

Claims

It is claimed:

1. An isolated human interleukin 15 (IL-15) variant comprising amino acid substitution at positions a) V49 and S51 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 cell line that produces the IL-15 variant of any one of claims 1-4.

25 6. An isolated nucleic acid encoding the IL-15 variant of any one of claims 1-4.

7. A recombinant expression vector comprising the nucleic acid of claim 6.

8. A host cell comprising the isolated nucleic acid of claim 6 or the expression vector of claim 7.

30 9. A pharmaceutical composition comprising the IL-15 variant of any one of claims 1-4 and a pharmaceutically acceptable carrier.

10. A kit for the treatment of cancer comprising the pharmaceutical composition of claim 9.