

Claims

It is claimed:

1. An isolated human interleukin 15 (IL-15) variant comprising amino acid substitution at positions a) V49 and I51 or b) V49, I50, and S51 of SEQ ID NO: 1, and further comprising one or more amino acid substitutions at positions N1, N4, S7, K10, K11, Y26, S29, D30, V31, H32, E53, G55, E64, I68, L69, E89, L91, M109, and/or I111 of SEQ ID NO: 1, wherein the IL-15 variant has decreased or no binding to the human IL-15 receptor alpha (IL-15R α) and the human IL-2 receptor beta/gamma (IL-2R $\beta\gamma$) as compared to the wild-type human IL-15 polypeptide or a wild-type IL-15 receptor alpha-IL-15 fusion polypeptide, and wherein the amino acid substitution at position V49 is glycosylated.
2. The isolated IL-15 variant of claim 1, wherein the IL-15 variant comprises amino acid substitutions at positions selected from the group consisting of:
 - a) V49, I50, S51, N4, D30, and E64;
 - b) V49, I50, S51, N4, D30, E64, and I68;
 - c) V49, I50, S51, N4, D30, E64, M109;
 - d) V49, I50, S51, N4, D30, E64, I68, and M109;
 - e) V49, I50, S51, D30, E64, and I68;
 - f) V49, I50, S51, D30, E64, M109;
 - g) V49, I50, S51, D30, E64, I68, and M109;
 - h) N1, V49, I50, and S51;
 - i) N4, V49, I50, and S51;
 - j) S7, V49, I50, and S51;
 - k) K10, V49, I50, and S51;
 - l) K11, V49, I50, and S51;
 - m) S29, V49, I50, and S51;
 - n) V31, V49, I50, and S51;
 - o) H32, V49, I50, and S51;
 - p) V49, I50, S51, and E64;
 - q) V49, I50, S51, and I68;
 - r) V49, I50, S51, and L69;

- 5 s) V49, I50, S51, and I111;
t) N4, V49, I50, S51, and E64;
u) N1, D30, V49, I50, and S51;
v) N4, D30, V49, I50, and S51;
w) S7 D30, V49, I50, and S51;
x) K10, D30, V49, I50, and S51;
y) K11, D30, V49, I50, and S51;
z) S29, D30, V49, I50, and S51;
aa) D30, V49, I50, S51, and E64;
10 bb) D30, V49, I50, S51, and I68;
cc) D30, V49, I50, S51, and L69; and
dd) D30, V49, I50, S51, and I111.
3. The isolated IL-15 variant of any one of claims 1-2, wherein the amino acid
15 substitutions comprise one or more specific substitutions at:
- a) V49N, V49K, V49E, V49H, V49Q or V49R;
b) I50A or I50G;
c) S51T;
d) N1K, N1G, N1Q, N1R, N1E, N1A, or N1D;
20 e) N4K, N4G, N4A, N4S, N4D, N4E, N4I, N4L, N4R, N4T, N4W, or
N4Q;
f) S7E, S7G, S7D, S7K, S7N, S7R, S7H, or S7T;
g) K10A, K10S, K10E, K10L, K10M, K10D, or K10G;
h) K11D, K11S, or K11W;
25 i) D30N;
j) E64Q, E64K, E64A, E64S, E64N, E64H, E64T, or E64R;
k) E53N;
l) G55S or G55T;
m) E89N;
30 n) L91S or L91T;
o) Y26K, Y26R, or Y26H;
p) S29N;
q) V31S, V31D, or V31K;

- r) H32G;
- s) I68S, I68A, I68R, I68T, I68K, I68N, I68M, I68F, I68Y, I68E, or I68H;
- t) L69A, L69S, L69D, L69T, L69M, L69G, L69Q, L69I, L69E, or L69V;
- 5 u) M109A, M109S, M109D, or M109K; and/or
- v) I111A, I111K, I111S, or I111D.

10 4. The isolated IL-15 variant of any one of claims 1-3, wherein the IL-15 variant comprises amino acid substitutions at positions selected from the group consisting of:

- a) N4K, D30N, V49N, I50A, S51T, and E64Q;
- b) N4Q, D30N, V49N, I50A, and S51T;
- c) D30N, V49N, I50A, S51T, and E64Q;
- d) N4Q, D30N, V49N, I50A, S51T, and E64Q;
- 15 e) N4Q, V49N, I50A, and S51T;
- f) V49N, I50A, S51T, and E64Q; and
- g) N4Q, V49N, I50A, S51T, and E64Q.

20 5. An isolated human interleukin 15 (IL-15) variant comprising amino acid substitutions at positions E46 and V49 of SEQ ID NO: 1, and at least one or more amino acid substitution(s) at positions N1, N4, S7, K10, K11, D22, Y26, S29, D30, V31, H32, E53, G55, E64, I68, L69, E89, E93, M109 and/or I111 of SEQ ID NO: 1, wherein the IL-15 variant has no binding to the human IL-15 receptor alpha (IL-15R α) and decreased binding to the human IL-2 receptor beta/gamma (IL-2R $\beta\gamma$) as compared to the wild-type human IL-15 polypeptide or
25 a wild-type IL-15 receptor alpha-IL-15 fusion polypeptide.

30 6. The isolated IL-15 variant of claim 5, wherein the IL-15 variant comprises amino acid substitutions at positions selected from the group consisting of:

- a) N1, E46, and V49;
- b) N4, E46, and V49;

- 5 c) S7, E46, and V49;
 d) K10, E46, and V49;
 e) K11, E46, and V49;
 f) S29, E46, and V49;
 g) V31, E46, and V49;
 h) H32, E46, and V49;
 i) E46, V49, and E64;
 j) E46, V49, and I68;
 k) E46, V49, and L69;
10 l) E46, V49, and I111;
 m) N4, E46, V49, and E64;
 n) E46, V49, N4, D30, and E64;
 o) E46, V49, N4, D30, E64, and I68;
 p) E46, V49, N4, D30, E64, and M109;
15 q) E46, V49, N4, D30, E64, I68, and M109;
 r) N1, D30, E46, and V49;
 s) N4, D30, E46, and V49;
 t) S7, D30, E46, and V49;
 u) K10, D30, E46, and V49;
20 v) K11, D30, E46, and V49;
 w) S29, D30, E46, and V49;
 x) D30, E46, V49, and E64;
 y) D30, E46, V49R, and I68;
 z) D30, E46, V49R, and L69;
25 aa)D30, E46, V49R, and I111;
 bb)N1, D30, E46, V49, and M109;
 cc) N4, D30, E46, V49, and M109;
 dd)S7, D30, E46, V49, and M109;
 ee)K10, D30, E46, V49, and M109;
30 ff) K11, D30, E46, V49, and M109;
 gg) D30, E46, V49, E64, and M109;
 hh) D30, E46, V49, I68, and M109;
 ii) D30, E46, V49, L69 and M109;

- jj) D30, E46, V49, M109, and I111;
- kk) D30, E46, V49, E64, I68, and M109;
- ll) E46, V49, D30, E64, and I68;
- mm) E46, V49, E64, and M109;
- nn) E46, V49, D30, E64, I68, and M109;
- oo) D22, Y26, V49, E46, E53, E89, and E93; and
- pp) N1, D30, E46, V49, and E64.

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7. The isolated IL-15 variant of claim 5 or 6, wherein the amino acid substitutions comprise one or more specific substitutions at:

- a) N1Q, N1K, N1R, N1E, N1A, N1D, or N1G;
- b) N4K, N4G, N4A, N4S, N4D, N4E, N4R, N4T, N4I, N4L, N4W, or N4Q;
- c) S7E, S7G, S7D, S7K, S7N, S7R, S7H, or S7T;
- d) K10D, K10A, K10S, K10E, K10L, K10M, K10D, or K10G;
- e) K11D, K11S, or K11W;
- f) D22N;
- g) Y26K, Y26R, or Y26H;
- h) S29N;
- i) D30N;
- j) V31S, V31D, or V31K;
- k) H32G;
- l) E46G or E46Q;
- m) V49N, V49K, or V49R V49E, V49H, or V49Q;
- n) E53Q;
- o) G55S or G55T
- p) E64Q, E64K, E64A, E64S, E64N, E64H, E64T, or E64R;
- q) I68S, I68A, I68R, I68T, I68K, I68N, I68M, I68F, I68Y, I68E, or I68H;
- r) L69S, L69A, L69D, L69T, L69M, L69G, L69Q, L69I, L69E, or L69V;
- s) E89Q;
- t) E93Q;

- u) M109A, M109S, M109D, or M109K; and/or
- v) I111A, I111K, I111S, or I111D.

8. The isolated IL-15 variant of any one of claims 5-7, wherein the IL-15 variant comprises amino acid substitutions at positions selected from the group consisting of:

- a) N1K, E46G, and V49R;
- b) N4K, E46G, and V49R;
- c) N4Q, E46G, and V49R;
- 10 d) S7T, E46G, and V49R;
- e) V31S, E46G, and V49R;
- f) V31K, E46G, and V49R;
- g) E46G, V49R, and E64Q;
- h) E46G, V49R, and E64K;
- 15 i) N4Q, E46G, V49R, and E64Q;
- j) N1G, D30N, E46G, and V49R;
- k) N1K, D30N, E46G, and V49R;
- l) N1Q, D30N, E46G, and V49R;
- m) N4G, D30N, E46G, and V49R;
- 20 n) N4K, D30N, E46G, and V49R;
- o) N4Q, D30N, E46G, and V49R;
- p) S7E, D30N, E46G, and V49R;
- q) S7G, D30N, E46G, and V49R;
- r) S7T, D30N, E46G, and V49R;
- 25 s) K10D, D30N, E46G, and V49R;
- t) D30N, E46G, V49R, and E64A;
- u) D30N, E46G, V49R, and E64Q;
- v) D30N, E46G, V49R, and E64K;
- w) D30N, E46G, V49R, and I68S;
- 30 x) D30N, E46G, V49R, and I68K;
- y) N4K, D30N, E46G, V49R, and E64K;
- z) N4Q, D30N, E46G, V49R, and E64K;
- aa) N4K, D30N, E46G, V49R, and E64Q;

- bb) N4Q, D30N, E46G, V49R, and E64Q;
- cc) N4K, D30N, E46G, V49R, and I68S;
- dd) D30N, E46G, V49R, E64Q, and I68S;
- ee) N1A, D30N, E46G, and V49R; and
- ff) N1G, D30N, E46G, V49R, and E64Q.

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9. An isolated fusion protein comprising: 1) an antibody comprising a Fc domain; and b) a human interleukin 15 (IL-15) variant comprising amino acid substitution at positions a) V49 and I51 or b) V49, I50, and S51 of SEQ ID NO: 1, wherein the amino acid substitution at position V49 of SEQ ID NO: 1 is glycosylated, and further comprising one or more amino acid substitutions at positions N1, N4, S7, K10, K11, Y26, S29, D30, V31, H32, E53, G55, E64, I68, L69, E89, L91, M109, and/or I111 of SEQ ID NO: 1, wherein the IL-15 variant is covalently linked to the Fc domain of the antibody, and wherein the Fc domain has decreased or no antibody dependent cellular cytotoxicity (ADCC) activity compared to the wild-type Fc.

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10. The fusion protein of claim 9, wherein the IL-15 variant comprises amino acid substitutions at positions selected from the group consisting of:

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- a) V49, I50, S51, N4, D30, and E64;
- b) V49, I50, S51, N4, D30, E64, and I68;
- c) V49, I50, S51, N4, D30, E64, M109;
- d) V49, I50, S51, N4, D30, E64, I68, and M109;
- e) V49, I50, S51, D30, E64, and I68;
- f) V49, I50, S51, D30, E64, M109;
- g) V49, I50, S51, D30, E64, I68, and M109;
- h) N1, V49, I50, and S51;
- i) N4, V49, I50, and S51;
- j) S7, V49, I50, and S51;
- k) K10, V49, I50, and S51;
- l) K11, V49, I50, and S51;
- m) S29, V49, I50, and S51;
- n) V31, V49, I50, and S51;

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- o) H32, V49, I50, and S51;
 - p) V49, I50, S51, and E64;
 - q) V49, I50, S51, and I68;
 - r) V49, I50, S51, and L69;
 - s) V49, I50, S51, and I111;
 - t) N4, V49, I50, S51, and E64;
 - u) N1, D30, V49, I50, and S51;
 - v) N4, D30, V49, I50, and S51;
 - w) S7 D30, V49, I50, and S51;
 - 10 x) K10, D30, V49, I50, and S51;
 - y) K11, D30, V49, I50, and S51;
 - z) S29, D30, V49, I50, and S51;
 - aa) D30, V49, I50, S51, and E64;
 - bb) D30, V49, I50, S51, and I68;
 - 15 cc) D30, V49, I50, S51, and L69; and
 - dd) D30, V49, I50, S51, and I111.

11. The fusion protein of claim 9 or 10, wherein the amino acid substitutions comprise one or more specific substitutions at:

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- a) V49N, V49K, or V49R;
 - b) I50A or I50G;
 - c) S51T;
 - d) N1K, N1G, N1Q, N1R, N1E, N1A, or N1D;
 - e) N4K, N4G, N4A, N4S, N4D, N4E, N4L, N4R, N4T, or N4Q;
 - 25 f) S7E, S7G, S7D, S7K, S7N, S7R, S7H, or S7T;
 - g) K10A, K10S, K10E, K10L, K10M, K10D, or K10G;
 - h) K11D, K11S, or K11W;
 - i) D30N;
 - j) E64Q, E64K, E64A, E64S, E64N, E64H, E64T, or E64R;
 - 30 k) E53N;
 - l) G55S or G55T;
 - m) E89N;
 - n) L91S or L91T;

- o) Y26K, Y26R, or Y26H;
- p) S29N;
- q) V31S, V31D, or V31K;
- r) H32G;
- 5 s) I68S, I68A, I68R, I68T, I68K, I68N, I68M, I68F, I68Y, I68E, or I68H;
- t) L69S, L69A, L69D, L69T, L69M, L69G, L69Q, L69I, L69E, or L69V;
- u) M109A, M109S, M109D, or M109K; and/or
- v) I111A, I111K, I111S, or I111D.

10 12. The fusion protein of any one of claims 9-11, wherein the IL-15 variant comprises amino acid substitutions at positions selected from the group consisting of:

- a) N4K, D30N, V49N, I50A, S51T, and E64Q;
- b) Y26K, V49R, N4K, D30N, and E64Q;
- 15 c) Y26K, V49K, N4K, D30N, and E64Q.
- d) N4Q, D30N, V49N, I50A, and S51T;
- e) D30N, V49N, I50A, S51T, and E64Q;
- f) N4Q, D30N, V49N, I50A, S51T, and E64Q;
- g) N4Q, V49N, I50A, and S51T;
- 20 h) V49N, I50A, S51T, and E64Q; and
- i) N4Q, V49N, I50A, S51T, and E64Q.

25 13. An isolated fusion protein comprising: 1) an antibody comprising a Fc domain; and b) a human interleukin 15 (IL-15) variant comprising amino acid substitutions at positions E46 and V49 of SEQ ID NO: 1, and at least one or more amino acid substitution(s) at positions N1, N4, S7, K10, K11, D22, Y26, S29, D30, V31, H32, E53, G55, E64, I68, L69, E89, E93, M109 and/or I111 of SEQ ID NO: 1, wherein the IL-15 variant is covalently linked to the Fc domain of the antibody, and wherein the Fc domain has decreased or no antibody
30 dependent cellular cytotoxicity (ADCC) activity compared to the wild-type Fc.

14. The fusion protein of claim 13, wherein the IL-15 variant comprises amino acid substitutions at positions selected from the group consisting of:

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- a) N1, E46, and V49;
 - b) N4, E46, and V49;
 - c) S7, E46, and V49;
 - d) K10, E46, and V49;
 - e) K11, E46, and V49;
 - f) S29, E46, and V49;
 - g) V31, E46, and V49;
 - h) H32, E46, and V49;
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- i) E46, V49, and E64;
 - j) E46, V49, and I68;
 - k) E46, V49, and L69;
 - l) E46, V49, and I111;
 - m) N4, E46, V49, and E64;
 - n) E46, V49, N4, D30, and E64;
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- o) E46, V49, N4, D30, E64, and I68;
 - p) E46, V49, N4, D30, E64, and M109;
 - q) E46, V49, N4, D30, E64, I68, and M109;
 - r) N1, D30, E46, and V49;
 - s) N4, D30, E46, and V49;
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- t) S7, D30, E46, and V49;
 - u) K10, D30, E46, and V49;
 - v) K11, D30, E46, and V49;
 - w) S29, D30, E46, and V49;
 - x) D30, E46, V49, and E64;
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- y) D30, E46, V49R, and I68;
 - z) D30, E46, V49R, and L69;
 - aa) D30, E46, V49R, and I111;
 - bb) N1, D30, E46, V49, and M109;
 - cc) N4, D30, E46, V49, and M109;
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- dd) S7, D30, E46, V49, and M109;
 - ee) K10, D30, E46, V49, and M109;
 - ff) K11, D30, E46, V49, and M109;
 - gg) D30, E46, V49, E64, and M109;

- hh) D30, E46, V49, I68, and M109;
- ii) D30, E46, V49, L69, and M109;
- jj) D30, E46, V49, M109, and I111;
- kk) D30, E46, V49, E64, I68, and M109;
- ll) E46, V49, D30, E64, and I68;
- mm) E46, V49, E64, and M109;
- nn) E46, V49, D30, E64, I68, and M109;
- oo) D22, Y26, V49, E46, E53, E89, and E93; and
- pp) N1, D30, E46, V49, and E64.

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15. The fusion protein of claim 13 or 14, wherein the IL-15 variant comprises amino acid substitutions at positions selected from the group consisting of:

- a) N1Q, N1K, N1R, N1E, N1A, N1D, or N1G;
- b) N4K, N4G, N4A., N4S, N4D, N4E, N4L, N4R, N4T, or N4Q;
- c) S7E, S7G, S7D, S7K, S7N, S7R, S7H, or S7T;
- d) K10D, K10A, K10S, K10E, K10L, K10M, K10D, K10G;
- e) K11D, K11S, or K11W;
- f) D22N;
- g) Y26K, Y26R, or Y26H;
- h) S29N;
- i) D30N;
- j) V31S, V31D, or V31K;
- k) H32G;
- l) E46G or E46Q;
- m) V49N, V49K, or V49R; V49E, V49H, or V49Q;
- n) E53Q;
- o) G55S or G55T;
- p) E64Q, E64K, E64A, E64S, E64N, E64H, E64T, or E64R;
- q) I68S, I68A, I68R, I68T, I68K, I68N, I68M, I68F, I68Y, I68E or I68H;
- r) L69S, L69A, L69D, L69T, L69M, L69G, L69Q, L69I, L69E, or L69V;

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- s) E89Q;
- t) E93Q;
- u) M109A, M109S, M109D, or M109K; and
- v) I111A, I111K, I111S, or I111D.

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16. The fusion protein of any one of claims 13-15, wherein the IL-15 variant comprises amino acid substitutions at positions selected from the group consisting of:

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- a) N1K, E46G, and V49R;
- b) N4K, E46G, and V49R;
- c) N4Q, E46G, and V49R;
- d) S7T, E46G, and V49R;
- e) V31S, E46G, and V49R;
- f) V31K, E46G, and V49R;
- g) E46G, V49R, and E64Q;
- h) E46G, V49R, and E64K;
- i) N4Q, E46G, V49R, and E64Q;
- j) N1G, D30N, E46G, and V49R;
- k) N1K, D30N, E46G, and V49R;

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- l) N1Q, D30N, E46G, and V49R;
- m) N4G, D30N, E46G, and V49R;
- n) N4K, D30N, E46G, and V49R;
- o) N4Q, D30N, E46G, and V49R;
- p) S7E, D30N, E46G, and V49R;

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- q) S7G, D30N, E46G, and V49R;
- r) S7T, D30N, E46G, and V49R;
- s) K10D, D30N, E46G, and V49R;
- t) D30N, E46G, V49R, and E64A;
- u) D30N, E46G, V49R, and E64Q;

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- v) D30N, E46G, V49R, and E64K;
- w) D30N, E46G, V49R, and I68S;
- x) D30N, E46G, V49R, and I68K;
- y) N4K, D30N, E46G, V49R, and E64K;

- z) N4Q, D30N, E46G, V49R, and E64K;
- aa) N4K, D30N, E46G, V49R, and E64Q;
- bb) N4Q, D30N, E46G, V49R, and E64Q;
- cc) N4K, D30N, E46G, V49R, and I68S;
- dd) D30N, E46G, V49R, E64Q, and I68S;
- ee) N1A, D30N, E46G, and V49R; and
- ff) N1G, D30N, E46G, V49R, and E64Q.

17. The fusion protein of any one of claims 13-16 comprising an amino acid sequence of SEQ ID NO: 86, 87, 89, or 90.

18. The fusion protein of any one of claims 9-17, wherein the antibody has an isotype that is selected from the group consisting of IgG₁, IgG₂, IgG_{2Δa}, IgG₄, IgG_{4Δb}, IgG_{4Δc}, IgG₄ S228P, IgG_{4Δb} S228P, and IgG_{4Δc} S228P.

19. The fusion protein of claim 18, wherein the antibody is a) an IgG₂, and the antibody variable domain comprises amino acid modifications at positions 223, 225, and/or 228 in the hinge region and at position 409 and/or 368 (EU numbering scheme) in the CH3 region of the human IgG₂ (SEQ ID NO: 3); b) an IgG₁, and the antibody variable domain comprises amino acid modifications at positions 221 and/or 228 in the hinge region and at position 409 and/or 368 (EU numbering scheme) in the CH3 region of the human IgG₁ (SEQ ID NO: 2); or c) an IgG₁, and the antibody variable domain comprise amino acid modifications at positions 349, 354, 366, 368, and/or 407 (EU numbering scheme) in the CH3 region of the human IgG₁ (SEQ ID NO: 2).

20. The fusion protein of claim 19, wherein the antibody further comprises an amino acid modification at a) one or more positions 265, 330, and/or 331 of the human IgG₂ (SEQ ID NO: 3); or b) one or more positions 234, 235, and/or 237 of the human IgG₁ (SEQ ID NO: 2).

21. The fusion protein of any one of claims 9-20, wherein the antibody is selected from the group consisting of an anti-CTLA-4 antibody, an anti-CD3

antibody, an anti-CD4 antibody, an anti-CD8 antibody, an anti-4-1BB antibody, an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-TIM3 antibody, an anti-LAG3 antibody, an anti-TIGIT antibody, an anti-OX40 antibody, an anti-IL-8 antibody, an anti-IL-7Ralpha (CD127) antibody, an anti-IL15 antibody, an anti-HVEM antibody, an anti-BTLA antibody, an anti-CD40 antibody, an anti-CD40L antibody, anti-CD47 antibody, an anti-CSF1R antibody, an anti-CSF1 antibody, an anti-MARCO antibody, an anti-CXCR4 antibodies, an anti-VEGFR1 antibody, an anti-VEGFR2 antibody, an anti-TNFR1 antibody, an anti-TNFR2 antibody, an anti-CD3 bispecific antibody, an anti-CD19 antibody, an anti-CD20, an anti-Her2 antibody, an anti-EGFR antibody, an anti-ICOS antibody, an anti-CD22 antibody, an anti-CD 52 antibody, an anti-CCR4 antibody, an anti-CCR8 antibody, an anti-CD200R antibody, an anti-VISG4 antibody, an anti-CCR2 antibody, an anti-LILRb2 antibody, an anti-CXCR4 antibody, an anti-CD206 antibody, an anti-CD163 antibody, an anti-KLRG1 antibody, an anti-FLT3 antibody, an anti-B7-H4 antibody, an anti-B7-H3 antibody, an KLRG1 antibody, and an anti-GITR antibody.

22. The fusion protein of claim 21, wherein the antibody is a PD-1 antibody comprising a heavy chain variable (VH) region comprising a VH complementarity determining region one (CDR1) comprising the amino acid sequence of SEQ ID NO: 14, 15, 80, 81, 91, or 92, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 16, 17, 82, or 83, and a VH CDR3 comprising the amino acid sequence shown in SEQ ID NO: 18 or 62; and/or a VL CDR1 comprising the amino acid sequence shown in SEQ ID NO: 19 or 31, a VL CDR2 comprising the amino acid sequence shown in SEQ ID NO: 20 or 32, and a VL CDR3 comprising the amino acid sequence shown in SEQ ID NO: 21 or 33.

23. The fusion protein of claim 21, wherein the antibody is a PD-1 antibody comprising a VH region comprising a CDR1, CDR2, and CDR3 of the VH having an amino acid sequence of SEQ ID NO: 12, 34, 78, or 36, and/or a VL region comprising a CDR1, CDR2, and CDR3 of the VL having an amino acid sequence of SEQ ID NO: 13, 35, 79, or 37.

24. The fusion protein of any one of claims 9-23, wherein the IL-15 variant is covalently linked to the antibody by a polypeptide linker and/or a polypeptide tag.

25. An isolated cell line that produces the IL-15 variant of any one of claims 1-8 or the IL-15 fusion protein of any one of claims 9-24.

26. An isolated nucleic acid encoding the IL-15 variant of any one of claims 1-8 or the fusion protein of any one of claims 9-24.

27. A recombinant expression vector comprising the nucleic acid of claim 26.

28. A host cell comprising the isolated nucleic acid of claim 26 or the expression vector of claim 27.

29. A pharmaceutical composition comprising the IL-15 variant of any one of claims 1-8 or the fusion protein of any one of claims 9-24, and a pharmaceutically acceptable carrier.

30. A kit for the treatment of cancer comprising the pharmaceutical composition of claim 29.

31. The IL-15 variant of any one of claims 1-8, the fusion protein of any one of claims 9-24, or the pharmaceutical composition of claim 29 for the use in the treatment of cancer.

32. The IL-15 variant, the fusion protein, or the pharmaceutical composition of claim 31, wherein the cancer is a solid cancer or a liquid cancer.

33. The IL-15 variant, the fusion protein, or the pharmaceutical composition of claim 32, wherein the solid cancer is selected from the group consisting of gastric cancer, small intestine cancer, sarcoma, head and

neck cancer, thymic cancer, epithelial cancer, salivary cancer, liver cancer, biliary cancer, neuroendocrine tumors, stomach cancer, thyroid cancer, lung

cancer, mesothelioma, ovarian cancer, breast cancer, prostate cancer, esophageal cancer, pancreatic cancer, glioma, renal cancer, bladder cancer, cervical cancer, uterine cancer, vulvar cancer, penile cancer, testicular cancer, anal cancer, choriocarcinoma, colorectal cancer, oral cancer, skin cancer, Merkel cell carcinoma, glioblastoma, brain tumor, bone cancer, eye cancer, and melanoma.

34. The IL-15 variant, the fusion protein, or the pharmaceutical composition of claim 32, wherein the liquid cancer is selected from the group consisting of multiple myeloma, malignant plasma cell neoplasm, Hodgkin's lymphoma, nodular lymphocyte predominant Hodgkin's lymphoma, Kahler's disease and Myelomatosis, plasma cell leukemia, plasmacytoma, B-cell prolymphocytic leukemia, hairy cell leukemia, B-cell non-Hodgkin's lymphoma (NHL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), follicular lymphoma, Burkitt's lymphoma, marginal zone lymphoma, mantle cell lymphoma, large cell lymphoma, precursor B-lymphoblastic lymphoma, myeloid leukemia, Waldenstrom's macroglobulinemia, diffuse large B cell lymphoma, follicular lymphoma, marginal zone lymphoma, mucosa-associated lymphatic tissue lymphoma, small cell lymphocytic lymphoma, mantle cell lymphoma, Burkitt lymphoma, primary mediastinal (thymic) large B-cell lymphoma, lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, nodal marginal zone B cell lymphoma, splenic marginal zone lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, T cell/histiocyte-rich large B-cell lymphoma, primary central nervous system lymphoma, primary cutaneous diffuse large B-cell lymphoma (leg type), EBV positive diffuse large B-cell lymphoma of the elderly, diffuse large B-cell lymphoma associated with inflammation, intravascular large B-cell lymphoma, ALK-positive large B-cell lymphoma, plasmablastic lymphoma, large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease, B-cell lymphoma unclassified with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma, B-cell lymphoma unclassified with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma, and other hematopoietic cells related cancer.

35. The IL-15 variant, the fusion protein, or the pharmaceutical composition of any one of claims 31-34, wherein the cancer is relapsed, refractory, or metastatic.

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36. The IL-15 variant, the fusion protein, or the pharmaceutical composition of any one of claims 31-35, wherein the use is in combination with an effective amount of a second therapeutic agent, optionally wherein the combination is for administration simultaneously, concurrently, or simultaneously.

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37. The IL-15 variant, the fusion protein, or the pharmaceutical composition of claim 36, wherein the second therapeutic agent is an antibody selected from the group consisting of an anti-CTLA-4 antibody, an anti-CD3 antibody, an anti-CD4 antibody, an anti-CD8 antibody, an anti-4-1BB antibody, an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-TIM3 antibody, an anti-LAG3 antibody, an anti-TIGIT antibody, an anti-OX40 antibody, an anti-IL-7Ralpha (CD127) antibody, an anti-IL-8 antibody, an anti-IL-15 antibody, an anti-HVEM antibody, an anti-BTLA antibody, an anti-CD40 antibody, an anti-CD40L antibody, anti-CD47 antibody, an anti-CSF1R antibody, an anti-CSF1 antibody, an anti-IL-7R antibody, an anti-MARCO antibody, an anti-CXCR4 antibodies, an anti-VEGF antibody, an anti-VEGFR1 antibody, an anti-VEGFR2 antibody, an anti-TNFR1 antibody, an anti-TNFR2 antibody, an anti-CD3 bispecific antibody, an anti-CD19 antibody, an anti-CD20, an anti-Her2 antibody, an anti-EGFR antibody, an anti-ICOS antibody, an anti-CD22 antibody, an anti-CD 52 antibody, an anti-CCR4 antibody, an anti-CCR8 antibody, an anti-CD200R antibody, an anti-VISG4 antibody, an anti-CCR2 antibody, an anti-LILRb2 antibody, an anti-CXCR4 antibody, an anti-CD206 antibody, an anti-CD163 antibody, an anti-KLRG1 antibody, an anti-FLT3 antibody, an anti-B7-H4 antibody, an anti-B7-H3 antibody, an KLRG1 antibody, a BTN1A1 antibody, and an anti-GITR antibody.

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38. The IL-15 variant, the fusion protein, or the pharmaceutical composition of claim 36, wherein the second therapeutic agent is a cytokine, an immunocytokine, TNF α , a PAP inhibitor, an oncolytic virus, a kinase inhibitor, an ALK inhibitor, a MEK inhibitor, an IDO inhibitor, a GLS1 inhibitor, a

tyrosine kinase inhibitor, a CART cell or T cell therapy, a TLR agonist, or a tumor vaccine.

39. An isolated fusion protein comprising: 1) a PD-1 antibody comprising a Fc domain; and b) a human interleukin 15 (IL-15) variant comprising amino acid substitutions at positions E46, V49, N1, E64, and D30 of SEQ ID NO: 1, wherein the IL-15 variant is covalently linked to the Fc domain of the antibody, and wherein the Fc domain has decreased or no antibody dependent cellular cytotoxicity (ADCC) activity compared to the wild-type Fc.

40. An isolated fusion protein comprising: 1) a PD-1 antibody comprising a Fc domain; and b) a human interleukin 15 (IL-15) variant comprising amino acid substitutions at positions E46G, V49R, N1G, E64Q, and D30N of SEQ ID NO: 1, wherein the IL-15 variant is covalently linked to the Fc domain of the antibody.

41. The fusion protein of claim 39 or 40, wherein the antibody comprises a heavy chain variable (VH) region comprising a VH complementarity determining region one (CDR1) comprising the amino acid sequence of SEQ ID NO: 80, 81, or 91, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 82, or 83, and a VH CDR3 comprising the amino acid sequence shown in SEQ ID NO: 62; and/or a VL CDR1 comprising the amino acid sequence shown in SEQ ID NO: 31, a VL CDR2 comprising the amino acid sequence shown in SEQ ID NO: 32, and a VL CDR3 comprising the amino acid sequence shown in SEQ ID NO: 33.

42. The fusion protein of claim 39 or 40, wherein the antibody comprises a VH region comprising a CDR1, CDR2, and CDR3 of the VH having an amino acid sequence of SEQ ID NO: 36, and/or a VL region comprising a CDR1, CDR2, and CDR3 of the VL having an amino acid sequence of SEQ ID NO: 37.