein the peptide or protein comprising the EDB binding domain is a diabody.
5. The composition according to claims 1 or 2, wherein the peptide or protein comprising the EDB binding domain is a single chain diabody.
6. The composition according to any one of claims 1 - 5, wherein the first subunit of the IL-12 protein is a p40 and the second subunit is a p35.
7. The composition according to claims 1 - 6, wherein the first subunit of the IL-12 protein is a p40 comprising an amino acid sequence having at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO:1 or a fragment thereof, wherein the IL-12 protein can activate an IL-12 receptor.
8. The composition according to claims 1 -7, wherein the second subunit of the IL-12 protein is a p35 comprising an amino acid sequence having at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid

sequence set forth in SEQ ID NO:3 or a fragment thereof, wherein the IL-12 protein can activate an IL-12 receptor.

9. The composition according to any one of claims 1 - 8, wherein the peptide or protein comprising an EDB binding domain is monospecific or bispecific.

10. The composition according to any one of claims 1 - 9, wherein the peptide or protein comprising an EDB binding domain binds to the extra-domain B (ED-B) of fibronectin

11. The composition according to any one of claims 1 - 10, wherein the peptide or protein comprising an EDB binding domain comprises an amino acid sequence having at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to one or more of the amino acid sequences set forth in SEQ ID NOs: 28 to 33.

12. The composition according to any one of claims 1 - 10, wherein the peptide or protein comprising an EDB binding domain comprises each of the amino acid sequences of SEQ ID NOs: 28 to 33.

13. The composition according to any one of claims 1 - 12, wherein the peptide or protein comprising an EDB binding domain comprises an amino acid sequence having at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to one or more of the amino acid sequences set forth in SEQ ID NOs: 7 and 5.

14. The composition according to any one of claims 1 - 13, wherein the peptide or protein comprising an EDB binding domain comprises each of the amino acid sequences set forth in SEQ ID NOs: 7 and 5.

15. The composition according to any one of claims 1 - 14, wherein the peptide or protein comprising an EDB binding domain comprises at least one of

a) the sequence pair of claim 14, with the proviso that at least one of the domains has a sequence identity of $\geq 80\%$ relative to SEQ ID NO: 7 or SEQ ID NO: 5, respectively and/or

b) the sequence pair of claim 14, with the proviso that at least one of the domains has up to 10 amino acid substitutions relative to SEQ ID NO: 7 or SEQ ID NO: 5, respectively,

while maintaining its capability to bind to the extra-domain B (ED-B) of fibronectin.

16. The composition according to claim 15, wherein at least one amino acid substitution is a conservative amino acid substitution.

17. The composition according to any one of claims 1 – 16, wherein the peptide or protein comprising an EDB binding domain

- has a target binding affinity of ≥ 50 % to the extra-domain B (ED-B) of fibronectin, compared to one of the peptides or proteins comprising an EDB binding domain of claims 11 - 16, and/or
- competes for binding to the extra-domain B (ED-B) of fibronectin with one of peptides or proteins comprising an EDB binding domain of claims 11 -16.

18. The composition according to any one of claims 1 - 17, wherein the peptide or protein comprising an EDB binding domain comprises two L19 VH domains and two L19 VL domains.

19. The composition according to claim 18, wherein:

- the two L19 VH domains have the same amino acid sequence;
- the two L19 VH domains have a different amino acid sequence;
- the two L19 VL domains have the same amino acid sequence; or
- the two L19 VL domains have a different amino acid sequence.

20. The composition according to any one of claims 1 - 17, wherein the peptide or protein comprising an EDB binding domain comprises one L19 VH domain and one L19 VL domain.

21. The composition according to any one of claims 1 - 17, wherein the composition comprises:

- a p40 domain linked to a p35 domain by a first linker;
- a first L19 VH domain linked to the p35 domain by a SAD linker;
- a first L19 VL domain linked to the first L19 VH domain by a third linker;
- a second L19 VH domain linked to the first L19 VL domain by a fourth linker;
- a second L19 VL domain linked to the second L19 VH domain by a fifth linker.

22. The composition according to claim 21, wherein the p40 domain comprises an amino acid sequence having at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO:1 or a fragment thereof.

23. The composition according to any one of claims 21 - 22, wherein the p35 domain comprises an amino acid sequence having at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO:3 or a fragment thereof.

24. The composition according to any one of claims 21 - 23, wherein the first linker is a GS linker.

25. The composition according to any one of claims 21 - 24, wherein the first linker comprises an amino acid sequence having at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 2.

26. The composition according to any one of claims 21 - 25, wherein the first L19 VH domain, the second L19 VH domain, or both comprise an amino acid sequence having at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to at least one amino acid sequence set forth in SEQ ID NOs: 28-30.

27. The composition according to any one of claims 21 - 26, wherein the first L19 VL domain, the second L19 VL domain, or both comprise an amino acid sequence having at least

75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to at least one amino acid sequence set forth in SEQ ID NOs: 31-33.

28. The composition according to any one of claims 21 - 27, wherein the first L19 VH domain, the second L19 VH domain, or both comprise an amino acid sequence having at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 7.

29. The composition according to any one of claims 21 - 27, wherein the first L19 VL domain, the second L19 VL domain, or both comprise an amino acid sequence having at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 5.

30. The composition according to any one of claims 21 - 29, wherein the SAD linker comprises an amino acid sequence having at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 4.

31. The composition according to any one of claims 21 - 30, wherein the third linker is a GS linker.

32. The composition according to any one of claims 21 - 31, wherein the third linker comprises an amino acid sequence having at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 6.

33. The composition according to any one of claims 21 - 32, wherein the fifth linker is a GS linker.

34. The composition according to any one of claims 21 - 33, wherein the third linker comprises an amino acid sequence having at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 6.

35. The composition according to any one of claims 21 - 34, wherein the third linker and fifth linker comprise the same amino acid sequence.

36. The composition according to any one of claims 21 - 35, wherein the fourth linker is a GS linker.

37. The composition according to any one of claims 21 - 36, wherein the fourth linker comprises an amino acid sequence having at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 8.

38. The composition according to any one of claims 1 - 37, wherein the composition comprises an amino acid sequence having at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 16.

39. The composition according to any one of claims 1 - 38, wherein the composition consists of an amino acid sequence having at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 16.

40. Use of the composition according to any one of claims 1 - 39 (for the manufacture of a medicament) in the treatment of a human or animal subject

- being diagnosed for,
- suffering from or
- being at risk of

developing a neoplastic disease, or for the prevention of such condition.

41. The use of claim 40, wherein the neoplastic disease is selected from the group consisting of malignant melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, urothelial carcinoma, head and neck squamous cell carcinoma (HNSCC), microsatellite

instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer, hepatocellular cancer, gastric cancer, squamous cell carcinoma of the skin, cervical cancer, and diffuse large B-cell lymphoma (DLBCL).

42. Use of the composition according to any one claims 1 - 39 (for the manufacture of a medicament) for the inhibition of angiogenesis in a human or animal subject.

43. A pharmaceutical composition comprising the composition according to any one of claims 1 – 39, and optionally one or more pharmaceutically acceptable excipients.

44. A combination comprising (i) the composition according to any one of claims 1 – 39 or the pharmaceutical composition according to claim 43 and (ii) one or more therapeutically active compounds.

45. A method for treating or preventing a disorder or condition associated with expression or overexpression of ED-B fibronectin, comprising administering to a subject in need thereof an effective amount of the composition according to any one of claims 1 – 39, the pharmaceutical composition according to claim 43, or the combination according to claim 44.

46. A therapeutic kit of parts comprising:

- a) the composition according to any one of claims 1 – 39, the pharmaceutical composition according to claim 43 or the combination according to claim 44,
- b) an apparatus for administering the composition, composition or combination, and
- c) instructions for use.