

CLAIMS

1. An interleukin 15 (IL15) construct comprising at least one IL15 molecule, at least one IL15 receptor alpha (IL15Ra) domain, at least one protease activatable moiety and at least one IgG1 Fc region, wherein the construct is a monovalent, heterodimeric interleukin 15 (IL15) construct comprising a first molecule comprising from N-terminus to C-terminus:

- a) an IL15 receptor alpha (IL15Ra) domain linked to;
- b) a first linker (L1) linked to;
- c) an IL15 domain linked to;
- d) a second linker (L2) containing a protease activatable moiety linked to;
- e) an Interleukin 2 receptor beta (IL2Rb) domain linked to;
- f) a third linker (L3) linked to;
- g) a first IgG1 Fc region.

2. The IL15 construct of claim 1, wherein the construct further comprises a second molecule comprising a second IgG1 Fc region, wherein the heterodimeric IL15 construct comprises:

(i) a first molecule set forth in SEQ ID NO:77 (MK150) and a second molecule set forth in SEQ ID NO:75 (MH8);

(ii) a first molecule set forth in SEQ ID NO:74 (MK145) and a second molecule set forth in SEQ ID NO:75 (MH8);

(iii) a first molecule set forth in SEQ ID NO:76 (MK149) and a second molecule set forth in SEQ ID NO:75 (MH8);

(iv) a first molecule set forth in SEQ ID NO:78 (MK151) and a second molecule set forth in SEQ ID NO:75 (MH8);

(v) a first molecule set forth in SEQ ID NO:79 (MK152) and a second molecule set forth in SEQ ID NO:75 (MH8);

(vi) a first molecule set forth in SEQ ID NO:80 (MK153) and a second molecule set forth in SEQ ID NO:75 (MH8);

(vii) a first molecule set forth in SEQ ID NO:81 (MK154) and a second molecule set forth in SEQ ID NO:75 (MH8);

(viii) a first molecule set forth in SEQ ID NO:82 (MK155) and a second molecule set forth in SEQ ID NO:52 (MH7); or

(ix) a first molecule set forth in SEQ ID NO:172 (MK157) and a second molecule set forth in SEQ ID NO:75 (MH8);

(x) a first molecule set forth in SEQ ID NO:51 (MK114) and a second molecule set forth in SEQ ID NO:52 (MH7);

(xi) a first molecule set forth in SEQ ID NO:53 (MK115) and a second molecule set forth in SEQ ID NO:52 (MH7);

(xii) a first molecule set forth in SEQ ID NO:54 (MK117) and a second molecule set forth in SEQ ID NO:52 (MH7);

(xiii) a first molecule set forth in SEQ ID NO:55 (MK118) and a second molecule set forth in SEQ ID NO:52 (MH7);

(xiv) a first molecule set forth in SEQ ID NO:56 (MK119) and a second molecule set forth in SEQ ID NO:52 (MH7);

(xv) a first molecule set forth in SEQ ID NO:57 (MK120) and a second molecule set forth in SEQ ID NO:52 (MH7);

(xvi) a first molecule set forth in SEQ ID NO:58 (MK121) and a second molecule set forth in SEQ ID NO:52 (MH7);

(xvii) a first molecule set forth in SEQ ID NO:59 (MK123) and a second molecule set forth in SEQ ID NO:52 (MH7);

(xviii) a first molecule set forth in SEQ ID NO:60 (MK124) and a second molecule set forth in SEQ ID NO:52 (MH7);

(xix) a first molecule set forth in SEQ ID NO:61 (MK125) and a second molecule set forth in SEQ ID NO:52 (MH7);

(xx) a first molecule set forth in SEQ ID NO:62 (MK126) and a second molecule set forth in SEQ ID NO:52 (MH7);

(xxi) a first molecule set forth in SEQ ID NO:67 (MK136) and a second molecule set forth in SEQ ID NO:52 (MH7);

(xxii) a first molecule set forth in SEQ ID NO:68 (MK137) and a second molecule set forth in SEQ ID NO:52 (MH7);

(xxiii) a first molecule set forth in SEQ ID NO:69 (MK138) and a second molecule set forth in SEQ ID NO:52 (MH7);

(xxiv) a first molecule set forth in SEQ ID NO:70 (MK139) and a second molecule set forth in SEQ ID NO:52 (MH7);

(xxv) a first molecule set forth in SEQ ID NO:71 (MK140) and a second molecule set forth in SEQ ID NO:52 (MH7);

(xxvi) a first molecule set forth in SEQ ID NO:72 (MK141) and a second molecule set forth in SEQ ID NO:52 (MH7);

(xxvii) a first molecule set forth in SEQ ID NO:73 (MK146) and a second molecule set forth in SEQ ID NO:52 (MH7).

3. The IL15 construct of claim 2, wherein the heterodimeric IL15 construct comprises a first molecule set forth in SEQ ID NO:77 (MK150) and a second molecule set forth in SEQ ID NO:75 (MH8), or a first molecule set forth in SEQ ID NO:68 (MK137) and a second molecule set forth in SEQ ID NO:52 (MH7).

4. The IL15 construct of claim 2, wherein the heterodimeric IL15 construct comprises a first molecule set forth in SEQ ID NO:77 (MK150) and a second molecule set forth in SEQ ID NO:75 (MH8).

5. Use of the IL 15 construct of any one of claims 1 to 3 in the manufacture of a medicament for the therapeutic treatment of cancer, wherein the cancer is gastric cancer, colon cancer, pancreatic cancer, breast cancer, head and neck cancer, kidney cancer, liver cancer, small cell lung cancer, non-small cell lung cancer, ovarian cancer, skin cancer, mesothelioma, lymphoma, leukemia, myeloma and sarcoma.

6. Use of the IL 15 construct of any one of claims 1 to 3 in the manufacture of a medicament for use in a combination therapy for the therapeutic treatment of cancer, wherein the medicament is to be administered in combination with another therapeutic agent comprising an immune checkpoint inhibitor, wherein the cancer is gastric cancer, colon cancer, pancreatic cancer, breast cancer, head and neck cancer, kidney cancer, liver cancer, small cell lung cancer, non-small cell lung cancer, ovarian cancer, skin cancer, mesothelioma, lymphoma, leukemia, myeloma and sarcoma.

7. The use of claim 6, wherein the immune checkpoint agent is a PD-1, PD-L1, PD-L2, TIM3, LAG-3, OX40 or TIGIT antibody.

8. Use of a pharmaceutical composition comprising the IL15 construct of any one of claims 1 to 3 for increasing the survival of an immune cell, wherein the pharmaceutical composition is to be administered to the immune cell prior to, during or after administration of an effective amount of immune cells.

9. The use of claim 8, wherein the immune cell expresses a chimeric antigen receptor (CAR).

10. The use of claim 8, wherein the immune cell is an NK cell.

11. The use of claim 8, wherein the immune cell is a T-cell.