CLAIMS

~~It is claimed:~~

1. An isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, and HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

a. SEQ ID NOs:89, 90, 91, 149, 150 and 151, respectively~~;~~, or SEQ ID NOs:209, 210, 211, 269, 270 and 271, respectively;

~~b.~~ SEQ ID NOs:41, 42, 43, 101, 102 and 103, respectively~~;~~

~~c. SEQ ID NOs:44, 45, 46, 104, 105 and 106, respectively;~~

~~d. SEQ ID NOs:47, 48, 49, 107, 108 and 109, respectively;~~

~~e. SEQ ID NOs:50, 51, 52, 110, 111 and 112, respectively;~~

~~f. SEQ ID NOs:53, 54, 55, 113, 114 and 115, respectively;~~

~~g. SEQ ID NOs:56, 57, 58, 116, 117 and 118, respectively;~~

~~h. SEQ ID NOs:59, 60, 61, 119, 120 and 121, respectively;~~

~~i. SEQ ID NOs:62, 63, 64, 122, 123 and 124, respectively;~~

~~j. SEQ ID NOs:65, 66, 67, 125, 126 and 127, respectively;~~

~~k. SEQ ID NOs:68, 69, 70, 128, 129 and 130, respectively;~~

~~l. SEQ ID NOs:71, 72, 73, 131, 132 and 133, respectively;~~

~~m. SEQ ID NOs:74, 75, 76, 134, 135 and 136, respectively;~~

~~n. SEQ ID NOs:77, 78, 79, 137, 138 and 139, respectively;~~

~~o. SEQ ID NOs:80, 81, 82, 140, 141 and 142, respectively;~~

~~p. SEQ ID NOs:83, 84, 85, 143, 144 and 145, respectively;~~

~~q. SEQ ID NOs:86, 87, 88, 146, 147 and 148, respectively;~~

~~r. SEQ ID NOs:92, 93, 94, 152, 153 and 154, respectively;~~

~~s. SEQ ID NOs:95, 96, 97, 155, 156 and 157, respectively;~~, or

~~t. SEQ ID NOs:98, 99, 100, 158, 159 and 160, respectively;~~

~~wherein the antibody or antigen-binding fragment thereof specifically binds to CD73, preferably human CD73.~~

~~2. An isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain~~

~~complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:~~

~~a. SEQ ID NOs:209, 210, 211, 269, 270 and 271, respectively;~~

~~u.~~b. SEQ ID NOs:161, 162, 163, 221, 222 and 223, respectively;

~~v.~~c. SEQ ID NOs:44, 45, 46, 104, 105 and 106, respectively, or SEQ ID NOs:164, 165, 166, 224, 225 and 226, respectively;

~~w.~~d. SEQ ID NOs:47, 48, 49, 107, 108 and 109, respectively, or SEQ ID NOs:167, 168, 169, 227, 228 and 229, respectively;

~~x.~~e. SEQ ID NOs:50, 51, 52, 110, 111 and 112, respectively, or SEQ ID NOs:170, 171, 172, 230, 231 and 232, respectively;

~~y.~~f. SEQ ID NOs:53, 54, 55, 113, 114 and 115, respectively, or SEQ ID NOs:173, 174, 175, 233, 234 and 235, respectively;

~~z.~~g. SEQ ID NOs:56, 57, 58, 116, 117 and 118, respectively, or SEQ ID NOs:176, 177, 178, 236, 237 and 238, respectively;

~~aa.~~h. SEQ ID NOs:59, 60, 61, 119, 120 and 121, respectively, or SEQ ID NOs:179, 180, 181, 239, 240 and 241, respectively;

~~bb.~~i. SEQ ID NOs:62, 63, 64, 122, 123 and 124, respectively, or SEQ ID NOs:182, 183, 184, 242, 243 and 244, respectively;

~~cc.~~j. SEQ ID NOs:65, 66, 67, 125, 126 and 127, respectively, or SEQ ID NOs:185, 186, 187, 245, 246 and 247, respectively;

~~dd.~~k. SEQ ID NOs:68, 69, 70, 128, 129 and 130, respectively, or SEQ ID NOs:188, 189, 190, 248, 249 and 250, respectively;

~~ee.~~l. SEQ ID NOs:71, 72, 73, 131, 132 and 133, respectively, or SEQ ID NOs:191, 192, 193, 251, 252 and 253, respectively;

~~ff.~~m. SEQ ID NOs:74, 75, 76, 134, 135 and 136, respectively, or SEQ ID NOs:194, 195, 196, 254, 255 and 256, respectively;

~~gg.~~n. SEQ ID NOs:77, 78, 79, 137, 138 and 139, respectively, or SEQ ID NOs:197, 198, 199, 257, 258 and 259, respectively;

~~hh.~~o. SEQ ID NOs:80, 81, 82, 140, 141 and 142, respectively, or SEQ ID NOs:200, 201, 202, 260, 261 and 262, respectively;

~~ii.~~p. SEQ ID NOs:83, 84, 85, 143, 144 and 145, respectively, or SEQ ID NOs:203, 204, 205, 263, 264 and 265, respectively;

~~jj.~~q. SEQ ID NOs:86, 87, 88, 146, 147 and 148, respectively, or SEQ ID NOs:206, 207, 208, 266, 267 and 268, respectively;

~~kk.~~r. SEQ ID NOs:92, 93, 94, 152, 153 and 154, respectively, or SEQ ID NOs:212, 213, 214, 272, 273 and 274, respectively;

~~ll.~~s. SEQ ID NOs:95, 96, 97, 155, 156 and 157, respectively, or SEQ ID NOs:215, 216, 217, 275, 276 and 277, respectively; or

~~mm.~~t. SEQ ID NOs:98, 99, 100, 158, 159 and 160, respectively, or SEQ ID NOs:218, 219, 220, 278, 279 and 280, respectively;

wherein the antibody or antigen-binding fragment thereof specifically binds to CD73~~, preferably human CD73~~.

~~3.~~2. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1~~ or 2~~, comprising a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:286, 33, 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 35, 37, 39, 282, 283, 284, 285, 287, 288, 289, 295, 296, 297, or ~~39,~~ 298, or a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO:293, 34, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 36, 38, 40, 290, 291, 292, 294, or ~~40~~299.

~~4.~~3. The isolated monoclonal antibody or antigen-binding fragment thereof of ~~any one of claims~~claim 1~~-3~~ or 2, comprising:

a. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:286, and a light chain variable region having the polypeptide sequence of SEQ ID NO:293;

~~a.~~b. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:33, and a light chain variable region having the polypeptide sequence of SEQ ID NO:34;

~~b.~~c. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:1, and a light chain variable region having the polypeptide sequence of SEQ ID NO:2;

~~c.~~d. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:3, and a light chain variable region having the polypeptide sequence of SEQ ID NO:4;

~~d.~~e. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:5, and a light chain variable region having the polypeptide sequence of SEQ ID NO:6;

~~e.~~f. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:7, and a light chain variable region having the polypeptide sequence of SEQ ID NO:8;

~~f.~~g. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:9, and a light chain variable region having the polypeptide sequence of SEQ ID NO:10;

~~g.~~h.a heavy chain variable region having the polypeptide sequence of SEQ ID NO:11, and a light chain variable region having the polypeptide sequence of SEQ ID NO:12;

~~h.~~i. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:13, and a light chain variable region having the polypeptide sequence of SEQ ID NO:14;

~~i.~~j. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:15, and a light chain variable region having the polypeptide sequence of SEQ ID NO:16;

~~j.~~k. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:17, and a light chain variable region having the polypeptide sequence of SEQ ID NO:18;

~~k.~~l. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:19, and a light chain variable region having the polypeptide sequence of SEQ ID NO:20;

~~l.~~m. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:21, and a light chain variable region having the polypeptide sequence of SEQ ID NO:22;

~~m.~~n. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:23, and a light chain variable region having the polypeptide sequence of SEQ ID NO:24;

~~n.~~o.a heavy chain variable region having the polypeptide sequence of SEQ ID NO:25, and a light chain variable region having the polypeptide sequence of SEQ ID NO:26;

~~o.~~p.a heavy chain variable region having the polypeptide sequence of SEQ ID NO:27, and a light chain variable region having the polypeptide sequence of SEQ ID NO:28;

~~p.~~q.a heavy chain variable region having the polypeptide sequence of SEQ ID NO:29, and a light chain variable region having the polypeptide sequence of SEQ ID NO:30;

~~q.~~r. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:31, and a light chain variable region having the polypeptide sequence of SEQ ID NO:32;

~~r.~~s. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:35, and a light chain variable region having the polypeptide sequence of SEQ ID NO:36;

~~s.~~t. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:37, and a light chain variable region having the polypeptide sequence of SEQ ID NO:38;

~~or~~

t.u. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:39, and a light chain variable region having the polypeptide sequence of SEQ ID NO:40.;

5. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein the monoclonal antibody or antigen-binding fragment thereof inhibits the enzyme activity of soluble and/or cell-surface CD73.

6. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of embodiments 1-4, wherein the monoclonal antibody or antigen-binding fragment thereof prevents the dimerization of CD73.

7. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of embodiments 1-4, wherein the monoclonal antibody or antigen-binding fragment thereof induces the internalization of CD73.

8. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-7, wherein the antibody or antigen-binding fragment thereof is chimeric.

9. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-8, wherein the antibody or antigen-binding fragment thereof is human or humanized.

10. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-9, wherein the antibody or antigen-binding fragment thereof comprises:

u.a. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:286, and a light chain variable region having the polypeptide sequence of SEQ ID NO:293;

v. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:282, and a light chain variable region having the polypeptide sequence of SEQ ID NO:290;

w. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:282, and a light chain variable region having the polypeptide sequence of SEQ ID NO:291;

x. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:282, and a light chain variable region having the polypeptide sequence of SEQ ID NO:292;

y. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:283, and a light chain variable region having the polypeptide sequence of SEQ ID NO:290;

z. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:283, and a light chain variable region having the polypeptide sequence of SEQ ID NO:291;

aa. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:283, and a light chain variable region having the polypeptide sequence of SEQ ID NO:292;

bb. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:284, and a light chain variable region having the polypeptide sequence of SEQ ID NO:290;

cc. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:284, and a light chain variable region having the polypeptide sequence of SEQ ID NO:291;

dd. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:284, and a light chain variable region having the polypeptide sequence of SEQ ID NO:292;

ee. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:285, and a light chain variable region having the polypeptide sequence of SEQ ID NO:290;

ff. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:285, and a light chain variable region having the polypeptide sequence of SEQ ID NO:291;

gg. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:285, and a light chain variable region having the polypeptide sequence of SEQ ID NO:292;

hh. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:283, and a light chain variable region having the polypeptide sequence of SEQ ID NO:293;

ii. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:284, and a light chain variable region having the polypeptide sequence of SEQ ID NO:293;

jj. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:285, and a light chain variable region having the polypeptide sequence of SEQ ID NO:293;

kk. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:286, and a light chain variable region having the polypeptide sequence of SEQ ID NO:290;

ll. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:286, and a light chain variable region having the polypeptide sequence of SEQ ID NO:291;

mm. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:286, and a light chain variable region having the polypeptide sequence of SEQ ID NO:292;

nn. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:287, and a light chain variable region having the polypeptide sequence of SEQ ID NO:294;

oo. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:288, and a light chain variable region having the polypeptide sequence of SEQ ID NO:294;

pp. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:289, and a light chain variable region having the polypeptide sequence of SEQ ID NO:294;

qq. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:284, and a light chain variable region having the polypeptide sequence of SEQ ID NO:299;

rr. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:295, and a light chain variable region having the polypeptide sequence of SEQ ID NO:299;

ss. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:296, and a light chain variable region having the polypeptide sequence of SEQ ID NO:299;

tt. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:297, and a light chain variable region having the polypeptide sequence of SEQ ID NO:299; or

uu. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:298, and a light chain variable region having the polypeptide sequence of SEQ ID NO:299.

~~11.~~4. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of ~~embodiments~~claims 1-~~10~~3, wherein the monoclonal antibody or antigen-binding fragment thereof inhibits the enzyme activity of soluble and/or cell-surface CD73, prevents the dimerization of CD73, induces the internalization of CD73, and/or is capable of activating T cells.

5. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein the antibody or antigen-binding fragment thereof is chimeric or human or humanized.

6. An isolated bispecific antibody or antigen-binding fragment thereof comprising the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-5.

~~12.~~7. An isolated nucleic acid encoding the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-~~11~~5 ~~1-6~~.

~~13.~~8. A vector comprising the isolated nucleic acid of claim ~~12~~7.

~~14.~~9. A host cell comprising the vector of claim ~~13~~8.

~~15.~~10. A pharmaceutical composition, comprising the isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-~~11~~5 and a pharmaceutically acceptable carrier.

~~16. A~~ The pharmaceutical composition of claim 10 for use in a method of inhibiting the nucleotidase activity of CD73 ~~in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 15.~~

~~17. A method of,~~ preventing the dimerization of CD73 ~~in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 15.~~

~~18. A method of,~~ inducing the internalization of CD73 ~~in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 15.~~

~~19.~~11. ~~A method of,~~ or treating cancer in a subject in need thereof, ~~comprising administering to the subject~~wherein the pharmaceutical composition ~~of claim 15~~is to be administered to the subject.

12. Use of the pharmaceutical composition of claim 10 in the manufacture of a medicament for the treatment of cancer in a subject in need thereof, wherein the medicament is to be administered to the subject.

~~20.~~13. A method of producing the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-~~11~~5, comprising culturing a cell comprising a nucleic acid encoding the monoclonal antibody or antigen-binding fragment thereof under conditions to produce the monoclonal antibody or antigen-binding fragment thereof, and recovering the monoclonal antibody or antigen-binding fragment thereof from the host cell ~~or culture~~.

~~21.~~14. A method of producing a pharmaceutical composition comprising the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-~~11~~5, comprising combining the monoclonal antibody or antigen-binding fragment thereof with a pharmaceutically acceptable carrier to obtain the pharmaceutical composition.

~~22.~~15. A method of determining a level of CD73 or determining the ecto-5' nucleotidase activity of CD73 in a subject, the method comprising:

a. obtaining a sample from the subject;
b. contacting the sample with an isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-~~11~~5; and
~~c.~~ determining a level of CD73 or determining the ecto-5' nucleotidase activity of CD73 in the subject.

~~23.~~16. The method of claim ~~22~~15, wherein the sample is a tissue sample or a blood sample.

~~24.~~17. The method of claim ~~23~~16, wherein the tissue sample is a cancer tissue sample.

~~25. The method of claim 22, wherein the sample is a blood sample.~~

~~26. A method of determining the ecto-5'nucleotidase activity of CD73 in a subject, the method comprising:~~

~~a. obtaining a sample from the subject;~~

~~27.~~18. ~~contacting the sample with an~~An isolated ~~monoclonal~~nucleic acid encoding the bispecific antibody or antigen-binding fragment thereof of ~~any one of claims 1-11; and~~claim 6.

~~b. determining the ecto-5' nucleotidase activity of CD73 in the subject.~~

~~28.~~19. ~~The method~~A vector comprising the isolated nucleic acid of claim ~~26, wherein the sample is a tissue sample~~18.

~~29. The method of claim 27, wherein the tissue sample is a cancer tissue sample.~~

~~30. The method of claim 26, wherein the sample is a blood sample.~~

20. A host cell comprising the vector of claim 19.

21. A pharmaceutical composition comprising the isolated bispecific antibody or antigen-binding fragment thereof of claim 6 and a pharmaceutically acceptable carrier.