those cells. Overexpression of GnTIII in production cell lines leads to antibodies enriched in bisected oligosaccharides, which are generally also non-fucosylated and of the hybrid type. If in addition to GnTIII, mannosidase II (ManII) is overexpressed in production cell lines, antibodies enriched in bisected, non-fucosylated oligosaccharides of the complex type are obtained (Ferrara et al., Biotechn Bioeng 93, 851-861 (2006)). Both types of antibodies show strongly enhanced ADCC, as compared to antibodies with unmodified glycans, but only antibodies in which the majority of the N-glycans are of the complex type are able to induce significant complement-dependent cytotoxicity (Ferrara et al., Biotechn Bioeng 93, 851-861 (2006)). Alterations in the composition of the Asn 297 carbohydrate or its elimination also affect binding of the antibody Fc-domain to Fcγ-receptor (FcγR) and complement C1q protein, which is important for ADCC and CDC, respectively (Umaña et al., Nat Biotechnol 17, 176-180 (1999); Davies et al., Biotechnol Bioeng 74, 288-294 (2001); Mimura et al., J Biol Chem 276, 45539-45547 (2001); Radaev et al., J Biol Chem 276, 16478-16483 (2001); Shields et al., J Biol Chem 276, 6591-6604 (2001); Shields et al., J Biol Chem 277, 26733-26740 (2002); Simmons et al., J Immunol Methods 263, 133-147 (2002)).

BRIEF SUMMARY OF THE INVENTION

The present ~~invention~~disclosure provides antibodies that specifically bind to Fibroblast Activation Protein (FAP), having a high affinity and/or enhanced effector function.

~~In one aspect, the~~ ~~invention~~disclosure is directed to an antibody that specifically binds FAP, comprising at least one (i.e. one, two, three, four, five or six) of the complementarity determining regions (CDRs) set forth in SEQ ID NOs 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 169, 171, 173, 175 and 177. In one embodiment, the antibody comprises three heavy chain CDRs (i.e. HCDR1, HCDR2, and HCDR3) and/or three light chain CDRs (i.e. LCDR1, LCDR2, and LCDR3) selected from SEQ ID NOs 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 169, 171, 173, 175 and 177.

In a first aspect, there is provided an antibody that specifically binds to Fibroblast Activation Protein (FAP), wherein said antibody comprises (i) a heavy chain variable region comprising a heavy chain CDR1 selected from the group of SEQ ID NO: 3, SEQ ID NO: 13, and SEQ ID NO: 23; a heavy chain CDR2 selected from the group of SEQ ID NO: 47, SEQ ID NO: 81, and SEQ ID NO: 113; and the heavy chain CDR3 of SEQ ID NO: 135, and a light chain variable region comprising the light chain CDR1 of SEQ ID NO: 143, the light chain CDR2 of SEQ ID NO: 151, and the light chain CDR3 of SEQ ID NO: 163,

or (ii) a heavy chain variable region comprising a heavy chain CDR1 selected from the group of SEQ ID NO: 9, SEQ ID NO: 19, and SEQ ID NO: 31; a heavy chain CDR2 selected from the group of SEQ ID NO: 61, SEQ ID NO: 95, and SEQ ID NO: 127; and the heavy chain CDR3 of SEQ ID NO: 137, and a light chain variable region comprising the light chain CDR1 of SEQ ID NO: 147, the light chain CDR2 of SEQ ID NO: 155, and the light chain CDR3 of SEQ ID NO: 167.

In a second aspect, there is provided an antibody that specifically binds to Fibroblast Activation Protein (FAP), wherein said antibody comprises (i) a heavy chain variable region comprising a heavy chain CDR1 selected from the group of SEQ ID NO: 3, SEQ ID NO: 13, and SEQ ID NO: 23; a heavy chain CDR2 selected from the group of SEQ ID NO: 35, SEQ ID NO: 69, and SEQ ID NO: 101; and the heavy chain CDR3 of SEQ ID NO:
137, and a light chain variable region comprising the light chain CDR1 of SEQ ID NO: 147, the light chain CDR2 of SEQ ID NO: 155, and the light chain CDR3 of SEQ ID NO: 167, or (ii) a heavy chain CDR1 selected from the group of SEQ ID NO: 3, SEQ ID NO: 13, and SEQ ID NO: 23; a heavy chain CDR2 selected from the group of SEQ ID NO: 35, SEQ ID NO: 69, and SEQ ID NO: 101; and the heavy chain CDR3 of SEQ ID NO: 135, and a light chain variable region comprising the light chain CDR1 of SEQ ID NO: 143, the light chain CDR2 of SEQ ID NO: 151, and the light chain CDR3 of SEQ ID NO: 163; and an Fc region of an immunoglobulin.

In a more specific embodiment, the antibody comprises an antibody heavy chain variable region and/or an antibody light chain variable region, particularly

both a heavy and light chain variable region, selected from the heavy and light chain variable region sequences set forth in SEQ ID NOs 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309 and 311. In one embodiment, the antibody comprises an Fc region, particularly an IgG Fc region. In a further embodiment, the antibody is a full-length antibody, particularly an IgG class antibody. In another embodiment, the antibody comprises a human antibody constant region. In one embodiment, the antibody is human. In one embodiment, the antibody is glycoengineered to have modified oligosaccharides in the Fc region. In one embodiment the antibody has an increased proportion of non-fucosylated and/or bisected oligosaccharides in the Fc region, as compared to a non-glycoengineered antibody. In a further embodiment, the antibody has increased effector function and/or increased Fc receptor binding affinity. In a particular embodiment, the increased effector function is increased antibody-dependent cell-mediated cytotoxicity (ADCC). In another embodiment the antibody binds to FAP with a K_D value of lower than about 1 μM, preferably lower than about 100 nM, most preferably lower than about 1 nM or even lower than about 0.1 nM. In one embodiment, the antibody is affinity matured. In one embodiment, the antibody binds to FAP in human tissues. In one embodiment, the antibody does not induce internalization of FAP.

T~~In other aspects, t~~he ~~invention~~disclosure is also directed to polypeptides, polynucleotides, host cells, and expression vectors related to the antibodies. In a third aspect, there is provided an isolated polynucleotide encoding an antibody heavy chain and/or an antibody light chain that forms part of the antibody as defined above. In a fourth aspect, there is provided an isolated polypeptide encoded by the polynucleotide as defined above. In a fifth aspect, there is provided a composition comprising (i) a first isolated polynucleotide encoding a polypeptide comprising the sequence of SEQ ID NO: 267, and a second isolated polynucleotide encoding a polypeptide comprising the sequence of SEQ ID NO: 265, (ii) a first isolated polynucleotide encoding a polypeptide comprising the sequence of SEQ ID NO: 299 and a second isolated polynucleotide encoding a polypeptide comprising the sequence of SEQ ID NO: 297, (iii) a first isolated polynucleotide encoding a polypeptide comprising the sequence of SEQ ID NO: 197 and a second isolated polynucleotide encoding a polypeptide comprising the sequence of SEQ ID NO: 195, or (iv) a first isolated polynucleotide encoding a polypeptide comprising the sequence of SEQ ID NO: 207 and a second isolated polynucleotide encoding a polypeptide comprising the sequence of SEQ ID NO: 205. In a sixth aspect, there is provided a vector comprising the polynucleotide as defined above.

In a seventh aspect, there is provided a host cell comprising the polynucleotide as defined above, the composition as defined above, or the vector as defined above. T~~In a further aspect, t~~he ~~invention~~disclosure also relates to methods of making the antibodies. In an eighth aspect, there is provided a method of producing an antibody that specifically binds to Fibroblast Activation Protein (FAP), said method comprising a) culturing the host cell as defined above in a medium under conditions allowing the expression of the antibody, and b) recovering the antibody. In a ninth aspect, there is provided a method of producing an antibody that specifically binds to Fibroblast Activation Protein (FAP), said method comprising a) culturing the host cell as defined above in a medium under conditions allowing the expression of the antibody and the modification of the oligosaccharides present on the Fc region of said antibody by said polypeptide having GnTIII activity, and b) recovering the antibody. In a tenth aspect, there is provided an antibody that specifically binds to FAP, wherein said antibody is produced by the method as defined above. T~~In a further aspect, t~~he ~~invention~~disclosure is also directed to methods of using the antibodies, particularly for the treatment of diseases characterized by expression of FAP, such as cancer. In an eleventh aspect, there is provided an antibody conjugate comprising the antibody as defined above and a cytotoxic agent. In a twelfth aspect, there is provided a pharmaceutical formulation comprising the antibody as defined above and a pharmaceutically acceptable carrier. In a thirteenth aspect, there is provided the antibody as defined above for use as a medicament. In a fourteenth aspect, there is provided the antibody as defined above for the treatment of a disease characterized by expression of FAP. In a fifteenth aspect, there is provided the antibody as defined above for use in inducing cell lysis of a tumor cell or a stromal cell of a tumor. In a sixteenth aspect, there is provided the use of the antibody as defined above in the manufacture of a medicament. In a seventeenth aspect, there is provided the use of the antibody as defined above for the manufacture of a medicament for treatment of a disease characterized by expression of FAP. In an eighteenth aspect, there is provided the use of the antibody as defined above for the manufacture of a medicament for inducing lysis of a tumor cell or a stromal cell of a tumor. In a nineteenth aspect, there is provided the antibody as defined above for use in a method of diagnosis or detection. In a twentieth aspect, there is provided a diagnostic agent comprising the antibody as defined above and a label that allows detection of a complex of said diagnostic agent and FAP.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1 shows Surface Plasmon Resonance (SPR)-based kinetic analyses of affinity-matured anti-FAP Fab fragments. Processed kinetic data sets are presented for clone 19G1 binding to human (hu) FAP (A) and murine (mu) FAP (B), for clone 20G8 binding to hu FAP (C), mu FAP (D) and for clone 4B9 binding to hu FAP (E) and mu FAP (F). Smooth lines represent a global fit of the data to a 1:1 interaction model.

FIGURE 2 shows SPR-based kinetic analyses of affinity-matured anti-FAP Fab fragments. Processed kinetic data sets are presented for clone 5B8 binding to hu FAP (A) and mu FAP (B),