FAP BINDING MOLECULES AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of U.S. Provisional Patent Application No. 63/127885, filed December 18, 2020, and U.S. Provisional Patent Application No. 63/262706, filed October 19, 2021, each of which is hereby expressly incorporated by reference in its entirety.

REFERENCE TO SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled BWGB011_SeqListing.TXT, which was created and last modified on December 16, 2021, which is 187,259 bytes in size. The information in the electronic Sequence Listing is hereby incorporated by reference in its entirety.

FIELD

[0003] Aspects of the present disclosure relate generally to fibroblast activation protein (FAP)-specific binding polypeptides. These binding polypeptides can be incorporated into chimeric antigen receptor (CAR) constructs to be expressed in immune cells. These binding polypeptides and CARs may be used in the treatment of cancer.

BACKGROUND

[0004] Chimeric antigen receptor (CAR) T cells and other adoptive cell therapies have been shown to be effective in the treatment of cancer. The CAR, which is made up of an extracellular antigen binding domain, a transmembrane domain, and an intracellular signaling domain, enables directed killing of cancer cells based on cell surface antigen expression while minimally affecting normal cells that are not expressing the targeted antigen. The extracellular antigen binding domain is often made up of an antibody or a binding fragment or derivative thereof, such as a single chain variable fragment (scFv) or single domain antibody (sdAb). There is a present need for improved extracellular antigen binding domains to be used in CARs for the treatment of various cancers or other diseases.

SUMMARY OF THE DISCLOSURE

[0005] Disclosed herein are binding polypeptides that are able to bind to fibroblast activation protein (FAP). These binding polypeptides may be incorporated in a chimeric antigen receptor (CAR), which can be expressed by a cell. In some embodiments, the binding polypeptides are single domain antibodies (sdAbs).

[0006] Disclosed herein in some embodiments are FAP binding polypeptides comprising an immunoglobulin heavy chain variable domain comprising a CDR-H1, CDR-H2, and CDR-H3. In some embodiments, the CDR-H1 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 1-108**. In some embodiments, the CDR-H2 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 109-216**. In some embodiments, the CDR-H3 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 217-324**. In some embodiments, the CDR-H1 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 1-108**, the CDR-H2 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 109-216**, and the CDR-H3 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 217-324**. In some embodiments, the immunoglobulin heavy chain variable domain comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 325-432**.

[0006a] Disclosed herein is a fibroblast activation protein (FAP) binding polypeptide comprising an immunoglobulin heavy chain variable domain comprising a CDR-H1, CDR-H2, and CDR-H3, wherein: the CDR-H1 comprises a sequence having at least 90% sequence identity to a sequence of SEQ ID NO: 75; the CDR-H2 comprises a sequence having at least 90% sequence identity to a sequence of SEQ ID NO: 183; and the CDR-H3 comprises a sequence having at least 90% sequence identity to a sequence of SEQ ID NO: 291.

[0007] Also disclosed herein are nucleic acids that encode for any one of the FAP binding polypeptides disclosed herein.

[0008] Also disclosed herein are methods of treating a cancer in a subject in need thereof. In some embodiments, the methods comprise administering a chimeric antigen receptor cell to the subject. In some embodiments, the chimeric antigen receptor cell is any one of the chimeric antigen receptor cells disclosed herein. In some embodiments, the chimeric antigen receptor cell comprises any one or more of the FAP binding polypeptides disclosed herein.

[0008a] Disclosed herein is a CAR cell as defined herein for use in treating a cancer in a subject in need thereof.

[0008b] Disclosed herein is the use of a CAR cell as disclosed herein in the manufacture of a medicament for treating cancer in a subject in need thereof.

[0009] Embodiments of the present invention provided herein are described by way of the following numbered alternatives:

[0010] 1. A fibroblast activation protein (FAP) binding polypeptide comprising an immunoglobulin heavy chain variable domain comprising a CDR-H1, CDR-H2, and CDR-H3, wherein:

the CDR-H1 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 1-108**;

the CDR-H2 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 109-216**; and

the CDR-H3 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 217-324**.

[0011] 2. The FAP binding polypeptide of alternative 1, wherein:

1) the CDR-H1 comprises the sequence of **SEQ ID NO: 1**, the CDR-H2 comprises the sequence of **SEQ ID NO: 109**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 217**;

2) the CDR-H1 comprises the sequence of **SEQ ID NO: 2**, the CDR-H2 comprises the sequence of **SEQ ID NO: 110**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 218**;

3) the CDR-H1 comprises the sequence of **SEQ ID NO: 3**, the CDR-H2 comprises the sequence of **SEQ ID NO: 111**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 219**;

4) the CDR-H1 comprises the sequence of **SEQ ID NO: 4**, the CDR-H2 comprises the sequence of **SEQ ID NO: 112**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 220**;

5) the CDR-H1 comprises the sequence of **SEQ ID NO: 5**, the CDR-H2 comprises the sequence of **SEQ ID NO: 113**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 221**;

6) the CDR-H1 comprises the sequence of **SEQ ID NO: 6**, the CDR-H2 comprises the sequence of **SEQ ID NO: 114**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 222**;

7) the CDR-H1 comprises the sequence of **SEQ ID NO: 7**, the CDR-H2 comprises the sequence of **SEQ ID NO: 115**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 223**;

8) the CDR-H1 comprises the sequence of **SEQ ID NO: 8**, the CDR-H2 comprises the sequence of **SEQ ID NO: 116**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 224**;

9) the CDR-H1 comprises the sequence of **SEQ ID NO: 9**, the CDR-H2 comprises the sequence of **SEQ ID NO: 117**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 225**;

10) the CDR-H1 comprises the sequence of **SEQ ID NO: 10**, the CDR-H2 comprises the sequence of **SEQ ID NO: 118**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 226**;

11) the CDR-H1 comprises the sequence of **SEQ ID NO: 11**, the CDR-H2 comprises the sequence of **SEQ ID NO: 119**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 227**;

12) the CDR-H1 comprises the sequence of **SEQ ID NO: 12**, the CDR-H2 comprises the sequence of **SEQ ID NO: 120**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 228**;

13) the CDR-H1 comprises the sequence of **SEQ ID NO: 13**, the CDR-H2 comprises the sequence of **SEQ ID NO: 121**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 229**;

14) the CDR-H1 comprises the sequence of **SEQ ID NO: 14**, the CDR-H2 comprises the sequence of **SEQ ID NO: 122**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 230**;

15) the CDR-H1 comprises the sequence of **SEQ ID NO: 15**, the CDR-H2 comprises the sequence of **SEQ ID NO: 123**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 231**;

16) the CDR-H1 comprises the sequence of **SEQ ID NO: 16**, the CDR-H2 comprises the sequence of **SEQ ID NO: 124**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 232**;

17) the CDR-H1 comprises the sequence of **SEQ ID NO: 17**, the CDR-H2 comprises the sequence of **SEQ ID NO: 125**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 233**;

18) the CDR-H1 comprises the sequence of **SEQ ID NO: 18**, the CDR-H2 comprises the sequence of **SEQ ID NO: 126**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 234**;

19) the CDR-H1 comprises the sequence of **SEQ ID NO: 19**, the CDR-H2 comprises the sequence of **SEQ ID NO: 127**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 235**;

20) the CDR-H1 comprises the sequence of **SEQ ID NO: 20**, the CDR-H2 comprises the sequence of **SEQ ID NO: 128**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 236**;

21) the CDR-H1 comprises the sequence of **SEQ ID NO: 21**, the CDR-H2 comprises the sequence of **SEQ ID NO: 129**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 237**;

22) the CDR-H1 comprises the sequence of **SEQ ID NO: 22**, the CDR-H2 comprises the sequence of **SEQ ID NO: 130**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 238**;

23) the CDR-H1 comprises the sequence of **SEQ ID NO: 23**, the CDR-H2 comprises the sequence of **SEQ ID NO: 131**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 239**;

24) the CDR-H1 comprises the sequence of **SEQ ID NO: 24**, the CDR-H2 comprises the sequence of **SEQ ID NO: 132**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 240**;

25) the CDR-H1 comprises the sequence of **SEQ ID NO: 25**, the CDR-H2 comprises the sequence of **SEQ ID NO: 133**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 241**;

26) the CDR-H1 comprises the sequence of **SEQ ID NO: 26**, the CDR-H2 comprises the sequence of **SEQ ID NO: 134**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 242**;

27) the CDR-H1 comprises the sequence of **SEQ ID NO: 27**, the CDR-H2 comprises the sequence of **SEQ ID NO: 135**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 243**;

28) the CDR-H1 comprises the sequence of **SEQ ID NO: 28**, the CDR-H2 comprises the sequence of **SEQ ID NO: 136**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 244**;

29) the CDR-H1 comprises the sequence of **SEQ ID NO: 29**, the CDR-H2 comprises the sequence of **SEQ ID NO: 137**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 245**;

30) the CDR-H1 comprises the sequence of **SEQ ID NO: 30**, the CDR-H2 comprises the sequence of **SEQ ID NO: 138**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 246**;

31) the CDR-H1 comprises the sequence of **SEQ ID NO: 31**, the CDR-H2 comprises the sequence of **SEQ ID NO: 139**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 247**;

32) the CDR-H1 comprises the sequence of **SEQ ID NO: 32**, the CDR-H2 comprises the sequence of **SEQ ID NO: 140**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 248**;

33) the CDR-H1 comprises the sequence of **SEQ ID NO: 33**, the CDR-H2 comprises the sequence of **SEQ ID NO: 141**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 249**;

34) the CDR-H1 comprises the sequence of **SEQ ID NO: 34**, the CDR-H2 comprises the sequence of **SEQ ID NO: 142**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 250**;

35) the CDR-H1 comprises the sequence of **SEQ ID NO: 35**, the CDR-H2 comprises the sequence of **SEQ ID NO: 143**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 251**;

36) the CDR-H1 comprises the sequence of **SEQ ID NO: 36**, the CDR-H2 comprises the sequence of **SEQ ID NO: 144**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 252**;

37) the CDR-H1 comprises the sequence of **SEQ ID NO: 37**, the CDR-H2 comprises the sequence of **SEQ ID NO: 145**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 253**;

38) the CDR-H1 comprises the sequence of **SEQ ID NO: 38**, the CDR-H2 comprises the sequence of **SEQ ID NO: 146**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 254**;

39) the CDR-H1 comprises the sequence of **SEQ ID NO: 39**, the CDR-H2 comprises the sequence of **SEQ ID NO: 147**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 255**;

40) the CDR-H1 comprises the sequence of **SEQ ID NO: 40**, the CDR-H2 comprises the sequence of **SEQ ID NO: 148**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 256**;

41) the CDR-H1 comprises the sequence of **SEQ ID NO: 41**, the CDR-H2 comprises the sequence of **SEQ ID NO: 149**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 257**;

42) the CDR-H1 comprises the sequence of **SEQ ID NO: 42**, the CDR-H2 comprises the sequence of **SEQ ID NO: 150**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 258**;

43) the CDR-H1 comprises the sequence of **SEQ ID NO: 43**, the CDR-H2 comprises the sequence of **SEQ ID NO: 151**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 259**;

44) the CDR-H1 comprises the sequence of **SEQ ID NO: 44**, the CDR-H2 comprises the sequence of **SEQ ID NO: 152**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 260**;

45) the CDR-H1 comprises the sequence of **SEQ ID NO: 45**, the CDR-H2 comprises the sequence of **SEQ ID NO: 153**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 261**;

46) the CDR-H1 comprises the sequence of **SEQ ID NO: 46**, the CDR-H2 comprises the sequence of **SEQ ID NO: 154**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 262**;

47) the CDR-H1 comprises the sequence of **SEQ ID NO: 47**, the CDR-H2 comprises the sequence of **SEQ ID NO: 155**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 263**;

48) the CDR-H1 comprises the sequence of **SEQ ID NO: 48**, the CDR-H2 comprises the sequence of **SEQ ID NO: 156**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 264**;

49) the CDR-H1 comprises the sequence of **SEQ ID NO: 49**, the CDR-H2 comprises the sequence of **SEQ ID NO: 157**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 265**;

50) the CDR-H1 comprises the sequence of **SEQ ID NO: 50**, the CDR-H2 comprises the sequence of **SEQ ID NO: 158**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 266**;

51) the CDR-H1 comprises the sequence of **SEQ ID NO: 51**, the CDR-H2 comprises the sequence of **SEQ ID NO: 159**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 267**;

52) the CDR-H1 comprises the sequence of **SEQ ID NO: 52**, the CDR-H2 comprises the sequence of **SEQ ID NO: 160**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 268**;

53) the CDR-H1 comprises the sequence of **SEQ ID NO: 53**, the CDR-H2 comprises the sequence of **SEQ ID NO: 161**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 269**;

54) the CDR-H1 comprises the sequence of **SEQ ID NO: 54**, the CDR-H2 comprises the sequence of **SEQ ID NO: 162**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 270**;

55) the CDR-H1 comprises the sequence of **SEQ ID NO: 55**, the CDR-H2 comprises the sequence of **SEQ ID NO: 163**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 271**;

56) the CDR-H1 comprises the sequence of **SEQ ID NO: 56**, the CDR-H2 comprises the sequence of **SEQ ID NO: 164**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 272**;

57) the CDR-H1 comprises the sequence of **SEQ ID NO: 57**, the CDR-H2 comprises the sequence of **SEQ ID NO: 165**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 273**;

58) the CDR-H1 comprises the sequence of **SEQ ID NO: 58**, the CDR-H2 comprises the sequence of **SEQ ID NO: 166**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 274**;

59) the CDR-H1 comprises the sequence of **SEQ ID NO: 59**, the CDR-H2 comprises the sequence of **SEQ ID NO: 167**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 275**;

60) the CDR-H1 comprises the sequence of **SEQ ID NO: 60**, the CDR-H2 comprises the sequence of **SEQ ID NO: 168**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 276**;

61) the CDR-H1 comprises the sequence of **SEQ ID NO: 61**, the CDR-H2 comprises the sequence of **SEQ ID NO: 169**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 277**;

62) the CDR-H1 comprises the sequence of **SEQ ID NO: 62**, the CDR-H2 comprises the sequence of **SEQ ID NO: 170**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 278**;

63) the CDR-H1 comprises the sequence of **SEQ ID NO: 63**, the CDR-H2 comprises the sequence of **SEQ ID NO: 171**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 279**;

64) the CDR-H1 comprises the sequence of **SEQ ID NO: 64**, the CDR-H2 comprises the sequence of **SEQ ID NO: 172**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 280**;

65) the CDR-H1 comprises the sequence of **SEQ ID NO: 65**, the CDR-H2 comprises the sequence of **SEQ ID NO: 173**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 281**;

66) the CDR-H1 comprises the sequence of **SEQ ID NO: 66**, the CDR-H2 comprises the sequence of **SEQ ID NO: 174**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 282**;

67) the CDR-H1 comprises the sequence of **SEQ ID NO: 67**, the CDR-H2 comprises the sequence of **SEQ ID NO: 175**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 283**;

68) the CDR-H1 comprises the sequence of **SEQ ID NO: 68**, the CDR-H2 comprises the sequence of **SEQ ID NO: 176**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 284**;

69) the CDR-H1 comprises the sequence of **SEQ ID NO: 69**, the CDR-H2 comprises the sequence of **SEQ ID NO: 177**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 285**;

70) the CDR-H1 comprises the sequence of **SEQ ID NO: 70**, the CDR-H2 comprises the sequence of **SEQ ID NO: 178**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 286**;

71) the CDR-H1 comprises the sequence of **SEQ ID NO: 71**, the CDR-H2 comprises the sequence of **SEQ ID NO: 179**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 287**;

72) the CDR-H1 comprises the sequence of **SEQ ID NO: 72**, the CDR-H2 comprises the sequence of **SEQ ID NO: 180**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 288**;

73) the CDR-H1 comprises the sequence of **SEQ ID NO: 73**, the CDR-H2 comprises the sequence of **SEQ ID NO: 181**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 289**;

74) the CDR-H1 comprises the sequence of **SEQ ID NO: 74**, the CDR-H2 comprises the sequence of **SEQ ID NO: 182**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 290**;

75) the CDR-H1 comprises the sequence of **SEQ ID NO: 75**, the CDR-H2 comprises the sequence of **SEQ ID NO: 183**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 291**;

76) the CDR-H1 comprises the sequence of **SEQ ID NO: 76**, the CDR-H2 comprises the sequence of **SEQ ID NO: 184**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 292**;

77) the CDR-H1 comprises the sequence of **SEQ ID NO: 77**, the CDR-H2 comprises the sequence of **SEQ ID NO: 185**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 293**;

78) the CDR-H1 comprises the sequence of **SEQ ID NO: 78**, the CDR-H2 comprises the sequence of **SEQ ID NO: 186**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 294**;

79) the CDR-H1 comprises the sequence of **SEQ ID NO: 79**, the CDR-H2 comprises the sequence of **SEQ ID NO: 187**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 295**;

80) the CDR-H1 comprises the sequence of **SEQ ID NO: 80**, the CDR-H2 comprises the sequence of **SEQ ID NO: 188**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 296**;

81) the CDR-H1 comprises the sequence of **SEQ ID NO: 81**, the CDR-H2 comprises the sequence of **SEQ ID NO: 189**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 297**;

82) the CDR-H1 comprises the sequence of **SEQ ID NO: 82**, the CDR-H2 comprises the sequence of **SEQ ID NO: 190**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 298**;

83) the CDR-H1 comprises the sequence of **SEQ ID NO: 83**, the CDR-H2 comprises the sequence of **SEQ ID NO: 191**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 299**;

84) the CDR-H1 comprises the sequence of **SEQ ID NO: 84**, the CDR-H2 comprises the sequence of **SEQ ID NO: 192**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 300**;

85) the CDR-H1 comprises the sequence of **SEQ ID NO: 85**, the CDR-H2 comprises the sequence of **SEQ ID NO: 193**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 301**;

86) the CDR-H1 comprises the sequence of **SEQ ID NO: 86**, the CDR-H2 comprises the sequence of **SEQ ID NO: 194**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 302**;

87) the CDR-H1 comprises the sequence of **SEQ ID NO: 87**, the CDR-H2 comprises the sequence of **SEQ ID NO: 195**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 303**;

88) the CDR-H1 comprises the sequence of **SEQ ID NO: 88**, the CDR-H2 comprises the sequence of **SEQ ID NO: 196**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 304**;

89) the CDR-H1 comprises the sequence of **SEQ ID NO: 89**, the CDR-H2 comprises the sequence of **SEQ ID NO: 197**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 305**;

90) the CDR-H1 comprises the sequence of **SEQ ID NO: 90**, the CDR-H2 comprises the sequence of **SEQ ID NO: 198**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 306**;

91) the CDR-H1 comprises the sequence of **SEQ ID NO: 91**, the CDR-H2 comprises the sequence of **SEQ ID NO: 199**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 307**;

92) the CDR-H1 comprises the sequence of **SEQ ID NO: 92**, the CDR-H2 comprises the sequence of **SEQ ID NO: 200**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 308**;

93) the CDR-H1 comprises the sequence of **SEQ ID NO: 93**, the CDR-H2 comprises the sequence of **SEQ ID NO: 201**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 309**;

94) the CDR-H1 comprises the sequence of **SEQ ID NO: 94**, the CDR-H2 comprises the sequence of **SEQ ID NO: 202**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 310**;

95) the CDR-H1 comprises the sequence of **SEQ ID NO: 95**, the CDR-H2 comprises the sequence of **SEQ ID NO: 203**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 311**;

96) the CDR-H1 comprises the sequence of **SEQ ID NO: 96**, the CDR-H2 comprises the sequence of **SEQ ID NO: 204**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 312**;

97) the CDR-H1 comprises the sequence of **SEQ ID NO: 97**, the CDR-H2 comprises the sequence of **SEQ ID NO: 205**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 313**;

98) the CDR-H1 comprises the sequence of **SEQ ID NO: 98**, the CDR-H2 comprises the sequence of **SEQ ID NO: 206**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 314**;

99) the CDR-H1 comprises the sequence of **SEQ ID NO: 99**, the CDR-H2 comprises the sequence of **SEQ ID NO: 207**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 315**;

100) the CDR-H1 comprises the sequence of **SEQ ID NO: 100**, the CDR-H2 comprises the sequence of **SEQ ID NO: 208**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 316**;

101) the CDR-H1 comprises the sequence of **SEQ ID NO: 101**, the CDR-H2 comprises the sequence of **SEQ ID NO: 209**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 317**;

102) the CDR-H1 comprises the sequence of **SEQ ID NO: 102**, the CDR-H2 comprises the sequence of **SEQ ID NO: 210**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 318**;

103) the CDR-H1 comprises the sequence of **SEQ ID NO: 103**, the CDR-H2 comprises the sequence of **SEQ ID NO: 211**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 319**;

104) the CDR-H1 comprises the sequence of **SEQ ID NO: 104**, the CDR-H2 comprises the sequence of **SEQ ID NO: 212**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 320**;

105) the CDR-H1 comprises the sequence of **SEQ ID NO: 105**, the CDR-H2 comprises the sequence of **SEQ ID NO: 213**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 321**;

106) the CDR-H1 comprises the sequence of **SEQ ID NO: 106**, the CDR-H2 comprises the sequence of **SEQ ID NO: 214**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 322**;

107) the CDR-H1 comprises the sequence of **SEQ ID NO: 107**, the CDR-H2 comprises the sequence of **SEQ ID NO: 215**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 323**; or

108) the CDR-H1 comprises the sequence of **SEQ ID NO: 108**, the CDR-H2 comprises the sequence of **SEQ ID NO: 216**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 324**.

[0012] 3. The FAP binding polypeptide of alternative 1 or 2, wherein the heavy chain variable domain comprises an amino acid sequence having at least 90%, 95%, 99%, or 100% sequence identity to any sequence selected from **SEQ ID NOs: 325-432**.

[0013] 4. The FAP binding polypeptide of any one of alternatives 1-3, wherein the FAP binding polypeptide is humanized.

[0014] 5. The FAP binding polypeptide of any one of alternatives 1-4, wherein the FAP binding polypeptide is a single domain antibody (sdAb).

[0015] 6. A FAP binding polypeptide comprising an immunoglobulin heavy chain variable domain comprising a CDR-H1, wherein the CDR-H1 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 1-108**.

[0016] 7. The FAP binding polypeptide of alternative 6, wherein the CDR-H1 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NO: 4**.

[0017] 8. The FAP binding polypeptide of alternative 6 or 7, wherein the immunoglobulin heavy chain variable domain further comprises a CDR-H2, wherein the CDR-H2 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 109-216**.

[0018] 9. The FAP binding polypeptide of any one of alternatives 6-8, wherein the immunoglobulin heavy chain variable domain further comprises a CDR-H3, wherein the CDR-H3 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 217-324**.

[0019] 10. The FAP binding polypeptide of any one of alternatives 6-9, wherein the immunoglobulin heavy chain variable domain comprises an amino acid sequence having at least 90%, 95%, 99%, or 100% sequence identity to any sequence selected from **SEQ ID NOs: 325-432**.

[0020] 11. A FAP binding polypeptide comprising an immunoglobulin heavy chain variable domain comprising a CDR-H2, wherein the CDR-H2 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 109-216**.

[0021] 12. The FAP binding polypeptide of alternative 11, wherein the CDR-H2 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NO: 110**.

[0022] 13. The FAP binding polypeptide of alternative 11 or 12, wherein the immunoglobulin heavy chain variable domain further comprises a CDR-H1, wherein the CDR-H1 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 1-108**.

[0023] 14. The FAP binding polypeptide of any one of alternatives 11-13, wherein the immunoglobulin heavy chain variable domain further comprises a CDR-H3, wherein the CDR-H3 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 217-324**.

[0024] 15. The FAP binding polypeptide of any one of alternatives 11-14, wherein the immunoglobulin heavy chain variable domain comprises an amino acid sequence having at least 90%, 95%, 99%, or 100% sequence identity to any sequence selected from **SEQ ID NOs: 325-432**.

[0025] 16. A chimeric antigen receptor (CAR) comprising the FAP binding polypeptide of any one of alternatives 1-15.

[0026] 17. A chimeric antigen receptor (CAR) cell comprising the CAR of alternative 16.

[0027] 18. The CAR cell of alternative 17, wherein the CAR cell is a CAR T cell.

[0028] 19. The CAR cell of alternative 17 or 18, wherein the CAR cell comprises at least two binding polypeptides and the CAR cell is a multivalent CAR cell.

[0029] 20. The CAR cell of any one of alternatives 17-19, wherein the CAR cell is derived from a subject or from a cell line.

[0030] 21. The CAR cell of alternative 20, wherein the subject has a cancer.

[0031] 22. The CAR cell of alternative 21, wherein the cancer is breast cancer, colorectal cancer, kidney cancer, liver cancer, lung cancer, brain cancer, pancreatic cancer, bladder cancer, testicular cancer, prostate cancer, gastric cancer, ovarian cancer, head and neck cancer, gallbladder cancer, a hematologic malignancy, or any combination thereof.

[0032] 23. A nucleic acid that encodes for a polypeptide comprising a sequence having at least 90%, 95%, 99%, or 100% sequence identity to the FAP binding polypeptide of any one of alternatives 1-15 or the CAR of alternative 16.

[0033] 24. A method of treating a cancer in a subject in need thereof, comprising administering the CAR cell of any one of alternatives 17-22.

[0034] 25. The method of alternative 24, wherein the chimeric antigen receptor cell is autologous or allogeneic to the subject.

[0035] 26. The method of alternative 24 or 25, wherein the subject is a mammal.

[0036] 27. The method of any one of alternatives 24-26, wherein the subject is a human.

[0037] 28. The method of any one of alternatives 24-27, wherein the cancer is breast cancer, colorectal cancer, kidney cancer, liver cancer, lung cancer, brain cancer, pancreatic cancer, bladder cancer, testicular cancer, prostate cancer, gastric cancer, ovarian cancer, head and neck cancer, gallbladder cancer, a hematologic malignancy, or any combination thereof.

[0038] 29. The method of any one of alternatives 24-28, wherein the chimeric antigen receptor cell is administered parenterally.

BRIEF DESCRIPTION OF THE DRAWINGS

[0039] In addition to the features described above, additional features and variations will be readily apparent from the following descriptions of the drawings and exemplary embodiments. It is to be understood that these drawings depict typical embodiments and are not intended to be limiting in scope.

[0040] **FIG. 1** depicts an exemplary alignment for the heavy chain variable domain CDRs disclosed herein.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0041] Disclosed herein are binding polypeptides that are incorporated into a chimeric antigen receptor cell. In some embodiments, the chimeric antigen receptor cell is a chimeric antigen receptor T cell (CAR-T cell). These CAR-Ts may be constructed through processes conventionally known in the art. The binding polypeptides provide specificity towards their respective tumor-associated antigens, enabling targeting of cancers expressing said tumor-associated antigens by the CAR-T cell.

[0042] In some embodiments, the binding polypeptides are single domain antibodies (sdAbs) disposed on the surface of the chimeric antigen receptor cells (e.g. CAR-T cell). The sdAbs may be specific for, or have binding affinity towards, a tumor-associated antigen. In some embodiments, the tumor-associated antigen is fibroblast activation protein (FAP).

[0043] Also disclosed herein are methods of treating a cancer in a subject in need thereof by administering a chimeric antigen receptor cell comprising one or more of the binding polypeptides disclosed herein. In some embodiments, the cancer may be breast cancer, colorectal cancer, kidney cancer, liver cancer, lung cancer, brain cancer, pancreatic cancer, bladder cancer, testicular cancer, prostate cancer, gastric cancer, ovarian cancer, head and neck cancer, gallbladder cancer, a hematologic malignancy, or any combination thereof. The CAR-T cell may be derived from the subject for an autologous treatment. In some embodiments, the hematologic malignancy may comprise leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy cell leukemia, lymphoma, Hodgkin's disease, Non-Hodgkin lymphoma, or multiple myeloma. Alternatively, the CAR-T cell may be derived from the same species as the subject for an allogeneic treatment.

Definitions

[0044] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. It is to be understood that the foregoing general description and the following

detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed.

[0045] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0046] The articles "a" and "an" are used herein to refer to one or to more than one (for example, at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0047] By "about" is meant a quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length that varies by as much as 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1% to a reference quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length.

[0048] Throughout this specification, unless the context requires otherwise, the words "comprise," "comprises," and "comprising" will be understood to imply the inclusion of a stated step or element or group of steps or elements but not the exclusion of any other step or element or group of steps or elements. By "consisting of" is meant including, and limited to, whatever follows the phrase "consisting of." Thus, the phrase "consisting of" indicates that the listed elements are required or mandatory, and that no other elements may be present. By "consisting essentially of" is meant including any elements listed after the phrase and limited to other elements that do not interfere with or contribute to the activity or action specified in the disclosure for the listed elements. Thus, the phrase "consisting essentially of" indicates that the listed elements are required or mandatory, but that other elements are optional and may or may not be present depending upon whether or not they materially affect the activity or action of the listed elements.

[0049] As used herein, the terms "individual(s)", "subject(s)" and "patient(s)" mean any mammal. In some embodiments, the mammal is a human. In some embodiments, the mammal is a non-human. None of the terms require or are limited to situations characterized by the supervision (e.g. constant or intermittent) of a health care worker (e.g. a doctor, a registered nurse, a nurse practitioner, a physician's assistant, an orderly or a hospice worker).

[0050] The term "administering" includes enteral, oral, intranasal, parenteral, intravenous, intraperitoneal, intramuscular, intra-arteriole, intraventricular, intradermal, intralesional, intracranial, intrathecal, or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject.

[0051] The terms "nucleic acid" or "nucleic acid molecule" as used herein refers to polynucleotides, such as deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), oligonucleotides, fragments generated by the polymerase chain reaction (PCR), and fragments generated by any of ligation, scission, endonuclease action, and exonuclease action. Nucleic acid

molecules can be composed of monomers that are naturally-occurring nucleotides (such as DNA and RNA), or analogs of naturally-occurring nucleotides (e.g., enantiomeric forms of naturally-occurring nucleotides), or a combination of both. Nucleic acid monomers can be linked by phosphodiester bonds or analogs of such linkages. A nucleic acid or nucleic acids can be contained in a nucleic acid vector or nucleic acid construct (e.g. plasmid, virus, bacteriophage, cosmid, fosmid, phagemid, bacterial artificial chromosome (BAC), yeast artificial chromosome (YAC), or human artificial chromosome (HAC)) that can be used for amplification and/or expression of the nucleic acid or nucleic acids in various biological systems. Typically, the vector or construct will also contain elements including but not limited to promoters, enhancers, terminators, inducers, ribosome binding sites, translation initiation sites, start codons, stop codons, polyadenylation signals, origins of replication, cloning sites, multiple cloning sites, restriction enzyme sites, epitopes, reporter genes, selection markers, antibiotic selection markers, targeting sequences, peptide purification tags, or accessory genes, or any combination thereof.

[0052] A nucleic acid or nucleic acid molecule can comprise one or more sequences encoding different peptides, polypeptides, or proteins. These one or more sequences can be joined in the same nucleic acid or nucleic acid molecule adjacently, or with extra nucleic acids in between, e.g. linkers, repeats or restriction enzyme sites, or any other sequence that is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 150, 200, or 300 bases long, or any length in a range defined by any two of the aforementioned lengths. The term “downstream” on a nucleic acid as used herein refers to a sequence being after the 3’-end of a previous sequence, on the strand containing the encoding sequence (sense strand) if the nucleic acid is double stranded. The term “upstream” on a nucleic acid as used herein refers to a sequence being before the 5’-end of a subsequent sequence, on the strand containing the encoding sequence (sense strand) if the nucleic acid is double stranded. The term “grouped” on a nucleic acid as used herein refers to two or more sequences that occur in proximity either directly or with extra nucleic acids in between, e.g. linkers, repeats, or restriction enzyme sites, or any other sequence that is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 150, 200, or 300 bases long, or any length in a range defined by any two of the aforementioned lengths, but generally not with a sequence in between that encodes for a functioning or catalytic polypeptide, protein, or protein domain.

[0053] The term “codon optimized” regarding a nucleic acid as used herein refers to the substitution of codons of the nucleic acid to enhance or maximize translation in a host of a particular species without changing the polypeptide sequence based on species-specific codon usage biases and relative availability of each aminoacyl-tRNA in the target cell cytoplasm. Codon

optimization and techniques to perform such optimization is known in the art. Those skilled in the art will appreciate that gene expression levels are dependent on many factors, such as promoter sequences and regulatory elements. In this aspect, many synthetic genes can be designed to increase their protein expression level.

[0054] The terms “peptide”, “polypeptide”, and “protein” as used herein refers to macromolecules comprised of amino acids linked by peptide bonds. The numerous functions of peptides, polypeptides, and proteins are known in the art, and include but are not limited to enzymes, structure, transport, defense, hormones, or signaling. Peptides, polypeptides, and proteins are often, but not always, produced biologically by a ribosomal complex using a nucleic acid template, although chemical syntheses are also available. By manipulating the nucleic acid template, peptide, polypeptide, and protein mutations such as substitutions, deletions, truncations, additions, duplications, or fusions of more than one peptide, polypeptide, or protein can be performed. These fusions of more than one peptide, polypeptide, or protein can be joined in the same molecule adjacently, or with extra amino acids in between, e.g. linkers, repeats, epitopes, or tags, or any other sequence that is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 150, 200, or 300 bases long, or any length in a range defined by any two of the aforementioned lengths. The term “downstream” on a polypeptide as used herein refers to a sequence being after the C-terminus of a previous sequence. The term “upstream” on a polypeptide as used herein refers to a sequence being before the N-terminus of a subsequent sequence.

[0055] In some embodiments, the nucleic acid or peptide sequences presented herein and used in the examples are functional in various biological systems including but not limited to humans, mice, rats, monkeys, primates, cats, dogs, rabbits, *E. coli*, yeast, and mammalian cells. In other embodiments, nucleic acid or peptide sequences sharing at least or lower than 0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity, or any percentage within a range defined by any two of the aforementioned percentages of identity to the nucleic acid or peptide sequences presented herein and used in the examples can also be used with little or no effect on the function of the sequences in biological systems. As used herein, the term “identity” refers to a nucleic acid or peptide sequence having the same overall order of nucleotide or amino acids, respectively, as a template nucleic acid or peptide sequence with specific changes such as substitutions, deletions, repetitions, or insertions within the sequence. In some embodiments, two nucleic acid sequences sharing as low as 0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity can encode for the same polypeptide by comprising different codons that encode for the same amino acid during translation.

[0056] As disclosed herein, sequences having a % homology to any of the sequences disclosed herein are envisioned and may be used. The term "% homology" refers to the degree of conservation between two sequences when considering their three-dimensional structure. For example, homology between two protein sequences may be dependent on structural motifs, such as beta strands, alpha helices, and other folds, as well as their distribution throughout the sequence. Homology may be determined through structural determination, either empirically or *in silico*. In some embodiments, any sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence homology to any of the sequences disclosed herein may be used. In some embodiments, any sequence having at least 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 substitutions, deletions, or additions relative to any of the sequences disclosed herein, which may or may not affect the overall % homology, may be used.

[0057] As applied herein, sequences having a certain % similarity to any of the sequence disclosed herein are envisioned and may be used. In some embodiments, these sequences may include peptide sequences, nucleic acid sequences, CDR sequences, variable region sequences, or heavy or light chain sequences. As understood in the art with respect to peptide sequences, "similarity" refers to the comparison of amino acids based on their properties, including but not limited to size, polarity, charge, pK, aromaticity, hydrogen bonding properties, or presence of functional groups (e.g. hydroxyl, thiol, amine, carboxyl, and the like). The term "% similarity" refers to the percentage of units (i.e. amino acids) that are the same between two or more sequences relative to the length of the sequence. When the two or more sequences being compared are the same length, the % similarity will be respective that length. When two or more sequences being compared are different lengths, deletions and/or insertions may be introduced to obtain the best alignment. The similarity of two amino acids may dictate whether a certain substitution is conservative or non-conservative. Methods of determining the conservativeness of an amino acid substitution are generally known in the art and may involve substitution matrices. Commonly used substitution matrices include BLOSUM45, BLOSUM62, BLOSUM80, PAM100, PAM120, PAM160, PAM200, PAM250, but other substitution matrices or approaches may be used as considered appropriate by the skilled person. A certain substitution matrix may be preferential over the others when considering aspects such as stringency, conservation and/or divergence of related sequences (e.g. within the same species or broader), and length of the sequences in question. As used herein, a peptide sequence having a certain % similarity to another sequence will have up to that % of amino acids that are either identical or an acceptable substitution as governed by the method of similarity determination used. In some embodiments, a

sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence similarity to any of the sequences disclosed herein may be used. In some embodiments, any sequence having at least 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 similar substitutions relative to any of the sequences disclosed herein may be used. As applied to antibody sequences, these similar substitutions may apply to antigen-binding regions (i.e. CDRs) or regions that do not bind to antigens or are only secondary to antigen binding (i.e. framework regions).

[0058] The term “consensus sequence” as used herein with regard to sequences refers to the generalized sequence representing all of the different combinations of permissible amino acids at each location of a group of sequences. A consensus sequence may provide insight into the conserved regions of related sequences where the unit (e.g. amino acid or nucleotide) is the same in most or all of the sequences, and regions that exhibit divergence between sequences. In the case of antibodies, the consensus sequence of a CDR may indicate amino acids that are important or dispensable for antigen binding. It is envisioned that consensus sequences may be prepared with any of the sequences provided herein, and the resultant various sequences derived from the consensus sequence can be validated to have similar effects as the template sequences.

[0059] As used herein, the term "antibody" denotes the meaning ascribed to it by one of skill in the art, and further it is intended to include any polypeptide chain-containing molecular structure with a specific shape that fits to and recognizes an epitope, where one or more non-covalent binding interactions stabilize the complex between the molecular structure and the epitope.

[0060] The term "antibody library" refers to a collection of antibodies and/or antibody fragments displayed for screening and/or combination into full antibodies. The antibodies and/or antibody fragments may be displayed on a ribosome; on a phage; or on a cell surface, in particular a yeast cell surface.

[0061] The term "compete," as used herein with regard to an antibody or binding polypeptide, means that a first antibody or binding polypeptide, or an antigen-binding portion thereof, binds to an epitope in a manner sufficiently similar to the binding of a second antibody or binding polypeptide, or an antigen-binding portion thereof, such that the result of binding of the first antibody or binding polypeptide with its cognate epitope is detectably decreased in the presence of the second antibody or binding polypeptide compared to the binding of the first antibody or binding polypeptide in the absence of the second antibody or binding polypeptide. The alternative, where the binding of the second antibody or binding polypeptide to its epitope is also detectably decreased in the presence of the first antibody or binding polypeptide, can, but

need not be the case. Regardless of the mechanism by which such competition occurs (e.g., steric hindrance, conformational change, or binding to a common epitope, or portion thereof), the skilled artisan would appreciate, based upon the teachings provided herein, that such competing antibodies or binding polypeptides are encompassed and can be useful for the methods disclosed herein.

[0062] An antibody or binding polypeptide that "preferentially binds" or "specifically binds" (used interchangeably herein) to an epitope is a term well understood in the art, and methods to determine such specific or preferential binding are also well known in the art. A molecule is said to exhibit "specific binding" or "preferential binding" if it reacts or associates more frequently, and/or more rapidly, and/or with greater duration and/or with greater affinity with a particular cell or substance than it does with alternative cells or substances. An antibody or binding polypeptide "specifically binds" or "preferentially binds" to a target if it binds with greater affinity, and/or avidity, and/or more readily, and/or with greater duration than it binds to other substances.

[0063] The term “humanized” as applies to a non-human (e.g. rodent or primate) antibodies are hybrid immunoglobulins, immunoglobulin chains or fragments thereof which contain minimal sequence derived from non-human immunoglobulin.

[0064] The term “single domain binding polypeptide” or “single domain antibody” (sdAb) as used herein refers to a single peptide strand (e.g. not bound to another peptide strand with disulfide bonds) comprising an intact immunoglobulin domain or other protein fold which can recognize antigens. Single domain binding polypeptides or sdAbs may be derived from typical heavy or light immunoglobulin chains, such as from human, or from alternative sources such as dromedaries (e.g. V_HH) and cartilaginous fish (e.g. V_{NAR}). In some embodiments, the single domain binding polypeptide or sdAb comprises one, two, or three complementarity determining regions (CDRs). In some embodiments, the single domain binding polypeptide or sdAb comprises one, two, or three of a CDR1, CDR2, and CDR3.

[0065] The term "single-chain variable fragment" (scFv) as used herein is a fusion protein comprising the variable regions of the heavy (VH) and light chains (VL) of an immunoglobulin, in which the VH and VL are covalently linked to form a VH:VL heterodimer. The VH and VL are either joined directly or joined by a peptide-encoding linker, which connects the N-terminus of the VH with the C-terminus of the VL, or the C-terminus of the VH with the N-terminus of the VL. The linker is usually rich in glycine for flexibility, as well as serine or threonine for solubility. Despite removal of the constant regions and the introduction of a linker, scFv proteins retain the specificity of the original immunoglobulin. Single chain Fv polypeptide antibodies can be expressed from a nucleic acid including VH- and VL-encoding sequences. In

some embodiments, the VH and VL of the scFv each comprises one, two, or three CDRs. In some embodiments, the VH and VL of the scFv each comprises one, two, or three of a CDR1, CDR2, and CDR3.

[0066] In certain embodiments, definitive delineation of a CDR and identification of residues comprising the binding site of an antibody or binding polypeptide is accomplished by solving the structure of the antibody or binding polypeptide and/or solving the structure of the antibody-ligand complex. In certain embodiments, that can be accomplished by any of a variety of techniques known to those skilled in the art, such as X-ray crystallography. In certain embodiments, various methods of analysis can be employed to identify or approximate the CDR regions. In certain embodiments, various methods of analysis can be employed to identify or approximate the CDR regions. Examples of such methods include, but are not limited to, the Kabat definition, the Chothia definition, the IMGT approach (Lefranc et al., 2003) Dev Comp Immunol. 27:55-77), computational programs such as Paratome (Kunik et al., 2012, Nucl Acids Res. W521-4), the AbM definition, and the conformational definition.

[0067] The Kabat definition is a standard for numbering the residues in an antibody and is typically used to identify CDR regions. See, e.g., Johnson & Wu, 2000, Nucleic Acids Res., 28: 214-8. The Chothia definition is similar to the Kabat definition, but the Chothia definition takes into account positions of certain structural loop regions. See, e.g., Chothia et al., 1986, J. Mol. Biol., 196: 901-17; Chothia et al., 1989, Nature, 342: 877-83. The AbM definition uses an integrated suite of computer programs produced by Oxford Molecular Group that model antibody structure. See, e.g., Martin et al., 1989, Proc Natl Acad Sci (USA), 86:9268-9272; "AbM.TM., A Computer Program for Modeling Variable Regions of Antibodies," Oxford, UK; Oxford Molecular, Ltd. The AbM definition models the tertiary structure of an antibody from primary sequence using a combination of knowledge databases and ab initio methods, such as those described by Samudrala et al., 1999, "Ab Initio Protein Structure Prediction Using a Combined Hierarchical Approach," in PROTEINS, Structure, Function and Genetics Suppl., 3:194-198. The contact definition is based on an analysis of the available complex crystal structures. See, e.g., MacCallum et al., 1996, J. Mol. Biol., 5:732-45. In another approach, referred to herein as the "conformational definition" of CDRs, the positions of the CDRs may be identified as the residues that make enthalpic contributions to antigen binding. See, e.g., Makabe et al., 2008, Journal of Biological Chemistry, 283:1156-1166. Still other CDR boundary definitions may not strictly follow one of the above approaches, but will nonetheless overlap with at least a portion of the Kabat CDRs, although they may be shortened or lengthened in light of prediction or experimental findings that particular residues or groups of residues do not significantly impact antigen binding. As used herein, a CDR may refer to CDRs defined by any approach known in the art, including

combinations of approaches. The methods used herein may utilize CDRs defined according to any of these approaches. For any given embodiment containing more than one CDR, the CDRs may be defined in accordance with any of Kabat, Chothia, extended, IMGT, Paratome, AbM, and/or conformational definitions, or a combination of any of the foregoing.

[0068] The term “chimeric antigen receptor (CAR)” as used herein refers to engineered biological receptors that confers an artificial specificity in an immune cell towards a certain antigen, such as a tumor-associated antigen. An exemplary immune cell in which CARs can be used are T cells, but it is envisioned that CARs can be engineered into any amenable cytotoxic immune cell, including but not limited to T cells, Natural Killer (NK) cells, Natural Killer T (NKT) cells, dendritic cells, or macrophages. In this aspect, any disclosure pertaining to CAR T cells can also be applied to other immune cells comprising CARs. At their core, CARs comprise an extracellular antigen-recognizing domain (e.g. tumor receptor ligand, or antibody), hinge, transmembrane, and intracellular signaling domain (endodomain). Different combinations of these CAR components may result in different specificities and efficacy against certain cancer antigens.

[0069] As used herein, the terms “treating” or “treatment” (and as well understood in the art) means an approach for obtaining beneficial or desired results in a subject's condition, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of a disease, stabilizing (i.e., not worsening) the state of disease, prevention of a disease's transmission or spread, delaying or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable. “Treating” and “treatment” as used herein also include prophylactic treatment. Treatment methods comprise administering to a subject a therapeutically effective amount of an active agent. The administering step may consist of a single administration or may comprise a series of administrations. The compositions are administered to the subject in an amount and for a duration sufficient to treat the subject. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age and genetic profile of the subject, the concentration of active agent, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required.

[0070] The terms “effective amount” or “effective dose” as used herein refers to that amount of a recited composition or compound that results in an observable designated effect. Actual dosage levels of active ingredients in an active composition of the presently disclosed subject matter can be varied so as to administer an amount of the active composition or compound that is effective to achieve the designated response for a particular subject and/or application. The selected dosage level can vary based upon a variety of factors including, but not limited to, the activity of the composition, formulation, route of administration, combination with other drugs or treatments, severity of the condition being treated, and the physical condition and prior medical history of the subject being treated. In some embodiments, a minimal dose is administered, and dose is escalated in the absence of dose-limiting toxicity to a minimally effective amount. Determination and adjustment of an effective dose, as well as evaluation of when and how to make such adjustments, are contemplated herein.

[0071] The term “administering” includes oral administration, topical contact, administration as a suppository, parenteral, intravenous, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal, subdermal, or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, etc. By “co-administer” it is meant that a first compound described herein is administered at the same time, just prior to, or just after the administration of a second compound described herein.

[0072] As used herein, the term "therapeutic target" refers to a gene or gene product that, upon modulation of its activity (e.g., by modulation of expression, biological activity, and the like), can provide for modulation of the disease phenotype. As used throughout, "modulation" is meant to refer to an increase or a decrease in the indicated phenomenon (e.g., modulation of a biological activity refers to an increase in a biological activity or a decrease in a biological activity).

[0073] As used herein, the term “standard of care”, “best practice” and “standard therapy” refers to the treatment that is accepted by medical practitioners to be an appropriate, proper, effective, and/or widely used treatment for a certain disease. The standard of care of a certain disease depends on many different factors, including the biological effect of treatment, region or location within the body, patient status (e.g. age, weight, gender, hereditary risks, other disabilities, secondary conditions), toxicity, metabolism, bioaccumulation, therapeutic index,

dosage, and other factors known in the art. Determining a standard of care for a disease is also dependent on establishing safety and efficacy in clinical trials as standardized by regulatory bodies such as the US Food and Drug Administration, International Council for Harmonisation, Health Canada, European Medicines Agency, Therapeutics Goods Administration, Central Drugs Standard Control Organization, National Medical Products Administration, Pharmaceuticals and Medical Devices Agency, Ministry of Food and Drug Safety, and the World Health Organization. The standard of care for a disease may include but is not limited to surgery, radiation, chemotherapy, targeted therapy, or immunotherapy.

[0074] The term "% w/w" or "% wt/wt" means a percentage expressed in terms of the weight of the ingredient or agent over the total weight of the composition multiplied by 100.

Antigen binding polypeptides

[0075] Unless otherwise specified, the complementarity determining regions (CDRs) disclosed herein follow the IMGT definition. However, the CDRs, either separately or within the context of the variable domains, can also be interpreted by Kabat, Chothia, or other definitions as understood by those of skill in the art.

[0076] Disclosed herein are fibroblast activation protein (FAP) binding polypeptides. In some embodiments, the FAP binding polypeptides comprise an immunoglobulin heavy chain variable domain comprising a CDR-H1, CDR-H2, and CDR-H3. In some embodiments, the CDR-H1 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 1-108**. In some embodiments, CDR-H2 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 109-216**. In some embodiments, the CDR-H3 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 217-324**. In some embodiments, the CDR-H1 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 1-108**; the CDR-H2 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 109-216**; and the CDR-H3 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 217-324**.

[0077] In some embodiments of the FAP binding polypeptides:

1) the CDR-H1 comprises the sequence of **SEQ ID NO: 1**, the CDR-H2 comprises the sequence of **SEQ ID NO: 109**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 217**;

2) the CDR-H1 comprises the sequence of **SEQ ID NO: 2**, the CDR-H2 comprises the sequence of **SEQ ID NO: 110**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 218**;

3) the CDR-H1 comprises the sequence of **SEQ ID NO: 3**, the CDR-H2 comprises the sequence of **SEQ ID NO: 111**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 219**;

4) the CDR-H1 comprises the sequence of **SEQ ID NO: 4**, the CDR-H2 comprises the sequence of **SEQ ID NO: 112**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 220**;

5) the CDR-H1 comprises the sequence of **SEQ ID NO: 5**, the CDR-H2 comprises the sequence of **SEQ ID NO: 113**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 221**;

6) the CDR-H1 comprises the sequence of **SEQ ID NO: 6**, the CDR-H2 comprises the sequence of **SEQ ID NO: 114**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 222**;

7) the CDR-H1 comprises the sequence of **SEQ ID NO: 7**, the CDR-H2 comprises the sequence of **SEQ ID NO: 115**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 223**;

8) the CDR-H1 comprises the sequence of **SEQ ID NO: 8**, the CDR-H2 comprises the sequence of **SEQ ID NO: 116**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 224**;

9) the CDR-H1 comprises the sequence of **SEQ ID NO: 9**, the CDR-H2 comprises the sequence of **SEQ ID NO: 117**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 225**;

10) the CDR-H1 comprises the sequence of **SEQ ID NO: 10**, the CDR-H2 comprises the sequence of **SEQ ID NO: 118**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 226**;

11) the CDR-H1 comprises the sequence of **SEQ ID NO: 11**, the CDR-H2 comprises the sequence of **SEQ ID NO: 119**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 227**;

12) the CDR-H1 comprises the sequence of **SEQ ID NO: 12**, the CDR-H2 comprises the sequence of **SEQ ID NO: 120**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 228**;

13) the CDR-H1 comprises the sequence of **SEQ ID NO: 13**, the CDR-H2 comprises the sequence of **SEQ ID NO: 121**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 229**;

14) the CDR-H1 comprises the sequence of **SEQ ID NO: 14**, the CDR-H2 comprises the sequence of **SEQ ID NO: 122**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 230**;

15) the CDR-H1 comprises the sequence of **SEQ ID NO: 15**, the CDR-H2 comprises the sequence of **SEQ ID NO: 123**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 231**;

16) the CDR-H1 comprises the sequence of **SEQ ID NO: 16**, the CDR-H2 comprises the sequence of **SEQ ID NO: 124**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 232**;

17) the CDR-H1 comprises the sequence of **SEQ ID NO: 17**, the CDR-H2 comprises the sequence of **SEQ ID NO: 125**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 233**;

18) the CDR-H1 comprises the sequence of **SEQ ID NO: 18**, the CDR-H2 comprises the sequence of **SEQ ID NO: 126**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 234**;

19) the CDR-H1 comprises the sequence of **SEQ ID NO: 19**, the CDR-H2 comprises the sequence of **SEQ ID NO: 127**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 235**;

20) the CDR-H1 comprises the sequence of **SEQ ID NO: 20**, the CDR-H2 comprises the sequence of **SEQ ID NO: 128**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 236**;

21) the CDR-H1 comprises the sequence of **SEQ ID NO: 21**, the CDR-H2 comprises the sequence of **SEQ ID NO: 129**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 237**;

22) the CDR-H1 comprises the sequence of **SEQ ID NO: 22**, the CDR-H2 comprises the sequence of **SEQ ID NO: 130**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 238**;

23) the CDR-H1 comprises the sequence of **SEQ ID NO: 23**, the CDR-H2 comprises the sequence of **SEQ ID NO: 131**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 239**;

24) the CDR-H1 comprises the sequence of **SEQ ID NO: 24**, the CDR-H2 comprises the sequence of **SEQ ID NO: 132**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 240**;

25) the CDR-H1 comprises the sequence of **SEQ ID NO: 25**, the CDR-H2 comprises the sequence of **SEQ ID NO: 133**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 241**;

26) the CDR-H1 comprises the sequence of **SEQ ID NO: 26**, the CDR-H2 comprises the sequence of **SEQ ID NO: 134**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 242**;

27) the CDR-H1 comprises the sequence of **SEQ ID NO: 27**, the CDR-H2 comprises the sequence of **SEQ ID NO: 135**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 243**;

28) the CDR-H1 comprises the sequence of **SEQ ID NO: 28**, the CDR-H2 comprises the sequence of **SEQ ID NO: 136**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 244**;

29) the CDR-H1 comprises the sequence of **SEQ ID NO: 29**, the CDR-H2 comprises the sequence of **SEQ ID NO: 137**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 245**;

30) the CDR-H1 comprises the sequence of **SEQ ID NO: 30**, the CDR-H2 comprises the sequence of **SEQ ID NO: 138**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 246**;

31) the CDR-H1 comprises the sequence of **SEQ ID NO: 31**, the CDR-H2 comprises the sequence of **SEQ ID NO: 139**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 247**;

32) the CDR-H1 comprises the sequence of **SEQ ID NO: 32**, the CDR-H2 comprises the sequence of **SEQ ID NO: 140**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 248**;

33) the CDR-H1 comprises the sequence of **SEQ ID NO: 33**, the CDR-H2 comprises the sequence of **SEQ ID NO: 141**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 249**;

34) the CDR-H1 comprises the sequence of **SEQ ID NO: 34**, the CDR-H2 comprises the sequence of **SEQ ID NO: 142**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 250**;

35) the CDR-H1 comprises the sequence of **SEQ ID NO: 35**, the CDR-H2 comprises the sequence of **SEQ ID NO: 143**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 251**;

36) the CDR-H1 comprises the sequence of **SEQ ID NO: 36**, the CDR-H2 comprises the sequence of **SEQ ID NO: 144**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 252**;

37) the CDR-H1 comprises the sequence of **SEQ ID NO: 37**, the CDR-H2 comprises the sequence of **SEQ ID NO: 145**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 253**;

38) the CDR-H1 comprises the sequence of **SEQ ID NO: 38**, the CDR-H2 comprises the sequence of **SEQ ID NO: 146**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 254**;

39) the CDR-H1 comprises the sequence of **SEQ ID NO: 39**, the CDR-H2 comprises the sequence of **SEQ ID NO: 147**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 255**;

40) the CDR-H1 comprises the sequence of **SEQ ID NO: 40**, the CDR-H2 comprises the sequence of **SEQ ID NO: 148**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 256**;

41) the CDR-H1 comprises the sequence of **SEQ ID NO: 41**, the CDR-H2 comprises the sequence of **SEQ ID NO: 149**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 257**;

42) the CDR-H1 comprises the sequence of **SEQ ID NO: 42**, the CDR-H2 comprises the sequence of **SEQ ID NO: 150**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 258**;

43) the CDR-H1 comprises the sequence of **SEQ ID NO: 43**, the CDR-H2 comprises the sequence of **SEQ ID NO: 151**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 259**;

44) the CDR-H1 comprises the sequence of **SEQ ID NO: 44**, the CDR-H2 comprises the sequence of **SEQ ID NO: 152**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 260**;

45) the CDR-H1 comprises the sequence of **SEQ ID NO: 45**, the CDR-H2 comprises the sequence of **SEQ ID NO: 153**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 261**;

46) the CDR-H1 comprises the sequence of **SEQ ID NO: 46**, the CDR-H2 comprises the sequence of **SEQ ID NO: 154**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 262**;

47) the CDR-H1 comprises the sequence of **SEQ ID NO: 47**, the CDR-H2 comprises the sequence of **SEQ ID NO: 155**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 263**;

48) the CDR-H1 comprises the sequence of **SEQ ID NO: 48**, the CDR-H2 comprises the sequence of **SEQ ID NO: 156**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 264**;

49) the CDR-H1 comprises the sequence of **SEQ ID NO: 49**, the CDR-H2 comprises the sequence of **SEQ ID NO: 157**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 265**;

50) the CDR-H1 comprises the sequence of **SEQ ID NO: 50**, the CDR-H2 comprises the sequence of **SEQ ID NO: 158**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 266**;

51) the CDR-H1 comprises the sequence of **SEQ ID NO: 51**, the CDR-H2 comprises the sequence of **SEQ ID NO: 159**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 267**;

52) the CDR-H1 comprises the sequence of **SEQ ID NO: 52**, the CDR-H2 comprises the sequence of **SEQ ID NO: 160**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 268**;

53) the CDR-H1 comprises the sequence of **SEQ ID NO: 53**, the CDR-H2 comprises the sequence of **SEQ ID NO: 161**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 269**;

54) the CDR-H1 comprises the sequence of **SEQ ID NO: 54**, the CDR-H2 comprises the sequence of **SEQ ID NO: 162**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 270**;

55) the CDR-H1 comprises the sequence of **SEQ ID NO: 55**, the CDR-H2 comprises the sequence of **SEQ ID NO: 163**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 271**;

56) the CDR-H1 comprises the sequence of **SEQ ID NO: 56**, the CDR-H2 comprises the sequence of **SEQ ID NO: 164**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 272**;

57) the CDR-H1 comprises the sequence of **SEQ ID NO: 57**, the CDR-H2 comprises the sequence of **SEQ ID NO: 165**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 273**;

58) the CDR-H1 comprises the sequence of **SEQ ID NO: 58**, the CDR-H2 comprises the sequence of **SEQ ID NO: 166**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 274**;

59) the CDR-H1 comprises the sequence of **SEQ ID NO: 59**, the CDR-H2 comprises the sequence of **SEQ ID NO: 167**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 275**;

60) the CDR-H1 comprises the sequence of **SEQ ID NO: 60**, the CDR-H2 comprises the sequence of **SEQ ID NO: 168**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 276**;

61) the CDR-H1 comprises the sequence of **SEQ ID NO: 61**, the CDR-H2 comprises the sequence of **SEQ ID NO: 169**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 277**;

62) the CDR-H1 comprises the sequence of **SEQ ID NO: 62**, the CDR-H2 comprises the sequence of **SEQ ID NO: 170**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 278**;

63) the CDR-H1 comprises the sequence of **SEQ ID NO: 63**, the CDR-H2 comprises the sequence of **SEQ ID NO: 171**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 279**;

64) the CDR-H1 comprises the sequence of **SEQ ID NO: 64**, the CDR-H2 comprises the sequence of **SEQ ID NO: 172**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 280**;

65) the CDR-H1 comprises the sequence of **SEQ ID NO: 65**, the CDR-H2 comprises the sequence of **SEQ ID NO: 173**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 281**;

66) the CDR-H1 comprises the sequence of **SEQ ID NO: 66**, the CDR-H2 comprises the sequence of **SEQ ID NO: 174**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 282**;

67) the CDR-H1 comprises the sequence of **SEQ ID NO: 67**, the CDR-H2 comprises the sequence of **SEQ ID NO: 175**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 283**;

68) the CDR-H1 comprises the sequence of **SEQ ID NO: 68**, the CDR-H2 comprises the sequence of **SEQ ID NO: 176**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 284**;

69) the CDR-H1 comprises the sequence of **SEQ ID NO: 69**, the CDR-H2 comprises the sequence of **SEQ ID NO: 177**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 285**;

70) the CDR-H1 comprises the sequence of **SEQ ID NO: 70**, the CDR-H2 comprises the sequence of **SEQ ID NO: 178**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 286**;

71) the CDR-H1 comprises the sequence of **SEQ ID NO: 71**, the CDR-H2 comprises the sequence of **SEQ ID NO: 179**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 287**;

72) the CDR-H1 comprises the sequence of **SEQ ID NO: 72**, the CDR-H2 comprises the sequence of **SEQ ID NO: 180**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 288**;

73) the CDR-H1 comprises the sequence of **SEQ ID NO: 73**, the CDR-H2 comprises the sequence of **SEQ ID NO: 181**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 289**;

74) the CDR-H1 comprises the sequence of **SEQ ID NO: 74**, the CDR-H2 comprises the sequence of **SEQ ID NO: 182**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 290**;

75) the CDR-H1 comprises the sequence of **SEQ ID NO: 75**, the CDR-H2 comprises the sequence of **SEQ ID NO: 183**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 291**;

76) the CDR-H1 comprises the sequence of **SEQ ID NO: 76**, the CDR-H2 comprises the sequence of **SEQ ID NO: 184**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 292**;

77) the CDR-H1 comprises the sequence of **SEQ ID NO: 77**, the CDR-H2 comprises the sequence of **SEQ ID NO: 185**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 293**;

78) the CDR-H1 comprises the sequence of **SEQ ID NO: 78**, the CDR-H2 comprises the sequence of **SEQ ID NO: 186**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 294**;

79) the CDR-H1 comprises the sequence of **SEQ ID NO: 79**, the CDR-H2 comprises the sequence of **SEQ ID NO: 187**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 295**;

80) the CDR-H1 comprises the sequence of **SEQ ID NO: 80**, the CDR-H2 comprises the sequence of **SEQ ID NO: 188**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 296**;

81) the CDR-H1 comprises the sequence of **SEQ ID NO: 81**, the CDR-H2 comprises the sequence of **SEQ ID NO: 189**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 297**;

82) the CDR-H1 comprises the sequence of **SEQ ID NO: 82**, the CDR-H2 comprises the sequence of **SEQ ID NO: 190**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 298**;

83) the CDR-H1 comprises the sequence of **SEQ ID NO: 83**, the CDR-H2 comprises the sequence of **SEQ ID NO: 191**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 299**;

84) the CDR-H1 comprises the sequence of **SEQ ID NO: 84**, the CDR-H2 comprises the sequence of **SEQ ID NO: 192**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 300**;

85) the CDR-H1 comprises the sequence of **SEQ ID NO: 85**, the CDR-H2 comprises the sequence of **SEQ ID NO: 193**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 301**;

86) the CDR-H1 comprises the sequence of **SEQ ID NO: 86**, the CDR-H2 comprises the sequence of **SEQ ID NO: 194**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 302**;

87) the CDR-H1 comprises the sequence of **SEQ ID NO: 87**, the CDR-H2 comprises the sequence of **SEQ ID NO: 195**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 303**;

88) the CDR-H1 comprises the sequence of **SEQ ID NO: 88**, the CDR-H2 comprises the sequence of **SEQ ID NO: 196**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 304**;

89) the CDR-H1 comprises the sequence of **SEQ ID NO: 89**, the CDR-H2 comprises the sequence of **SEQ ID NO: 197**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 305**;

90) the CDR-H1 comprises the sequence of **SEQ ID NO: 90**, the CDR-H2 comprises the sequence of **SEQ ID NO: 198**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 306**;

91) the CDR-H1 comprises the sequence of **SEQ ID NO: 91**, the CDR-H2 comprises the sequence of **SEQ ID NO: 199**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 307**;

92) the CDR-H1 comprises the sequence of **SEQ ID NO: 92**, the CDR-H2 comprises the sequence of **SEQ ID NO: 200**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 308**;

93) the CDR-H1 comprises the sequence of **SEQ ID NO: 93**, the CDR-H2 comprises the sequence of **SEQ ID NO: 201**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 309**;

94) the CDR-H1 comprises the sequence of **SEQ ID NO: 94**, the CDR-H2 comprises the sequence of **SEQ ID NO: 202**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 310**;

95) the CDR-H1 comprises the sequence of **SEQ ID NO: 95**, the CDR-H2 comprises the sequence of **SEQ ID NO: 203**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 311**;

96) the CDR-H1 comprises the sequence of **SEQ ID NO: 96**, the CDR-H2 comprises the sequence of **SEQ ID NO: 204**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 312**;

97) the CDR-H1 comprises the sequence of **SEQ ID NO: 97**, the CDR-H2 comprises the sequence of **SEQ ID NO: 205**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 313**;

98) the CDR-H1 comprises the sequence of **SEQ ID NO: 98**, the CDR-H2 comprises the sequence of **SEQ ID NO: 206**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 314**;

99) the CDR-H1 comprises the sequence of **SEQ ID NO: 99**, the CDR-H2 comprises the sequence of **SEQ ID NO: 207**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 315**;

100) the CDR-H1 comprises the sequence of **SEQ ID NO: 100**, the CDR-H2 comprises the sequence of **SEQ ID NO: 208**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 316**;

101) the CDR-H1 comprises the sequence of **SEQ ID NO: 101**, the CDR-H2 comprises the sequence of **SEQ ID NO: 209**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 317**;

102) the CDR-H1 comprises the sequence of **SEQ ID NO: 102**, the CDR-H2 comprises the sequence of **SEQ ID NO: 210**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 318**;

103) the CDR-H1 comprises the sequence of **SEQ ID NO: 103**, the CDR-H2 comprises the sequence of **SEQ ID NO: 211**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 319**;

104) the CDR-H1 comprises the sequence of **SEQ ID NO: 104**, the CDR-H2 comprises the sequence of **SEQ ID NO: 212**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 320**;

105) the CDR-H1 comprises the sequence of **SEQ ID NO: 105**, the CDR-H2 comprises the sequence of **SEQ ID NO: 213**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 321**;

106) the CDR-H1 comprises the sequence of **SEQ ID NO: 106**, the CDR-H2 comprises the sequence of **SEQ ID NO: 214**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 322**;

107) the CDR-H1 comprises the sequence of **SEQ ID NO: 107**, the CDR-H2 comprises the sequence of **SEQ ID NO: 215**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 323**; or

108) the CDR-H1 comprises the sequence of **SEQ ID NO: 108**, the CDR-H2 comprises the sequence of **SEQ ID NO: 216**, and the CDR-H3 comprises the sequence of **SEQ ID NO: 324**.

[0078] In some embodiments, the FAP binding polypeptide comprise an immunoglobulin heavy chain variable domain comprising a CDR-H1, CDR-H2, and CDR-H3, where one or more of these CDRs are defined by a consensus sequence. The consensus sequences provided herein have been derived from the alignments of CDRs depicted in **FIG. 1**. However, it is envisioned that alternative alignments may be done (e.g. using global or local alignment, or with different algorithms, such as Hidden Markov Models, seeded guide trees, Needleman-Wunsch algorithm, or Smith-Waterman algorithm, or other known methods) and as such, alternative consensus sequences can be derived (including those done with a subset of the sequences provided herein).

[0079] In some embodiments, the CDR-H1 is defined by the formula $X_1X_2X_3X_4X_5X_6X_7X_8X_9$, where X_1 is G; X_2 is F, G, R, S, or Y; X_3 is I or T; X_4 is F, L, S, or Y; X_5 is D, G, N, R, or S; X_6 is A, D, F, H, I, L, N, P, S, V, or Y; X_7 is D, N, or Y; X_8 is A, D, F, H, I, N, P, S, T, V, or Y; X_9 is M. In some embodiments, the CDR-H1 comprises a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to this consensus sequence. In some embodiments, the CDR-H1 comprises a sequence having 0, 1, 2, 3, 4, 5, or 6 substitutions from this consensus sequence.

[0080] In some embodiments, the CDR-H2 is defined by the formula $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$, where X_1 is no amino acid, A, S, or T; X_2 is I or T; X_3 is I, N, S, or T; X_4 is A, G, P, R, S, T, or W; X_5 is A, D, F, I, L, N, S, T, V, or Y; X_6 is D, G, or S; X_7 is A, D, G, or S; X_8 is I, N, S, or T; X_9 is T; X_{10} is Y or N. In some embodiments, the CDR-H2 comprises a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to this consensus sequence. In some embodiments, the CDR-H2 comprises a sequence having 0, 1, 2, 3, 4, 5, or 6 substitutions from this consensus sequence.

[0081] In some embodiments, the CDR-H3 is defined by the formula $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}X_{21}X_{22}X_{23}$, where X_1 is no amino acid or A; X_2 is no amino acid or H; X_3 is no amino acid or Y; X_4 is no amino acid or N; X_5 is no

amino acid or R; X_6 is no amino acid or Y; X_7 is no amino acid, A, or V; X_8 is no amino acid, A, P, S, or V; X_9 is no amino acid, D, P, or T; X_{10} is no amino acid, A, F, or V; X_{11} is no amino acid, A, G, K, L, R, S, T, or W; X_{12} is no amino acid, A, D, E, I, N, P, S, T, or Y; X_{13} is A, G, H, K, L, P, R, S, T, V, W, or Y; X_{14} is A, D, F, G, I, M, N, P, Q, R, S, T, or W; X_{15} is no amino acid, A, D, E, F, G, H, I, L, M, N, P, Q, R, S, T, V, W, or Y; X_{16} is no amino acid, A, D, E, F, H, I, K, L, M, N, P, Q, R, S, T, V, W, or Y; X_{17} is A, D, E, F, G, H, I, K, L, M, N, P, Q, S, T, V, W, or Y; X_{18} is A, D, F, G, H, K, L, M, N, P, Q, R, S, W, or Y; X_{19} is A, F, G, H, K, M, S, T, or V; X_{20} is F, H, L, M, or Y; X_{21} is D, G, N, S, or Y; X_{22} is no amino acid or Y; X_{23} is no amino acid or W.

[0082] In some embodiments, the CDR-H3 comprises a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to this consensus sequence. In some embodiments, the CDR-H3 comprises a sequence having 0, 1, 2, 3, 4, 5, or 6 substitutions from this consensus sequence.

[0083] In some embodiments of the FAP binding polypeptides, the heavy chain variable domain comprises an amino acid sequence having at least 90%, 95%, 99%, or 100% sequence identity to any sequence selected from **SEQ ID NOs: 325-432**.

[0084] Also disclosed herein are FAP binding polypeptides. In some embodiments, the FAP binding polypeptides comprise an immunoglobulin heavy chain variable domain comprising a CDR-H1. In some embodiments, the CDR-H1 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 1-108**. In some embodiments, the CDR-H1 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NO: 4**, or in the alternative, **SEQ ID NOs: 5, 9, 14, 23, 25, 28, 33, 34, 36, 40, 47, 50, 51, 54, 57, 64, 66, 83, 88, 90, 96, 97, 98, or 99**. In some embodiments, the immunoglobulin heavy chain variable domain further comprises a CDR-H2, wherein the CDR-H2 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 109-216**. In some embodiments, the immunoglobulin heavy chain variable domain further comprises a CDR-H3, wherein the CDR-H3 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 217-324**. In some embodiments, the immunoglobulin heavy chain variable domain comprises an amino acid sequence having at least 90%, 95%, 99%, or 100% sequence identity to any sequence selected from **SEQ ID NOs: 325-432**.

[0085] Also disclosed herein are FAP binding polypeptides. In some embodiments, the FAP binding polypeptides comprise an immunoglobulin heavy chain variable domain comprising a CDR-H2. In some embodiments, the CDR-H2 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 109-216**. In some embodiments, the CDR-H2 comprises a sequence having at least 90%, 95%, 99%, or 100%

sequence identity to a sequence selected from **SEQ ID NO: 110**, or in the alternative, **SEQ ID NOs: 112-118, 121-124, 126, 127, 129-133, 135, 136, 141, 142, 148-152, 155, 158-162, 165, 170, 172, 174, 175, 180, 181, 190, 191, 194-198, 201, 204-207, 211, or 216**. In some embodiments, the immunoglobulin heavy chain variable domain further comprises a CDR-H1, wherein the CDR-H1 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 1-108**. In some embodiments, the immunoglobulin heavy chain variable domain further comprises a CDR-H3, wherein the CDR-H3 comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to a sequence selected from **SEQ ID NOs: 217-324**. In some embodiments, the immunoglobulin heavy chain variable domain comprises an amino acid sequence having at least 90%, 95%, 99%, or 100% sequence identity to any sequence selected from **SEQ ID NOs: 325-432**.

[0086] In some embodiments, the FAP binding polypeptide is humanized. In some embodiments, the FAP binding polypeptide is a single domain antibody (sdAb).

[0087] In some embodiments, the FAP binding polypeptide binds to FAP with a dissociation constant (KD) of less than 1 nM, 2 nM, 5 nM, 10 nM, 15 nM, 20 nM, 30 nM, 40 nM, 50 nM, 60 nM, 70 nM, 80 nM, 90 nM, 100 nM, 200 nM, 300 nM, 400 nM, 500 nM, 600 nM, 700 nM, 800 nM, 900 nM, or 1000 nM, or any KD within a range defined by any two of the aforementioned KD.

[0088] The binding polypeptides disclosed herein may be obtained from an antibody library. In some embodiments, the antibody library is an immune antibody library, a naïve antibody library, a synthetic antibody library, or a semi-synthetic antibody library. In some embodiments, the antibody library comprises antibodies derived from human, or antibodies that are not immunogenic in humans, or both. In some embodiments, the antibody library comprises antibodies that are humanized, e.g. from mouse, rat, guinea pig, rabbit, cat, dog, cow, horse, sheep, goat, horse, donkey. In some embodiments, the antibody library comprises single domain antibodies (sdAb), nanobodies, V_HH fragments, V_{NAR} fragments, single-chain variable fragments (scFv), camelid antibodies, or cartilaginous fish antibodies, or any combination thereof. One exemplary library that can be used is a fully humanized, synthetic, sdAb library, but any other antibody library that can be prepared or is available can be used for the methods disclosed herein. In some embodiments, the antibody library comprises sdAb. In some embodiments, the antibody library comprises at least 100, 500, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 20000, 30000, 40000, 50000, 60000, 70000, 80000, 90000, 100000, 500000, or 1000000 unique antibodies, or any number of antibodies within a range defined by any two of the aforementioned number of antibodies.

[0089] Antibody libraries may be generated computationally or using machine learning processes. An exemplary method of generating an antibody library computationally includes modifying a universal V_HH framework with synthetic diversity in one or more complementary determining regions (CDRs), such as CDR1, CDR2, or CDR3, or any combination thereof. The diversity of the CDRs are introduced by randomizing the library of sequences encoding for the antibodies with degenerate codons. For example, an NNK codon library can be employed, where the NNK codon comprises N (25% mix of A/T/C/G) and K (50% mix of T/G). In some embodiments, the NNK codon library is constructed with all possible amino acids, or with some amino acids (e.g. cysteine) and stop codon combinations excluded. Other degenerate codon mixes can be substituted for said NNK codon library with minimal experimentation. In other embodiments, the antibody library can be generated using a trimer codon mix, which improves balanced representation of sense codons while reducing the chance of stop codons, improving efficiency of antibody generation and testing. In some embodiments, artificial intelligence-based prediction can be used to randomize specific binding pockets of the antibodies using available binding models or structure data.

[0090] In some embodiments, panning the antibody library comprises screening for the candidate binding polypeptides by phage display, yeast display, bacterial display, ribosome display, or mRNA display, or any combination thereof. In some embodiments, panning the antibody library comprises one or more rounds of selection, wherein the candidate binding polypeptides are selected for specificity towards a cancer-associated antigen (e.g. FAP) or cells or tissues displaying the cancer-associated antigen. In some embodiments, the candidate binding polypeptides are selected under conditions including but not limited to tumor microenvironment-like conditions, immunosuppressive conditions, low or high pH, low or high oxygen concentrations, low or high temperatures, low or high viscosity, or any combination thereof, or for specificity towards modified or derivative forms of the one or more cancer-associated antigens. In some embodiments, the immunosuppressive conditions may comprise the presence of tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), tumor-associated neutrophils (TANs), cancer-associated fibroblasts (CAFs), or other immunosuppressive cells, or the presence of adenosine, or both.

[0091] In some embodiments, the chimeric antigen receptor cells are from a cell line (e.g. Jurkat). In some embodiments, the chimeric antigen receptor cells are derived from a subject. In some embodiments, the subject has a cancer. In some embodiments, the subject has a cancer, and that cancer expresses any one or more of the cancer-associated antigens disclosed herein (e.g. FAP). In some embodiments, the cancer is breast cancer, colorectal cancer, kidney cancer, liver cancer, lung cancer, brain cancer, pancreatic cancer, bladder cancer, testicular cancer, prostate

cancer, gastric cancer, ovarian cancer, head and neck cancer, gallbladder cancer, a hematologic malignancy, or any combination thereof. In some embodiments, the hematologic malignancy may comprise leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy cell leukemia, lymphoma, Hodgkin's disease, Non-Hodgkin lymphoma, or multiple myeloma. In some embodiments, the subject is a mammal, such as a human, cat, dog, mouse, rat, hamster, rodent, cow, pig, horse, goat, sheep, donkey, or monkey. In some embodiments, the subject is a human.

Chimeric Antigen Receptors (CARs) and Cells

[0092] Also disclosed herein are chimeric antigen receptors (CARs) comprising any one or more of the FAP binding polypeptides disclosed herein.

[0093] In some embodiments, the CAR comprises at least two binding polypeptides and the CAR is a multivalent CAR. In some embodiments, the CAR comprises two binding polypeptides and the CAR is a bivalent CAR. In some embodiments, the CAR comprises three binding polypeptides and the CAR is a trivalent CAR.

[0094] In some embodiments, the CAR further comprises one or more signal peptides, linkers with various lengths and composition, hinges, transmembrane domains, costimulatory domains, signaling domains, cytoplasmic domains, functionality signals, proliferation signals, anti-exhaustion signals, anti-inhibitory receptors, tumor/cancer homing proteins, or regulatory molecules, or any combination thereof. In some embodiments, the hinges comprise CD3ζ, CD4, CD8 or CD28 hinges, or computationally designed synthetic hinges with various lengths. In some embodiments, the transmembrane domains comprise CD3ζ, CD4, CD8 or CD28 transmembrane domains, or computationally designed synthetic transmembrane domains. In some embodiments, the costimulatory domains comprise CD8, CD28, ICOS, 4-1BB, OX40 (CD134), CD27, CD40, CD40L, TLR or other TNFR superfamily member or Ig superfamily member costimulatory domains, or other signaling via cytoplasmic domains of IL-2Rβ, IL-15R-α, MyD88, or CD40 or any other Toll-like receptor or IL-1 receptor signaling pathway members.

[0095] In some embodiments, the CARs disclosed herein are constructed by assembling CAR expression constructs from nucleic acids encoding for any one of the binding polypeptides disclosed herein and a mixture of compatible nucleic acids encoding for different CAR modules. In some embodiments, different combinations of CARs are produced for use in a CAR library for screening for CAR efficacy (*in vitro* or *in vivo*). In some embodiments, unique CARs are produced separately. In some embodiments, the CARs are specific for one target. In some embodiments, the CARs are specific for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 targets. In some embodiments, the CARs are bi-specific or tri-specific.

[0096] To construct any one of CARs disclosed herein, the nucleic acids encoding for the binding polypeptides identified by panning of the antibody library are assembled into CAR expression constructs with other CAR modules. In some embodiments, the CAR expression constructs are assembled using multi-fragment assembly reactions known in the art. One exemplary method of assembling CAR expression constructs involves using Type IIS restriction enzymes to generate nucleic acid fragments with compatible overhang sequences and ligating the nucleic acid fragments with a ligase. As Type IIS restriction enzymes cleave outside of their recognition sites, multiple compatible nucleic acid fragments may be prepared simultaneously. In other embodiments, the CAR expression constructs can be assembled by overlap extension PCR. It is envisioned that any other method of assembling nucleic acid constructs from more than one nucleic acid fragment can be employed. In some embodiments, the different CAR modules comprise signal peptides, linkers, hinges, transmembrane domains, costimulatory domains, activation domains, signaling domains, cytoplasmic domains, functionality signals, proliferation signals, anti-exhaustion signals, anti-inhibitor receptors, cancer homing proteins, or regulatory molecules, or any combination thereof. Some exemplary hinges comprise CD8 hinge, CD28 hinge, IgG1 hinge, or IgG4 hinge. Some exemplary transmembrane domains comprise CD3ζ transmembrane domain, CD8α transmembrane domain, CD4 transmembrane domain, CD28 transmembrane domain, or ICOS transmembrane domain. Some exemplary costimulatory domains comprise CD8 costimulatory domain, CD28 costimulatory domain, 4-1BB costimulatory domain, OX40 (CD134) costimulatory domain, ICOS costimulatory domain, CD27 costimulatory domain, CD40 costimulatory domain, CD40L costimulatory domain, TLR costimulatory domains, MYD88-CD40 costimulatory domain, or KIR2DS2 costimulatory domain. In some embodiments, the different CAR modules are derived from CD8, CD28, 4-1BB, CD3ζ, or any combination thereof. The CAR may also be modified with various additions, including but not limited to cytokines, chemokines, cytokine receptors, chemokine receptors, antigen receptors or ligands, antibodies, or enzymes.

[0097] Also disclosed herein are chimeric antigen receptor (CAR) cells comprising any one of the CARs disclosed herein. In some embodiments, the CAR cell is a CAR-T cell. In some embodiments, the CAR cell is derived from a subject or from a cell line. In some embodiments, the subject has a cancer. In some embodiments, the subject has a cancer, and that cancer expresses any one or more of the cancer-associated antigens disclosed herein (e.g. FAP). In some embodiments, the cancer is breast cancer, colorectal cancer, kidney cancer, liver cancer, lung cancer, brain cancer, pancreatic cancer, bladder cancer, testicular cancer, prostate cancer, gastric cancer, ovarian cancer, head and neck cancer, gallbladder cancer, a hematologic malignancy, or any combination thereof. In some embodiments, the hematologic malignancy may comprise

leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy cell leukemia, lymphoma, Hodgkin's disease, Non-Hodgkin lymphoma, or multiple myeloma.

Nucleic Acids

[0098] Also disclosed herein are nucleic acids that encode for a polypeptide. In some embodiments, the polypeptide is a binding polypeptide. In some embodiments, the polypeptide is a single domain binding polypeptide. In some embodiments, the polypeptide is any one of the binding polypeptides disclosed herein. In some embodiments, the polypeptide comprises a sequence having at least 90%, 95%, 99%, or 100% sequence identity to: any one or more of the FAP binding polypeptides disclosed herein. In some embodiments, the polypeptide is any one of the CARs disclosed herein.

[0099] Any one of the nucleic acids that encode for a binding polypeptide can be prepared by recombinant DNA technology, synthetic chemistry techniques, or a combination thereof. For example, sequences of nucleic acids encoding for the binding polypeptide may be cloned into an expression vector using standard molecular techniques known in the art. Sequences can be obtained from other vectors encoding the desired protein sequence, from PCR-generated fragments using respective template nucleic acids, or by assembly of synthetic oligonucleotides encoding the desired sequences. In some embodiments, the expression vector may be a CAR expression vector, in which it is provided to an immune cell so that it expresses the CAR. In some embodiments, the expression vector may be an expression vector suited for large scale antibody or binding polypeptide production, from which the peptide products can be isolated for further use.

[0100] Expression of binding polypeptides or CARs may be confirmed by nucleic acid or protein assays known in the art. For example, the presence of transcribed mRNA of binding polypeptides or CARs can be detected and/or quantified by conventional hybridization assays (e.g. Northern blot analysis), amplification procedures (e.g. RT-PCR), SAGE (U.S. Pat. No. 5,695,937), and array-based technologies (see e.g. U.S. Pat. Nos. 5,405,783, 5,412,087 and 5,445,934), using probes complementary to any region of a polynucleotide that encodes for the binding polypeptides or CARs. Expression of the binding polypeptides or CARs can also be determined by examining the expressed peptide. A variety of techniques are available in the art for protein analysis. They include but are not limited to radioimmunoassays, ELISA (enzyme linked immunoradiometric assays), "sandwich" immunoassays, immunoradiometric assays, in situ immunoassays (using e.g., colloidal gold, enzyme or radioisotope labels), western blot analysis, immunoprecipitation assays, immunofluorescent assays, and SDS-PAGE.

Methods of Use or Treatment

[0101] Also disclosed herein are methods of treating a cancer in a subject in need thereof. In some embodiments, the methods comprise administering a chimeric antigen receptor cell to the subject. In some embodiments, the methods comprise administering any one of the chimeric antigen receptor cells disclosed herein. In some embodiments, the chimeric antigen receptor cell expresses and/or comprises any one or more of the FAP binding polypeptides disclosed herein. In some embodiments, the chimeric antigen receptor cell is a CAR-T cell. In some embodiments, the chimeric antigen receptor cell is derived from the subject and is autologous to the subject. In some embodiments, the chimeric antigen receptor cell is allogeneic to the subject. In some embodiments, the chimeric antigen receptor cell is from a cell line (e.g. Jurkat). In some embodiments, the subject is a mammal, such as a human, cat, dog, mouse, rat, hamster, rodent, cow, pig, horse, goat, sheep, donkey, or monkey. In some embodiments, the subject is a human. In some embodiments, the subject has a cancer that expresses any one or more of the cancer-associated antigens disclosed herein (e.g. FAP). In some embodiments, the cancer is breast cancer, colorectal cancer, kidney cancer, liver cancer, lung cancer, brain cancer, pancreatic cancer, bladder cancer, testicular cancer, prostate cancer, gastric cancer, ovarian cancer, head and neck cancer, gallbladder cancer, a hematologic malignancy, or any combination thereof. In some embodiments, the hematologic malignancy may comprise leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy cell leukemia, lymphoma, Hodgkin's disease, Non-Hodgkin lymphoma, or multiple myeloma. In some embodiments, the chimeric antigen receptor cell is administered parenterally.

[0102] In some embodiments, the chimeric antigen receptor cell is administered once per day, twice per day, three times per day or more. In some embodiments, the chimeric antigen receptor cell is administered daily, every day, every alternate day, five days a week, once a week, every other week, two weeks per month, three weeks per month, once a month, twice a month, three times per month, or more. In some embodiments, the immune cell is administered for at least 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 18 months, 2 years, 3 years, or more.

[0103] In some embodiments, the amount of a given agent that correspond to such an amount varies depending upon factors such as the particular compound, the severity of the disease, the identity (e.g., weight) of the subject or host in need of treatment, but nevertheless is routinely determined in a manner known in the art according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, and

the subject or host being treated. In some instances, the desired dose is conveniently presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[0104] The ranges for administration are merely suggestive, as the number of variables in regard to an individual treatment regime is large, and considerable excursions from these recommended values are not uncommon. Such dosages is altered depending on a number of variables, not limited to the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[0105] In some embodiments, toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD50 and ED50. Compounds exhibiting high therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with minimal toxicity. The dosage varies within this range depending upon the dosage form employed and the route of administration utilized.

EXAMPLES

[0106] Some aspects of the embodiments discussed above are disclosed in further detail in the following examples, which are not in any way intended to limit the scope of the present disclosure. Those in the art will appreciate that many other embodiments also fall within the scope of the invention, as it is described herein above and in the claims.

Example 1. Methodology

[0107] Plasmid preparation and quality check (QC)

[0108] The Maxi Plasmid Purification kit (Zymo, D4203) was used for CAR plasmid preparation. Plasmid concentration and quality was analyzed by Nanodrop (260/280 ratio and 260/230 ratio) and the ToxinSensor Chromogenic LAL Endotoxin Assay (Genescript, L00350). Good-quality plasmid DNA will have an A260/A280 ratio of 1.8-2.0, an A260/A230 ratio greater than 2.0, and less than 0.1 EU/μg of endotoxin.

[0109] Plasmid assembly and QC

[0110] All CARs were synthesized by Genewiz. Synthetic single domain antibody genes encoding antibodies which bind to FAP were cloned into the pLenti vector and the construct was confirmed using Sanger sequencing. The CAR constructs contain a signal peptide (e.g. CD8 signal peptide), hinge (e.g. CD8α stalk), transmembrane domain (e.g. CD8 transmembrane domain or CD28 transmembrane domain), and signaling domains (e.g. 4-1BB costimulatory domain or CD3ζ signaling domain) and the anti-FAP sdAb.

[0111] To monitor CAR expression levels, the expressed cassette of the CAR plasmids can also be engineered to express fluorescent eGFP+T2A self-cleaving peptide sequences. Alternatively, truncated CD19 or truncated EGFR cassettes can be used to monitor by antibody detection. Human sequences (e.g. CD8, 4-1BB, CD3ζ) are accessible on GenBank.

[0112] Virus production and titration

[0113] To produce the lentivirus with the anti-FAP CAR construct, human embryonic kidney 293T (HEK293T) cells were co-transfected with CAR transgene-encoding pLenti transfer plasmid and one or more necessary packaging plasmids (i.e. encoding for Gag, Pol, Rev, VSVG, and optionally Tat). The supernatants of the HEK293T cultures were collected at either 48 or 72 hours after transfection, centrifuged, and filtered with a 0.45 μm filter.

[0114] Virus titration was done in Jurkat cells transduced with diluted lentivirus collections. After 48 hours, transduced Jurkat cells were stained with biotinylated recombinant protein L and phycoerythrin (PE)-conjugated streptavidin, and anti-FAP CAR abundance was measured by flow cytometry.

[0115] T cell transduction and expansion

[0116] Human PBMCs were isolated from peripheral blood of healthy human donors by density gradient centrifugation with the Lymphoprep reagent (StemCell Technologies). PBMCs were resuspended at $1x10^6$ cells/mL in X-VIVO 15 serum-free hematopoietic medium (Lonza, 04-418QCN) with 10 ng/mL IL-2 (Novoprotein, GMP-CD66) and 10 ng/mL IL-7 (Novoprotein, GMP-CD47). PBMCs were stimulated with 50 ng/mL anti-CD3 antibody (Novoprotein, GMP-A018) for 24 hours. Then, PBMCs were transduced with anti-FAP CAR lentivirus (at MOI of 1-10) and expanded in appropriate flasks for 9-10 days in RPMI 1640 basal medium supplemented with 10% fetal bovine serum. T cells were rested for 24 hours at 37°C before any assay. CAR surface levels, CD3, and CD4/CD8 ratios (using antibodies from Biolegend, 317344, 301012, and 317412) were measured 12 or 14 days after initial stimulation of PBMCs with the anti-CD3 antibody.

[0117] T cell cryopreservation and thawing

[0118] After 14 days of CAR-T expansion, anti-FAP CAR-T cells were centrifuged and the supernatant was discarded. The cell pellet was resuspended in chilled CryoStor CS10

(StemCell Technologies, 07930) at a viable cell density of 5 x 10^7 cells/mL. Aliquots of cell suspension were dispensed into cryovials. The cryovials were cooled with a 1°C/minute decrease. The frozen cells were transferred to liquid nitrogen.

[0119] To thaw, the cells are quickly thawed in a 37°C water bath with gentle agitation. The thawed cells are transferred to a 50 mL conical tube and washed by adding 20 mL of fresh growth medium dropwise. The cells are centrifuged and resuspended in X-VIVO 15 medium at a cell density of 1 x 10^6 cells/mL.

[0120] Cytotoxicity assay

[0121] The cytotoxicity of anti-FAP CAR T-cells was determined by standard luciferase-based assays. Briefly, target cells expressing firefly luciferase were co-cultured with CAR-T cells in triplicate at the indicated effector:target ratios using white-walled 96-well plates with 2 x 10^4 target cells in a total volume of 100 µL per well in X-VIVO 15 medium. Target cells alone as a control were plated at the same cell density. After 48 hours of co-culture, 100 µL of luciferase substrate (ONE-Glo, Promega) was directly added to each well. Emitted light was detected with a luminescence plate reader.

[0122] In a similar luciferase based cytotoxicity assay, target cancer cells that are engineered to overexpress luciferase are prepared in a cell culture medium (such as RPMI) and seeded on to 96 well plates with 5 x 10^4 to 5 x 10^6 cells in a volume of 100 µL/well, and incubated at 37°C for 24 hours. Then, CAR T-cells are seeded in corresponding wells with CAR T cells at various effector:target (E:T) ratios (e.g., 5:1, 1:1, and 1:5) in 100 µL/well. The co-cultures are then incubated at 37°C for 24 or 48 hours. Subsequently, the cells are processed with the Luciferase Assay System (Promega, E1501) according to manufacturer's instructions using a plate reader. Luminescence is read in endpoint mode using a BioTek Synergy H4 hybrid microplate reader for 10 seconds. Percentage of specific lysis was calculated using the luciferase activity of digitonin-treated cells as maximum cell death and untreated cells as spontaneous cell death, using the formula % specific lysis = 100% x [(experimental luminescence – spontaneous cell death luminescence)/(maximum cell death luminescence – spontaneous cell death luminescence)].

[0123] Additional information regarding exemplary luciferase cytotoxicity assays may be found in Matta H et al. "Development and characterization of a novel luciferase based cytotoxicity assay" *Scientific Reports* (2018) 8,199, which is hereby expressly incorporated by reference in its entirety.

[0124] IFN-γ evaluation

[0125] 1 x 10^6 per well of anti-FAP CAR T-cells were stimulated with target cells at indicated effector:target cell ratios in 6-well tissue culture plates for 24 hours. Interferon gamma

(IFN-γ) and IL-2 secretion was quantitated through enzyme-linked immunosorbent assay (ELISA) using the human IL-2 ELISA Kit II (BD, 550611) and human IFN-γ ELISA Kit II (BD, 550612)

[0126] CD25/CD69 assay

[0127] 1 x 10^6 per well of anti-FAP CAR T-cells were stimulated with target cells at indicated effector:target cell ratios in 6-well tissue culture plates for 24 hours. Cells were stained with LIVE/DEAD Fixable Near-IR Dead Cell Stain Kit (ThermoFisher) to label dead cells and with anti-CD3, and CAR-T cells were identified as CD3+ GFP+ cells by flow cytometry. CD69 and CD25 on CAR-T cells were stained with Alexa Fluor 700 anti-human CD69 antibody (Biolegend) and PE anti-CD25 antibody (Biolegend).

[0128] Sequencing of CAR T cell libraries

[0129] Cells were collected from anti-FAP CAR-T library screens. Genomic DNA (gDNA) was extracted using the Blood/Cell Genome DNA Mini kit (Tiangen, DP304-03). 75 ng of gDNA was used for PCT to amplify the CAR region of the library. The amplified region was TA cloned with the TA/Blunt-Zero Cloning kit (Vazyme, C601) and sequenced.

Example 2. Anti-FAP CAR-T cells for the treatment of cancer

[0130] A patient presents with a cancer, for example, a cancer that expresses or overexpresses FAP (e.g., such that FAP can be used as a biomarker to detect and target the cancer). In some cases, the cancer is breast cancer, colorectal cancer, kidney cancer, liver cancer, lung cancer, brain cancer, pancreatic cancer, bladder cancer, testicular cancer, prostate cancer, gastric cancer, ovarian cancer, head and neck cancer, gallbladder cancer, a hematologic malignancy, or any combination thereof. In some cases, the hematologic malignancy may comprise leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy cell leukemia, lymphoma, Hodgkin's disease, Non-Hodgkin lymphoma, or multiple myeloma.

[0131] One or more of the CAR T-cells disclosed herein, which may include any one or more of the anti-FAP CARs and/or anti-FAP binders, are administered to the patient enterally, orally, intranasally, parenterally, intravenously, intraperitoneally, intramuscularly, intra-arterially, intraventricularly, intradermally, intralesionally, intracranially, intrathecally, or subcutaneously.

[0132] The CAR T-cells are administered as doses in the amount of 10^4, 10^5, 10^6, 10^7, 10^8, or 10^9 cells per dose, or any number of cells within a range defined by any two of the aforementioned cells per dose, or any number of cells that is effective and/or safe as determined by a trained medical practitioner. The doses are administered every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24, 36, or 48 days, or weeks, or any time within a range defined by any two of the

aforementioned times, or any timing of dosing that is effective and/or safe as determined by a trained medical practitioner.

[0133] An improvement of the cancer or symptoms thereof is observed in the patient following administration of the one or more CAR T-cells. Administration of the CAR T-cells may be performed in conjunction with another therapy for cancer, including but not limited to immunotherapy, chemotherapy, radiation therapy, surgery, photodynamic therapy, or targeted therapy.

[0134] In at least some of the previously described embodiments, one or more elements used in an embodiment can interchangeably be used in another embodiment unless such a replacement is not technically feasible. It will be appreciated by those skilled in the art that various other omissions, additions and modifications may be made to the methods and structures described above without departing from the scope of the claimed subject matter. All such modifications and changes are intended to fall within the scope of the subject matter, as defined by the appended claims.

[0135] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity.

[0136] It will be understood by those within the art that, in general, terms used herein, and especially in the appended claims (e.g., bodies of the appended claims) are generally intended as "open" terms (e.g., the term "including" should be interpreted as "including but not limited to," the term "having" should be interpreted as "having at least," the term "includes" should be interpreted as "includes but is not limited to," etc.). It will be further understood by those within the art that if a specific number of an introduced claim recitation is intended, such an intent will be explicitly recited in the claim, and in the absence of such recitation no such intent is present. For example, as an aid to understanding, the following appended claims may contain usage of the introductory phrases "at least one" and "one or more" to introduce claim recitations. However, the use of such phrases should not be construed to imply that the introduction of a claim recitation by the indefinite articles "a" or "an" limits any particular claim containing such introduced claim recitation to embodiments containing only one such recitation, even when the same claim includes the introductory phrases "one or more" or "at least one" and indefinite articles such as "a" or "an" (e.g., "a" and/or "an" should be interpreted to mean "at least one" or "one or more"); the same holds true for the use of definite articles used to introduce claim recitations. In addition, even if a specific number of an introduced claim recitation is explicitly recited, those skilled in the art will

recognize that such recitation should be interpreted to mean at least the recited number (e.g., the bare recitation of "two recitations," without other modifiers, means at least two recitations, or two or more recitations). Furthermore, in those instances where a convention analogous to "at least one of A, B, and C, etc." is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (e.g., "a system having at least one of A, B, and C" would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). In those instances where a convention analogous to "at least one of A, B, or C, etc." is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (e.g., " a system having at least one of A, B, or C" would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). It will be further understood by those within the art that virtually any disjunctive word and/or phrase presenting two or more alternative terms, whether in the description, claims, or drawings, should be understood to contemplate the possibilities of including one of the terms, either of the terms, or both terms. For example, the phrase "A or B" will be understood to include the possibilities of "A" or "B" or "A and B."

[0137] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[0138] As will be understood by one skilled in the art, for any and all purposes, such as in terms of providing a written description, all ranges disclosed herein also encompass any and all possible sub-ranges and combinations of sub-ranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as "up to," "at least," "greater than," "less than," and the like include the number recited and refer to ranges which can be subsequently broken down into sub-ranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. Thus, for example, a group having 1-3 articles refers to groups having 1, 2, or 3 articles. Similarly, a group having 1-5 articles refers to groups having 1, 2, 3, 4, or 5 articles, and so forth.

[0139] While various aspects and embodiments have been disclosed herein, other aspects and embodiments will be apparent to those skilled in the art. The various aspects and embodiments disclosed herein are for purposes of illustration and are not intended to be limiting, with the true scope and spirit being indicated by the following claims.

[0140] All references cited herein, including but not limited to published and unpublished applications, patents, and literature references, are incorporated herein by reference in their entirety and are hereby made a part of this specification. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

Sequence List

FAP sequences

Name	CDR-H1	SEQ ID NO	CDR-H2	SEQ ID NO	CDR-H3	SEQ ID NO
FAP-FR2-A01	GSTSNNYFM	1	AINPLDSNTY	109	AGHWDSHFNYW	217
FAP-FR2-B01	GFTSGVYFM	2	AISRTGGSTY	110	VGDWDIFHYSYW	218
FAP-FR2-C01	GFTFGFNYM	3	AISRISDSTY	111	AGIVQYHYNYW	219
FAP-FR2-E01	GRTFSYNPM	4	AISRTGGSTY	112	AGEWMMHFNYW	220
FAP-FR2-F01	GRTFSYNPM	5	AISRTGGSTY	113	AGTDTWHYNYW	221
FAP-FR2-G01	GSIFSHYSM	6	AISRTGGSTY	114	AGPWHAHFSYW	222
FAP-FR2-H01	GYILRDDPM	7	AISRTGGSTY	115	VSTYRADARSLGYW	223
FAP-FR2-B02	GSTFSYYFM	8	AISRTGGSTY	116	AATTQFHFGYW	224
FAP-FR2-C02	GRTFSYNPM	9	AISRTGGSTY	117	AGTFDQHFNYW	225
FAP-FR2-D02	GFIYSNYYM	10	AISRTGGSTY	118	ASRTWMHFNYW	226
FAP-FR2-E02	GFIFSAYYM	11	TINSVDDITY	119	AGQYQYHYSYW	227
FAP-FR2-H02	GSTYDVDYM	12	TINSYGGITY	120	ASATKDHYNYW	228
FAP-FR2-B03	GSIYSFYFM	13	AISRTGGSTY	121	AGNIHYHYNYW	229
FAP-FR2-C03	GRTFSYNPM	14	AISRTGGSTY	122	AGESDRHYNYW	230
FAP-FR2-D03	GRIYRNYSM	15	AISRTGGSTY	123	VGYVFQHFNYW	231
FAP-FR2-F03	GFIFSFYFM	16	AISRTGGSTY	124	AAFWDYHYDYW	232
FAP-FR2-H03	GYIFSVNFM	17	TINWFDDITY	125	AGGTEWHFNYW	233
FAP-FR2-B04	GSIFDYYYM	18	AISRTGGSTY	126	ASVISFHYNYW	234
FAP-FR2-D04	GSIYSNYYM	19	AISRTGGSTY	127	AGPMNWHYGYW	235
FAP-FR2-E04	GFIFNIYSM	20	SINWSDSSTY	128	AGPYYWGLSYW	236
FAP-FR2-G04	GSIYDLYTM	21	AISRTGGSTY	129	VGQYDWHFDYW	237
FAP-FR2-A05	GRIYDLYNM	22	AISRTGGSTY	130	AGQPMYHFNYW	238
FAP-FR2-C05	GRTFSYNPM	23	AISRTGGSTY	131	VVTVWYSPFKVKMYNYW	239
FAP-FR2-D05	GFTYGFNYM	24	AISRTGGSTY	132	AGIWHMHYNYW	240
FAP-FR2-E05	GRTFSYNPM	25	AISRTGGSTY	133	ATSWRSPPPAYGYW	241
FAP-FR2-F05	GSIYRFDSM	26	TITSLDSITY	134	AGAWKNHFNYW	242

FAP-FR2-G05	GFISSAYSM	27	AISRTGGSTY	135	AGDSDLHYSYW	243
FAP-FR2-H05	GRTFSYNPM	28	AISRTGGSTY	136	ATSPRGLSAGHGYW	244
FAP-FR2-A06	GSIFSSYIM	29	SINSYDSTTY	137	ATEVPMHYNYW	245
FAP-FR2-B06	GFTLNIYHM	30	AINSFSDITY	138	AGEWPLHYSYW	246
FAP-FR2-C06	GGTFSFYFM	31	TINSFDDITY	139	AGLWHQHYNYW	247
FAP-FR2-D06	GRIYDANFM	32	TINTYSDITY	140	AGNWTFHFNYW	248
FAP-FR2-E06	GRTFSYNPM	33	AISRTGGSTY	141	AGRYLWHYNYW	249
FAP-FR2-F06	GRTFSYNPM	34	AISRTGGSTY	142	AGLQEYHYNYW	250
FAP-FR2-A07	GFIFDYYFM	35	TINSFSSSTY	143	AGDYDRHYSYW	251
FAP-FR2-B07	GRTFSYNPM	36	TISFSGITY	144	AGVEQFHFNYW	252
FAP-FR2-C07	GFTFSFYFM	37	SINAYSDSTY	145	AGHWNHHYNYW	253
FAP-FR2-D07	GRIFSSYSM	38	TISSFSDITY	146	VGDWDWHFNYW	254
FAP-FR2-E07	GSTFGYDNM	39	TINSFGDITN	147	AGYYPMHYSYW	255
FAP-FR2-F07	GRTFSYNPM	40	AISRTGGSTY	148	AGDNWMHHNYW	256
FAP-FR2-G07	GGISDYYSM	41	AISRTGGSTY	149	AGYWFAHFNYW	257
FAP-FR2-H07	GYIFSFYFM	42	AISRTGGSTY	150	AGDHDLHYNYW	258
FAP-FR2-A08	GFIFGIYFM	43	AISRTGGSTY	151	VGLYDRHYNYW	259
FAP-FR2-C08	GSIYGYDYM	44	AISRTGGSTY	152	VGIWDFYHFNYW	260
FAP-FR2-D08	GSILGSYIM	45	TINSNDSITY	153	AGDIMYHYNYW	261
FAP-FR2-E08	GFIYSFYVM	46	TINSFDDTTY	154	VKERFTTPYAHSYW	262
FAP-FR2-G08	GRTFSYNPM	47	AISRTGGSTY	155	AGPLWQLYRSHGYW	263
FAP-FR2-A09	GFTFSFYSM	48	SINAIDSITY	156	VGPVYLHYNYW	264
FAP-FR2-B09	GGTFGVNPM	49	TITSTDDITY	157	AGRFPFHYDYW	265
FAP-FR2-C09	GRTFSYNPM	50	AISRTGGSTY	158	VSSKGSSAASLNYW	266
FAP-FR2-D09	GRTFSYNPM	51	AISRTGGSTY	159	AGDYYGHHNYW	267
FAP-FR2-E09	GFISGHYYM	52	AISRTGGSTY	160	AGYVQWHYGYW	268
FAP-FR2-F09	GGILRIYFM	53	AISRTGGSTY	161	AGTAHQHYDYW	269
FAP-FR2-G09	GRTFSYNPM	54	AISRTGGSTY	162	VTNHMERHASYGYW	270
FAP-FR2-H09	GFIFNVYYM	55	TISWYSDITY	163	ATRTDWHFNYW	271
FAP-FR2-B10	GSIYSFYFM	56	TINSFDSITY	164	AGQYNFHYSYW	272

FAP-FR2-C10	GRTFSYNPM	57	AISRTGGSTY	165	AGTTGLHYNYW	273
FAP-FR2-D10	GSIFGAYYM	58	AINPDSDITY	166	AGTILHHFNYW	274
FAP-FR2-E10	GSTFRFYSM	59	TISSFDDITY	167	AGPWHFHFGYW	275
FAP-FR2-F10	GFILGSDTM	60	SINSFDSITY	168	AGDYPWHYNYW	276
FAP-FR2-G10	GFIFSVYSM	61	AINTVDSITY	169	AGPAMLHFSYW	277
FAP-FR2-H10	GRTFNFYAM	62	AISRTGGSTY	170	AGMFKYHFNYW	278
FAP-FR2-A11	GRTLSSYTM	63	SISWVDSITY	171	VIFPEQVYDYW	279
FAP-FR2-C11	GRTFSYNPM	64	AISRTGGSTY	172	VATFRTTNDYYSSHGYW	280
FAP-FR2-D11	GYISSSYSM	65	AISSFSDITY	173	AGGSMFHYNYW	281
FAP-FR2-F11	GRTFSYNPM	66	AISRTGGSTY	174	AGRIMMHFNYW	282
FAP-FR2-G11	GSIYSHNFM	67	AISRTGGSTY	175	ASYTAFHYNYW	283
FAP-FR2-H11	GFIFSFYSM	68	TINTFSDITY	176	AGPWAFHYNYW	284
FAP-FR2-B12	GFIFDFYFM	69	TINSISDITY	177	ATDTADHYNYW	285
FAP-FR2-C12	GFIYSSNNM	70	SINSFDDSTY	178	AGMIQFHHNYW	286
FAP-FR2-D12	GRILRHYHM	71	TINTLDSITY	179	AGIWFRHYNYW	287
FAP-FR2-F12	GFIFGSYFM	72	AISRTGGSTY	180	ASPTWMHFNYW	288
FAP-FR2-G12	GYIFSSYAM	73	AISRTGGSTY	181	VGATHLHYSYW	289
FAP-FR2-H12	GFTFGAYHM	74	TINWFGGITY	182	AGDFPHHFNYW	290
FAP-FR3-A01	GRTFGLDFM	75	SINSFDDITN	183	AGRWDRHYNY	291
FAP-FR3-B01	GYILSFYYM	76	TINSFSDITY	184	AGLVAFHYNYW	292
FAP-FR3-E01	GFISSLYSM	77	TITGSSSITY	185	AGDFHRHYNYW	293
FAP-FR3-F01	GFIFNYYYM	78	TISAFDDSTY	186	ADIFPLHFSYW	294
FAP-FR3-H01	GSTSGAYNM	79	TINWFDDITY	187	AGQYEWHYSYW	295
FAP-FR3-A02	GFIYNFNSM	80	AINRFDDITY	188	AGHAWLHHNYW	296
FAP-FR3-C02	GSTSRDYSM	81	TINSNSDITY	189	AGPWNHHYNYW	297
FAP-FR3-D02	GSTYNVYPM	82	AISRTGGSTY	190	AGDNFMHHNYW	298
FAP-FR3-F02	GRTFSYNPM	83	AISRTGGSTY	191	AADFPMHFNYW	299
FAP-FR3-G02	GSTFNYYDM	84	TINRFSSITY	192	ATVTPFHFSYW	300
FAP-FR3-A03	GFISGVYFM	85	TISSASDITY	193	AGIYMWHYNYW	301
FAP-FR3-B03	GFILGANPM	86	AISRTGGSTY	194	AGDEDYHYNYW	302

FAP-FR3-C03	GFIYGYNHM	87	AISRTGGSTY	195	AAEFQWHFGYW	303
FAP-FR3-D03	GRTFSYNPM	88	AISRTGGSTY	196	AGHSWLHFNYW	304
FAP-FR3-A04	GFIYNYNHM	89	AISRTGGSTY	197	VGQEHLHYNYW	305
FAP-FR3-B04	GRTFSYNPM	90	AISRTGGSTY	198	ATTYQGRDDGFNYW	306
FAP-FR3-E04	GSTYSFNTM	91	SINSSDSSTY	199	AGDYDRHFNYW	307
FAP-FR3-G04	GSTFSAYSM	92	AINSFDDITY	200	AGPLYLHHDYW	308
FAP-FR3-H04	GSTFNPYFM	93	AISRTGGSTY	201	AGWWQMHYNYW	309
FAP-FR3-D05	GFIFSLYSM	94	TINALDDITY	202	AGTAPFHYNYW	310
FAP-FR3-E05	GFIFGYYSM	95	AISSFDDITY	203	AHYNRYAPPAADGNTALGTLGYW	311
FAP-FR3-G05	GRTFSYNPM	96	AISRTGGSTY	204	AGHHYHHYNYW	312
FAP-FR3-H05	GRTFSYNPM	97	AISRTGGSTY	205	ASDALAADGVDWHYNYW	313
FAP-FR3-C06	GRTFSYNPM	98	AISRTGGSTY	206	AGDMHHHYNYW	314
FAP-FR3-E06	GRTFSYNPM	99	AISRTGGSTY	207	AGMHGLHYNYW	315
FAP-FR3-F06	GRIFSSYSM	100	TINSFSDITY	208	VGDWDWLFMY	316
FAP-FR3-G06	GGISSVYAM	101	SINSIDAITY	209	AGYAPLHFNYW	317
FAP-FR3-H06	GRTLNVDHM	102	AINSIDSITY	210	AGYSTFHYNYW	318
FAP-FR3-A07	GFISSYYYM	103	AISRTGGSTY	211	AGDINYHYNYW	319
FAP-FR3-B07	GYIYSYNFM	104	SINSFDDITY	212	AGPWNLHFNYW	320
FAP-FR3-D07	GYTFRIYFM	105	AINPYGDITN	213	ATFTPGHYNYW	321
FAP-FR3-E07	GFIYRYYSM	106	SINAFDDITY	214	AGDYIFHFNYW	322
FAP-FR3-F07	GSIFDFNHM	107	SISSFDDITY	215	AIAHQQKLSYW	323
FAP-FR3-G07	GRTFSYNPM	108	AISRTGGSTY	216	AGETAYHFNYW	324

Name	Heavy Chain Variable Domain Sequence	SEQ ID NO:
FAP-FR2-A01	EVQLVESGGGLVQPGGSLRLSCAASGSTSNNYFMGWFRQAPGKGRELVAAINPLD SNTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGHWDSHFNYW GQGTQVTVSS	325
FAP-FR2-B01	EVQLVESGGGLVQPGGSLRLSCAASGFTSGVYFMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAVGDWDIFHYSYW GQGTQVTVSS	326
FAP-FR2-C01	EVQLVESGGGLVQPGGSLRLSCAASGFTFGFNYMGWFRQAPGKGRELVAAISRIS DSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGIVQYHYNYW GQGTQVTVSS	327
FAP-FR2-E01	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGEWMMHFNY WGQGTQVTVSS	328

Name	Heavy Chain Variable Domain Sequence	SEQ ID NO:
FAP-FR2-F01	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGTDTWHYNYW GQGTQVTVSS	329
FAP-FR2-G01	EVQLVESGGGLVQPGGSLRLSCAASGSIFSHYSMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGPWHAHFSYW GQGTQVTVSS	330
FAP-FR2-H01	EVQLVESGGGLVQPGGSLRLSCAASGYILRDDPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAVSTYRADARSLG YWGQGTQVTVSS	331
FAP-FR2-B02	EVQLVESGGGLVQPGGSLRLSCAASGSTFSYYFMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAATTQFHFGYWG QGTQVTVSS	332
FAP-FR2-C02	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGTFDQHFNYW GQGTQVTVSS	333
FAP-FR2-D02	EVQLVESGGGLVQPGGSLRLSCAASGFIYSNYYMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAASRTWMHFNYW GQGTQVTVSS	334
FAP-FR2-E02	EVQLVESGGGLVQPGGSLRLSCAASGFIFSAYYMGWFRQAPGKGRELVATINSVD DITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGQYQYHYSYW GQGTQVTVSS	335
FAP-FR2-H02	EVQLVESGGGLVQPGGSLRLSCAASGSTYDVDYMGWFRQAPGKGRELVATINSY GGITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAASATKDHYNYW GQGTQVTVSS	336
FAP-FR2-B03	EVQLVESGGGLVQPGGSLRLSCAASGSIYSFYFMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGNIHYHYNYW GQGTQVTVSS	337
FAP-FR2-C03	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGESDRHYNYW GQGTQVTVSS	338
FAP-FR2-D03	EVQLVESGGGLVQPGGSLRLSCAASGRIYRNYSMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAVGYVFQHFNYW GQGTQVTVSS	339
FAP-FR2-F03	EVQLVESGGGLVQPGGSLRLSCAASGFIFSFYFMGWFRQAPGKGRELVAAISRTGG STYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAAFWDYHYDYWG QGTQVTVSS	340
FAP-FR2-H03	EVQLVESGGGLVQPGGSLRLSCAASGYIFSVNFMGWFRQAPGKGRELVATINWFD DITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGGTEWHFNYW GQGTQVTVSS	341
FAP-FR2-B04	EVQLVESGGGLVQPGGSLRLSCAASGSIFDYYYMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAASVISFHYNYWG QGTQVTVSS	342
FAP-FR2-D04	EVQLVESGGGLVQPGGSLRLSCAASGSIYSNYYMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGPMNWHYGYW GQGTQVTVSS	343
FAP-FR2-E04	EVQLVESGGGLVQPGGSLRLSCAASGFIFNIYSMGWFRQAPGKGRELVASINWSDS STYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGPYYWGLSYWG QGTQVTVSS	344
FAP-FR2-G04	EVQLVESGGGLVQPGGSLRLSCAASGSIYDLYTMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAVGQYDWHFDYW GQGTQVTVSS	345
FAP-FR2-A05	EVQLVESGGGLVQPGGSLRLSCAASGRIYDLYNMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGQPMYHFNYW GQGTQVTVSS	346
FAP-FR2-C05	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAVVTVWYSPFKVK MYNYWGQGTQVTVSS	347

Name	Heavy Chain Variable Domain Sequence	SEQ ID NO:
FAP-FR2-D05	EVQLVESGGGLVQPGGSLRLSCAASGFTYGFNYMGWFRQAPGKGRELVAAISRTGGSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGIWHMHYNYWGQGTQVTVSS	348
FAP-FR2-E05	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTGGSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAATSWRSPPPAYGYWGQGTQVTVSS	349
FAP-FR2-F05	EVQLVESGGGLVQPGGSLRLSCAASGSIYRFDSMGWFRQAPGKGRELVATITSLDSITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGAWKNHFNYWGQGTQVTVSS	350
FAP-FR2-G05	EVQLVESGGGLVQPGGSLRLSCAASGFISSAYSMGWFRQAPGKGRELVAAISRTGGSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGDSDLHYSYWGQGTQVTVSS	351
FAP-FR2-H05	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTGGSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAATSPRGLSAGHGYWGQGTQVTVSS	352
FAP-FR2-A06	EVQLVESGGGLVQPGGSLRLSCAASGSIFSSYIMGWFRQAPGKGRELVASINSYDSTTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAATEVPMHYNYWGQGTQVTVSS	353
FAP-FR2-B06	EVQLVESGGGLVQPGGSLRLSCAASGFTLNIYHMGWFRQAPGKGRELVAAINSFSDITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGEWPLHYSYWGQGTQVTVSS	354
FAP-FR2-C06	EVQLVESGGGLVQPGGSLRLSCAASGGTFSFYFMGWFRQAPGKGRELVATINSFDDITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGLWHQHYNYWGQGTQVTVSS	355
FAP-FR2-D06	EVQLVESGGGLVQPGGSLRLSCAASGRIYDANFMGWFRQAPGKGRELVATINTYSDITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGNWTFHFNYWGQGTQVTVSS	356
FAP-FR2-E06	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTGGSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGRYLWHYNYWGQGTQVTVSS	357
FAP-FR2-F06	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTGGSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGLQEYHYNYWGQGTQVTVSS	358
FAP-FR2-A07	EVQLVESGGGLVQPGGSLRLSCAASGFIFDYYFMGWFRQAPGKGRELVATINSFSSSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGDYDRHYSYWGQGTQVTVSS	359
FAP-FR2-B07	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVATISFSGITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGVEQFHFNYWGQGTQVTVSS	360
FAP-FR2-C07	EVQLVESGGGLVQPGGSLRLSCAASGFTFSFYFMGWFRQAPGKGRELVASINAYSDSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGHWNHHYNYWGQGTQVTVSS	361
FAP-FR2-D07	EVQLVESGGGLVQPGGSLRLSCAASGRIFSSYSMGWFRQAPGKGRELVATISSFSDITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAVGDWDWHFNYWGQGTQVTVSS	362
FAP-FR2-E07	EVQLVESGGGLVQPGGSLRLSCAASGSTFGYDNMGWFRQAPGKGRELVATINSFGDITNYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGYYPMHYSYWGQGTQVTVSS	363
FAP-FR2-F07	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTGGSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGDNWMHHNYWGQGTQVTVSS	364
FAP-FR2-G07	EVQLVESGGGLVQPGGSLRLSCAASGGISDYYSMGWFRQAPGKGRELVAAISRTGGSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGYWFAHFNYWGQGTQVTVSS	365
FAP-FR2-H07	EVQLVESGGGLVQPGGSLRLSCAASGYIFSFYFMGWFRQAPGKGRELVAAISRTGGSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGDHDLHYNYWGQGTQVTVSS	366

Name	Heavy Chain Variable Domain Sequence	SEQ ID NO:
FAP-FR2-A08	EVQLVESGGGLVQPGGSLRLSCAASGFIFGIYFMGWFRQAPGKGRELVAAISRTGG STYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAVGLYDRHYNYWG QGTQVTVSS	367
FAP-FR2-C08	EVQLVESGGGLVQPGGSLRLSCAASGSIYGYDYMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAVGIWDFYHFNYW GQGTQVTVSS	368
FAP-FR2-D08	EVQLVESGGGLVQPGGSLRLSCAASGSILGSYIMGWFRQAPGKGRELVATINSNDS ITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGDIMYHYNYWG QGTQVTVSS	369
FAP-FR2-E08	EVQLVESGGGLVQPGGSLRLSCAASGFIYSFYVMGWFRQAPGKGRELVATINSFD DTTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAVKERFTTPYAHS YWGQGTQVTVSS	370
FAP-FR2-G08	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGPLWQLYRSHG YWGQGTQVTVSS	371
FAP-FR2-A09	EVQLVESGGGLVQPGGSLRLSCAASGFTFSFYSMGWFRQAPGKGRELVASINAIDS ITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAVGPVYLHYNYWGQ GTQVTVSS	372
FAP-FR2-B09	EVQLVESGGGLVQPGGSLRLSCAASGGTFGVNPMGWFRQAPGKGRELVATITSTD DITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGRFPFHYDYWG QGTQVTVSS	373
FAP-FR2-C09	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAVSSKGSSAASLN YWGQGTQVTVSS	374
FAP-FR2-D09	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGDYYGHHNYW GQGTQVTVSS	375
FAP-FR2-E09	EVQLVESGGGLVQPGGSLRLSCAASGFISGHYYMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGYVQWHYGYW GQGTQVTVSS	376
FAP-FR2-F09	EVQLVESGGGLVQPGGSLRLSCAASGGILRIYFMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGTAHQHYDYW GQGTQVTVSS	377
FAP-FR2-G09	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAVTNHMERHASYG YWGQGTQVTVSS	378
FAP-FR2-H09	EVQLVESGGGLVQPGGSLRLSCAASGFIFNVYYMGWFRQAPGKGRELVATISWYS DITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAATRTDWHFNYW GQGTQVTVSS	379
FAP-FR2-B10	EVQLVESGGGLVQPGGSLRLSCAASGSIYSFYFMGWFRQAPGKGRELVATINSFDS ITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGQYNFHYSYWGQ GTQVTVSS	380
FAP-FR2-C10	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGTTGLHYNYW GQGTQVTVSS	381
FAP-FR2-D10	EVQLVESGGGLVQPGGSLRLSCAASGSIFGAYYMGWFRQAPGKGRELVAAINPDS DITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGTILHHFNYWG QGTQVTVSS	382
FAP-FR2-E10	EVQLVESGGGLVQPGGSLRLSCAASGSTFRFYSMGWFRQAPGKGRELVATISSFD DITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGPWHFHFGYWG QGTQVTVSS	383
FAP-FR2-F10	EVQLVESGGGLVQPGGSLRLSCAASGFILGSDTMGWFRQAPGKGRELVASINSFDS ITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGDYPWHYNYWG QGTQVTVSS	384
FAP-FR2-G10	EVQLVESGGGLVQPGGSLRLSCAASGFIFSVYSMGWFRQAPGKGRELVAAINTVD SITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGPAMLHFSYWG QGTQVTVSS	385

Name	Heavy Chain Variable Domain Sequence	SEQ ID NO:
FAP-FR2-H10	EVQLVESGGGLVQPGGSLRLSCAASGRTFNFYAMGWFRQAPGKGRELVAAISRTGGSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGMFKYHFNYWGQGTQVTVSS	386
FAP-FR2-A11	EVQLVESGGGLVQPGGSLRLSCAASGRTLSSYTMGWFRQAPGKGRELVASISWVDSITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAVIFPEQVYDYWGQGTQVTVSS	387
FAP-FR2-C11	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTGGSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAVATFRTTNDYYSSHGYWGQGTQVTVSS	388
FAP-FR2-D11	EVQLVESGGGLVQPGGSLRLSCAASGYISSSYSMGWFRQAPGKGRELVAAISSFSDITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGGSMFHYNYWGQGTQVTVSS	389
FAP-FR2-F11	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTGGSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGRIMMHFNYWGQGTQVTVSS	390
FAP-FR2-G11	EVQLVESGGGLVQPGGSLRLSCAASGSIYSHNFMGWFRQAPGKGRELVAAISRTGGSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAASYTAFHYNYWGQGTQVTVSS	391
FAP-FR2-H11	EVQLVESGGGLVQPGGSLRLSCAASGFIFSFYSMGWFRQAPGKGRELVATINTFSDITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGPWAFHYNYWGQGTQVTVSS	392
FAP-FR2-B12	EVQLVESGGGLVQPGGSLRLSCAASGFIFDFYFMGWFRQAPGKGRELVATINSISDITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAATDTADHYNYWGQGTQVTVSS	393
FAP-FR2-C12	EVQLVESGGGLVQPGGSLRLSCAASGFIYSSNNMGWFRQAPGKGRELVASINSFDDSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGMIQFHHNYWGQGTQVTVSS	394
FAP-FR2-D12	EVQLVESGGGLVQPGGSLRLSCAASGRILRHYHMGWFRQAPGKGRELVATINTLDSITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGIWFRHYNYWGQGTQVTVSS	395
FAP-FR2-F12	EVQLVESGGGLVQPGGSLRLSCAASGFIFGSYFMGWFRQAPGKGRELVAAISRTGGSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAASPTWMHFNYWGQGTQVTVSS	396
FAP-FR2-G12	EVQLVESGGGLVQPGGSLRLSCAASGYIFSSYAMGWFRQAPGKGRELVAAISRTGGSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAVGATHLHYSYWGQGTQVTVSS	397
FAP-FR2-H12	EVQLVESGGGLVQPGGSLRLSCAASGFTFGAYHMGWFRQAPGKGRELVATINWFGGITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGDFPHHFNYWGQGTQVTVSS	398
FAP-FR3-A01	EVQLVESGGGLVQPGGSLRLSCAASGRTFGLDFMGWFRQAPGKGRELVASINSFDDITNYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGRWDRHYNYWGQGTQVTVSS	399
FAP-FR3-B01	EVQLVESGGGLVQPGGSLRLSCAASGYILSFYYMGWFRQAPGKGRELVATINSFSDITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGLVAFHYNYWGQGTQVTVSS	400
FAP-FR3-E01	EVQLVESGGGLVQPGGSLRLSCAASGFISSLYSMGWFRQAPGKGRELVATITGSSSITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGDFHRHYNYWGQGTQVTVSS	401
FAP-FR3-F01	EVQLVESGGGLVQPGGSLRLSCAASGFIFNYYYMGWFRQAPGKGRELVATISAFDDSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAADIFPLHFSYWGQGTQVTVSS	402
FAP-FR3-H01	EVQLVESGGGLVQPGGSLRLSCAASGSTSGAYNMGWFRQAPGKGRELVATINWFDDITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGQYEWHYSYWGQGTQVTVSS	403
FAP-FR3-A02	EVQLVESGGGLVQPGGSLRLSCAASGFIYNFNSMGWFRQAPGKGRELVAAINRFDDITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGHAWLHHNYWGQGTQVTVSS	404

Name	Heavy Chain Variable Domain Sequence	SEQ ID NO:
FAP-FR3-C02	EVQLVESGGGLVQPGGSLRLSCAASGSTSRDYSMGWFRQAPGKGRELVATINSNS DITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGPWNHHYNYW GQGTQVTVSS	405
FAP-FR3-D02	EVQLVESGGGLVQPGGSLRLSCAASGSTYNVYPMGWFRQAPGKGRELVAAISRT GGSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGDNFMHHNY WGQGTQVTVSS	406
FAP-FR3-F02	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAADFPMHFNYW GQGTQVTVSS	407
FAP-FR3-G02	EVQLVESGGGLVQPGGSLRLSCAASGSTFNYYDMGWFRQAPGKGRELVATINRFS SITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAATVTPFHFSYWGQ GTQVTVSS	408
FAP-FR3-A03	EVQLVESGGGLVQPGGSLRLSCAASGFISGVYFMGWFRQAPGKGRELVATISSAS DITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGIYMWHYNYW GQGTQVTVSS	409
FAP-FR3-B03	EVQLVESGGGLVQPGGSLRLSCAASGFILGANPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGDEDYHYNYW GQGTQVTVSS	410
FAP-FR3-C03	EVQLVESGGGLVQPGGSLRLSCAASGFIYGYNHMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAAEFQWHFGYW GQGTQVTVSS	411
FAP-FR3-D03	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGHSWLHFNYW GQGTQVTVSS	412
FAP-FR3-A04	EVQLVESGGGLVQPGGSLRLSCAASGFIYNYNHMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAVGQEHLHYNYW GQGTQVTVSS	413
FAP-FR3-B04	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAATTYQGRDDGFN YWGQGTQVTVSS	414
FAP-FR3-E04	EVQLVESGGGLVQPGGSLRLSCAASGSTYSFNTMGWFRQAPGKGRELVASINSSD SSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGDYDRHFNYW GQGTQVTVSS	415
FAP-FR3-G04	EVQLVESGGGLVQPGGSLRLSCAASGSTFSAYSMGWFRQAPGKGRELVAAINSFD DITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGPLYLHHDYWG QGTQVTVSS	416
FAP-FR3-H04	EVQLVESGGGLVQPGGSLRLSCAASGSTFNPYFMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGWWQMHYNY WGQGTQVTVSS	417
FAP-FR3-D05	EVQLVESGGGLVQPGGSLRLSCAASGFIFSLYSMGWFRQAPGKGRELVATINALD DITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGTAPFHYNYWG QGTQVTVSS	418
FAP-FR3-E05	EVQLVESGGGLVQPGGSLRLSCAASGFIFGYYSMGWFRQAPGKGRELVAAISSFD DITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAHYNRYAPPAAD GNTALGTLGYWGQGTQVTVSS	419
FAP-FR3-G05	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGHHYHHYNYW GQGTQVTVSS	420
FAP-FR3-H05	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAASDALAADGVD WHYNYWGQGTQVTVSS	421
FAP-FR3-C06	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGDMHHHYNYW GQGTQVTVSS	422
FAP-FR3-E06	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGMHGLHYNYW GQGTQVTVSS	423

Name	Heavy Chain Variable Domain Sequence	SEQ ID NO:
FAP-FR3-F06	EVQLVESGGGLVQPGGSLRLSCAASGRIFSSYSMGWFRQAPGKGRELVATINSFSD ITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAVGDWDWLFMYWG QGTKVTVSS	424
FAP-FR3-G06	EVQLVESGGGLVQPGGSLRLSCAASGGISSVYAMGWFRQAPGKGRELVASINSID AITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGYAPLHFNYWG QGTQVTVSS	425
FAP-FR3-H06	EVQLVESGGGLVQPGGSLRLSCAASGRTLNVDHMGWFRQAPGKGRELVAAINSID SITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGYSTFHYNYWG QGTQVTVSS	426
FAP-FR3-A07	EVQLVESGGGLVQPGGSLRLSCAASGFISSYYYMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGDINYHYNYW GQGTQVTVSS	427
FAP-FR3-B07	EVQLVESGGGLVQPGGSLRLSCAASGYIYSYNFMGWFRQAPGKGRELVASINSFD DITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGPWNLHFNYW GQGTQVTVSS	428
FAP-FR3-D07	EVQLVESGGGLVQPGGSLRLSCAASGYTFRIYFMGWFRQAPGKGRELVAAINPYG DITNYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAATFTPGHYNYWG QGTQVTVSS	429
FAP-FR3-E07	EVQLVESGGGLVQPGGSLRLSCAASGFIYRYYSMGWFRQAPGKGRELVASINAFD DITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGDYIFHFNYWG QGTQVTVSS	430
FAP-FR3-F07	EVQLVESGGGLVQPGGSLRLSCAASGSIFDFNHMGWFRQAPGKGRELVASISSFDD ITYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAIAHQQKLSYWGQ GTQVTVSS	431
FAP-FR3-G07	EVQLVESGGGLVQPGGSLRLSCAASGRTFSYNPMGWFRQAPGKGRELVAAISRTG GSTYYPDSVEGRFTISRDNAKRMVYLQMNSLRAEDTAVYYCAAGETAYHFNYW GQGTQVTVSS	432

WHAT IS CLAIMED IS:

1. A fibroblast activation protein (FAP) binding polypeptide comprising an immunoglobulin heavy chain variable domain comprising a CDR-H1, CDR-H2, and CDR-H3, wherein:

the CDR-H1 comprises a sequence having at least 90% sequence identity to a sequence of SEQ ID NO: 75;

the CDR-H2 comprises a sequence having at least 90%sequence identity to a sequence of SEQ ID NO: 183; and

the CDR-H3 comprises a sequence having at least 90% sequence identity to a sequence of SEQ ID NO: 291.

2. The FAP binding polypeptide of claim 1, wherein the heavy chain variable domain comprises an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO: 399.

3. The FAP binding polypeptide of claim 1 or 2, wherein the FAP binding polypeptide is humanized.

4. The FAP binding polypeptide of any one of claims 1-3, wherein the FAP binding polypeptide is a single domain antibody (sdAb).

5. A chimeric antigen receptor (CAR) comprising the FAP binding polypeptide of any one of claims 1-4.

6. A chimeric antigen receptor (CAR) cell comprising the CAR of claim 5.

7. The CAR cell of claim 6, wherein the CAR cell is a CAR T cell.

8. The CAR cell of claim 6 or 7, wherein the CAR cell comprises at least two binding polypeptides and the CAR cell is a multivalent CAR cell.

9. The CAR cell of any one of claims 6-8, wherein the CAR cell is derived from a subject or from a cell line.

10. The CAR cell of claim 9, wherein the subject has a cancer.

11. The CAR cell of claim 10, wherein the cancer is breast cancer, colorectal cancer, kidney cancer, liver cancer, lung cancer, brain cancer, pancreatic cancer, bladder cancer, testicular cancer, prostate cancer, gastric cancer, ovarian cancer, head and neck cancer, gallbladder cancer, a hematologic malignancy, or any combination thereof.

12. A nucleic acid that encodes for a polypeptide comprising a sequence having at least 90% sequence identity to the FAP binding polypeptide of any one of claims 1-4 or the CAR of claim 5.

13. The CAR cell of any one of claims 6-11 for use in treating a cancer in a subject in need thereof.

14. Use of the CAR cell of any one of claims 6-11 in the manufacture of a medicament for treating a cancer in a subject in need thereof.

15. The CAR cell for use of claim 13 or the use of claim 14, wherein the chimeric antigen receptor cell is autologous or allogeneic to the subject.

16. The CAR cell for use of claim 13 or 15 or the use of claim 14 or 15, wherein the subject is a mammal.

17. The CAR cell for use of claim 13 or any one of claims 15 or 16, or the use of claim 14 or any one of claims 15 or 16, wherein the subject is a human.

18. The CAR cell for use of claim 13 or any one of claims 15 to 17, or the use of claim 14 or any one of claims 15 to 17, wherein the cancer is breast cancer, colorectal cancer, kidney cancer, liver cancer, lung cancer, brain cancer, pancreatic cancer, bladder cancer, testicular cancer, prostate cancer, gastric cancer, ovarian cancer, head and neck cancer, gallbladder cancer, a hematologic malignancy, or any combination thereof.

19. The CAR cell for use of claim 13 or any one of claims 15 to 18, or the use of claim 14 or any one of claims 15 to 18, wherein the chimeric antigen receptor cell is to be administered parenterally.