

## **B CELL MATURATION ANTIGEN BINDING PROTEINS**

### **CROSS-REFERENCE**

[0001] This application claims the benefit of U.S. Provisional Application No. 62/572,375 filed October 13, 2017 which is incorporated by reference herein in its entirety.

### **SEQUENCE LISTING**

[0001.1] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on October 11, 2018, is named 47517-722\_601\_SL.txt and is 232,688 bytes in size.

### **BACKGROUND OF THE INVENTION**

[0002] Cancer is the second leading cause of human death next to coronary disease. Worldwide, millions of people die from cancer every year. In the United States alone, cancer causes the death of well over a half-million people each year, with some 1.4 million new cases diagnosed per year. While deaths from heart disease have been declining significantly, those resulting from cancer generally are on the rise. In the early part of the next century, cancer is predicted to become the leading cause of death.

[0003] Moreover, even for those cancer patients that initially survive their primary cancers, common experience has shown that their lives are dramatically altered. Many cancer patients experience strong anxieties driven by the awareness of the potential for recurrence or treatment failure. Many cancer patients experience significant physical debilitations following treatment.

[0004] Generally speaking, the fundamental problem in the management of the deadliest cancers is the lack of effective and non-toxic systemic therapies. Cancer is a complex disease characterized by genetic mutations that lead to uncontrolled cell growth. Cancerous cells are present in all organisms and, under normal circumstances, their excessive growth is tightly regulated by various physiological factors.

### **SUMMARY OF THE DISCLOSURE**

[0005] The present disclosure provides single domain B cell maturation antigen (BCMA) binding proteins which can be used for diagnosing and treating indications correlated to the expression of BCMA.

[0006] Provided herein is a single domain B cell maturation agent (BCMA) binding protein, comprising complementarity determining regions CDR1, CDR2, and CDR3, wherein (a) the amino acid sequence of CDR1 is as set forth in X<sub>1</sub>X<sub>2</sub>X<sub>3</sub>X<sub>4</sub>X<sub>5</sub>X<sub>6</sub>X<sub>7</sub>PX<sub>8</sub>G (SEQ ID NO: 1),

wherein X<sub>1</sub> is T or S; X<sub>2</sub> is N, D, or S; X<sub>3</sub> is I, D, Q, H, V, or E; X<sub>4</sub> is F, S, E, A, T, M, V, I, D, Q, P, R, or G; X<sub>5</sub> is S, M, R, or N; X<sub>6</sub> is I, K, S, T, R, E, D, N, V, H, L, A, Q, or G; X<sub>7</sub> is S, T, Y, R, or N; and X<sub>8</sub> is M, G, or Y; (b) the amino acid sequence of CDR2 is as set forth in AIX<sub>9</sub>GX<sub>10</sub>X<sub>11</sub>TX<sub>12</sub>YADSVK (SEQ ID NO: 2), wherein X<sub>9</sub> is H, N, or S; X<sub>10</sub> is F, G, K, R, P, D, Q, H, E, N, T, S, A, I, L, or V; X<sub>11</sub> is S, Q, E, T, K, or D; and X<sub>12</sub> is L, V, I, F, Y, or W; and (c) the amino acid sequence of CDR3 is as set forth in VPWGX<sub>13</sub>YHPX<sub>14</sub>X<sub>15</sub>VX<sub>16</sub> (SEQ ID NO: 3), wherein X<sub>13</sub> is D, I, T, K, R, A, E, S, or Y; X<sub>14</sub> is R, G, L, K, T, Q, S, or N; X<sub>15</sub> is N, K, E, V, R, M, or D; and X<sub>16</sub> is Y, A, V, K, H, L, M, T, R, Q, C, S, or N.

**[0006a]** In one aspect, provided herein is a single domain B cell maturation agent (BCMA) binding protein, that comprises complementarity determining regions CDR1, CDR2, and CDR3, wherein the CDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 5, 15, 18, 19, 22, 29, 34, 35, 43, 46, 76, and 95, the CDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 118, 121, 122, 125, 126, 129, 133, 137, 147, 156, 164, 173, 174, 190, and 203, and the CDR3 comprises an amino acid sequence set forth as SEQ ID NO: 304, and wherein the BCMA binding protein is from 80% to 99% identical to the sequence set forth as SEQ ID NO: 472.

**[0006b]** In one aspect, provided herein is a single domain B cell maturation agent (BCMA) binding protein, that comprises complementarity determining regions CDR1, CDR2, and CDR3; wherein the CDR1 comprises the amino acid sequence of SEQ ID NO: 76, the CDR2 comprises the amino acid sequence of SEQ ID NO: 190, and the CDR3 comprises the amino acid sequence of SEQ ID NO: 304, and wherein the BCMA binding protein is from 80% to 99% identical to the amino acid sequence set forth as SEQ ID NO: 472.

**[0006c]** In one aspect, provided herein is a single domain B cell maturation agent (BCMA) binding protein, comprising: (i) a CDR1 comprising the sequence of SEQ ID NO: 76, a CDR2 comprising the sequence of SEQ ID NO: 190, and a CDR3 comprising the sequence of SEQ ID NO: 304; (ii) a CDR1 comprising the sequence of SEQ ID NO: 114, a CDR2 comprising the sequence of SEQ ID NO: 163, and a CDR3 comprising the sequence of SEQ ID NO: 304; (iii) a CDR1 comprising the sequence of SEQ ID NO: 115, a CDR2 comprising the sequence of SEQ ID NO: 163, and a CDR3 comprising the sequence of SEQ ID NO: 304; (iv) a CDR1 comprising the sequence of SEQ ID NO: 116, a CDR2 comprising the sequence of SEQ ID NO: 174, and a CDR3 comprising the sequence of SEQ ID NO: 304; or (v) a CDR1 comprising the sequence of SEQ ID NO: 117, a CDR2 comprising the sequence of SEQ ID NO: 174, and a CDR3 comprising the sequence of SEQ ID NO: 304.

**[0007]** In one example, the CDR1 does not comprise an amino acid sequence of SEQ ID NO: 473. In one example, the CDR2 does not comprise an amino acid sequence of SEQ ID NO: 474. In one example, the CDR3 does not comprise an amino acid sequence of SEQ ID NO: 475. In one example, the CDR1 and CDR2 do not comprise amino acid sequences of SEQ ID NO: 473 and 474, respectively. In one example, the CDR1 and CDR3 do not comprise amino acid sequences of SEQ ID NO: 473 and 475, respectively. In one example, the CDR2 and CDR3 do not comprise amino acid sequences of SEQ ID NO: 474 and 475, respectively. In one example, the CDR1, CDR2 and CDR3 do not comprise amino acid sequences of SEQ ID NO: 473, 474 and 475, respectively.

**[0008]** Provided herein is a single domain BCMA binding protein wherein said protein comprises the following formula: f1-r1-f2-r2-f3-r3-f4, wherein, r1 is SEQ ID NO: 1; r2 is SEQ ID NO: 2; and r3 is SEQ ID NO: 3; and wherein f1, f2, f3 and f4 are framework residues selected so that said protein is from about eighty percent (80%) to about 99% identical to the amino acid sequence set forth in SEQ ID NO: 346 or 472. Provided herein is a single domain BCMA binding protein wherein said protein comprises the following formula: f1-r1-f2-r2-f3-r3-f4, wherein, r1 is SEQ ID NO: 1; r2 is SEQ ID NO: 2; and r3 is SEQ ID NO: 3; and wherein f1, f2, f3 and f4 are framework residues selected so that said protein is from about 80% to about 90% identical to the amino acid sequence set forth in SEQ ID NO: 346 or 472. In one example, the amino acid sequence of the single domain BCMA binding protein does not comprise SEQ ID NO: 472.

**[0009]** In some non-limiting examples, r1 comprises an amino acid sequence set forth as any one of SEQ ID NOS: 4-117.

**[0010]** In some non-limiting examples, r2 comprises an amino acid sequence set forth as any one of SEQ ID NOS: 118-231.

**[0011]** In some non-limiting examples, r3 comprises an amino acid sequence set forth as any one of SEQ ID NOS: 232-345.

**[0012]** In other non-limiting examples, the protein comprises an amino sequence set forth as any one of SEQ ID NOS: 346-460.

**[0013]** In a single domain BCMA binding protein, f1 can comprise SEQ ID NO: 461 or 462.

**[0014]** In a single domain BCMA binding protein, f2 can comprise SEQ ID NO: 463.

**[0015]** In a single domain BCMA binding protein, f3 can comprise SEQ ID NO: 464 or 465.

**[0016]** In a single domain BCMA binding protein, wherein f4 can comprise SEQ ID NO: 466 or 467.

**[0017]** In one non-limiting example, r1 comprises SEQ ID NO: 76, 114, 115, 116 or 117. In one non-limiting example, r1 comprises SEQ ID NO: 76.

**[0018]** In one non-limiting example, r1 comprises SEQ ID NO: 76, r2 is SEQ ID NO: 190, and r3 is SEQ ID NO: 304.

**[0019]** In one non-limiting example, r1 comprises SEQ ID NO: 114, r2 comprises SEQ ID NO: 228 and r3 comprises SEQ ID NO: 342.

**[0020]** In one non-limiting example, r1 comprises SEQ ID NO: 115, r2 comprises SEQ ID NO: 229 and r3 comprises SEQ ID NO: 343.

**[0021]** In one non-limiting example, r1 comprises SEQ ID NO: 117, r2 comprises SEQ ID NO: 231 and r3 comprises SEQ ID NO: 345.

**[0022]** In one non-limiting example, r1 comprises SEQ ID NO: 116, r2 comprises SEQ ID NO: 230 and r3 comprises SEQ ID NO: 344.

**[0023]** A domain BCMA binding protein can have an elimination half-time of at least 12 hours, at least 20 hours, at least 25 hours, at least 30 hours, at least 35 hours, at least 40 hours, at least 45 hours, at least 50 hours, at least 100 hours or more. In some examples, the single domain BCMA binding protein further comprises a Fc domain. In some examples, the single domain BCMA binding protein further comprises an anti-cancer agent.

**[0024]** Provided herein is a single domain BCMA binding protein parental llama anti-BCMA 253BH10 SEQ ID NO: 472 or a humanized version of this llama sequence, BH2T, SEQ ID NO 346, wherein one or more amino acid residues selected from amino acid positions 26, 27, 28, 29, 30, 31, 32 and 34 of CDR1; positions 52, 54, 55 and 57 of CDR2; and positions 101, 105, 106 and 108 of CDR3 are substituted, wherein amino acid position 26, if substituted, is substituted with S; amino acid position 27, if substituted, is substituted with D or S; amino acid position 28, if substituted, is substituted with D, Q, H, V, or E; amino acid position 29, if substituted, is substituted with S, E, A, T, M, V, I, D, Q, P, R, or G; amino acid position 30, if substituted, is substituted with M, R, or N; amino acid position 31, if substituted, is substituted with K, S, T, R, E, D, N, V, H, L, A, Q, or G; amino acid position 32, if substituted, is substituted with T, Y,

## CLAIMS

What is claimed is:

1. A single domain B cell maturation agent (BCMA) binding protein, that comprises complementarity determining regions CDR1, CDR2, and CDR3, wherein the CDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 5, 15, 18, 19, 22, 29, 34, 35, 43, 46, 76, and 95, the CDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 118, 121, 122, 125, 126, 129, 133, 137, 147, 156, 164, 173, 174, 190, and 203, and the CDR3 comprises an amino acid sequence set forth as SEQ ID NO: 304, and wherein the BCMA binding protein is from 80% to 99% identical to the sequence set forth as SEQ ID NO: 472.
2. The single domain BCMA binding protein of claim 1, wherein said protein comprises the following formula: f1-r1-f2-r2-f3-r3-f4 wherein, r1 is the CDR1; r2 is the CDR2; and r3 is the CDR3; and wherein f<sub>1</sub>, f<sub>2</sub>, f<sub>3</sub> and f<sub>4</sub>, are framework residues.
3. The single domain BCMA binding protein of claim 1, wherein the protein comprises an amino sequence set forth as SEQ ID NOS: 374, 383, 402, 403, 406, 411, 412, or 416.
4. The single domain BCMA binding protein of claim 2, wherein f1 comprises SEQ ID NO: 461 or 462.
5. The single domain BCMA binding protein of claim 2, wherein f2 comprises SEQ ID NO: 463.
6. The single domain BCMA binding protein of claim 2, wherein f3 comprises SEQ ID NO: 464 or 465.
7. The single domain BCMA binding protein of claim 2, wherein f4 comprises SEQ ID NO: 466 or 467.
8. The single domain BCMA binding protein of claim 1, wherein said protein has an elimination half-time of at least 12 hours, at least 20 hours, at least 25 hours, at least 30 hours, at least 35 hours, at least 40 hours, at least 45 hours, at least 50 hours, or at least 100 hours, when administered to a subject.
9. The single domain BCMA binding protein of claim 1, wherein said protein is human, humanized, or affinity matured.
10. The single domain BCMA binding protein of claim 1, that further comprises an Fc domain.
11. The single domain BCMA binding protein of claim 1, that further comprises an anti-cancer agent.
12. The single domain BCMA binding protein of claim 11, wherein the anti-cancer agent is conjugated to the single domain BCMA binding protein.
13. A multispecific binding protein comprising the single domain BCMA binding protein according to claim 1.
14. The single domain BCMA binding protein of claim 1, wherein the BCMA binding protein comprises a sequence that is at least 90% identical to a sequence selected from the group consisting of SEQ ID NOS: 374, 383, 402, 403, 406, 411, 412, and 416.

15. The single domain BCMA binding protein of claim 1, wherein the BCMA binding protein comprises a sequence that is at least 95% identical to a sequence selected from the group consisting of SEQ ID NOS: 374, 383, 402, 403, 406, 411, 412, and 416.

16. The single domain BCMA binding protein of claim 1, wherein the BCMA binding protein recognizes an epitope within the human BCMA protein comprising the sequence set forth as SEQ ID NO: 468.

17. A single domain B cell maturation agent (BCMA) binding protein, that comprises complementarity determining regions CDR1, CDR2, and CDR3; wherein the CDR1 comprises the amino acid sequence of SEQ ID NO: 76, the CDR2 comprises the amino acid sequence of SEQ ID NO: 190, and the CDR3 comprises the amino acid sequence of SEQ ID NO: 304, and wherein the BCMA binding protein is from 80% to 99% identical to the amino acid sequence set forth as SEQ ID NO: 472.

18. A single domain B cell maturation agent (BCMA) binding protein, comprising:

- (i) a CDR1 comprising the sequence of SEQ ID NO: 76, a CDR2 comprising the sequence of SEQ ID NO: 190, and a CDR3 comprising the sequence of SEQ ID NO: 304;
- (ii) a CDR1 comprising the sequence of SEQ ID NO: 114, a CDR2 comprising the sequence of SEQ ID NO: 163, and a CDR3 comprising the sequence of SEQ ID NO: 304;
- (iii) a CDR1 comprising the sequence of SEQ ID NO: 115, a CDR2 comprising the sequence of SEQ ID NO: 163, and a CDR3 comprising the sequence of SEQ ID NO: 304;
- (iv) a CDR1 comprising the sequence of SEQ ID NO: 116, a CDR2 comprising the sequence of SEQ ID NO: 174, and a CDR3 comprising the sequence of SEQ ID NO: 304; or
- (v) a CDR1 comprising the sequence of SEQ ID NO: 117, a CDR2 comprising the sequence of SEQ ID NO: 174, and a CDR3 comprising the sequence of SEQ ID NO: 304.