Claims

1. A cyclic polypeptide which specifically binds to and inhibits sestrin-MAPK complexes (sMAC), independently of mTOR, rejuvenating senescent T cells which consists of a portion of the first 160 amino acids of sestrin not acting via mTOR regulation.

2. The cyclic polypeptide, according to claim 1, wherein the cyclic polypeptide, consists of an amino acid sequence derived from the first 160 amino acids forming sestrin 2.

3. The cyclic polypeptide, according to any preceding claim, wherein the cyclic polypeptide binds at the interface between domain A and C of sestrin 2.

4. The cyclic polypeptide, according to any preceding claim, wherein the cyclic polypeptide, consists of between 2 and 15 amino acid residues, more preferably between 3 and 9 amino acid residues, more preferably between 3 and 8 amino acid residues, and even more preferably between 4 and 7 amino acids.

5. The cyclic polypeptide, according to any preceding claim, wherein the cyclic polypeptide consists of most preferably 5 amino acid residues.

6. The cyclic polypeptide, according to any preceding claim, wherein the cyclic polypeptide consists of a pentameric amino acid sequence selected from the first 160 amino acids of sestrin 2 as set out in: SEQ ID Nos: 8 to 84.

7. The cyclic polypeptide, according to any preceding claim, wherein the cyclic polypeptide consists of a sMAC disruption motif (consensus) conserved in at least one other sestrin protein and made of at least 3 essential amino acids not necessarily in continuation within the same pentameric sequence.

8. The cyclic polypeptide, according to any preceding claim, wherein the cyclic polypeptide consists of a sMAC disruption motif comprising preferably 3 essential amino acids as per SEQ ID Nos 86, 88, 92, 93, 94, 99, 100, 101, 108, 109, 110, 113, 115, 131, 134, 137, 144, 145, 147, 152, 153, 158, 161, 189, 193, 198, 199, 200, 203, 237, 238;

more preferably 4 essential amino acids as per SEQ ID Nos 104, 105, 106, 111, 125, 140, 141, 163, 185, 192, 201, 204, 205, 240, 252;

and most preferably 5 essential amino acids as per SEQ ID Nos 58, 59, 60, 62, 63, 64, 65, 107, 191, 239, 247, 251.

9. The cyclic polypeptide, according to any preceding claim, wherein the cyclic polypeptide consists of a pentameric sequence identified by chemical similarities as an sMAC disruption motif comprising preferably 3 chemical analogue residues as per SEQ ID Nos: 89, 90, 97, 206, 209, 212, 217, 218, 221, 225, 233, 234, and even more preferably 4 chemical analogue residues as per SEQ ID Nos: 91, 211.

10. The cyclic polypeptide, according to any preceding claim, wherein the cyclic polypeptide consists of a functional sequence exerting 60% or greater sequence identity with any pentameric fragment thereof.

11. The cyclic polypeptide, according to any preceding claim, wherein the cyclic polypeptide consists of an amino acid sequence as set out in SEQ ID No: 22, or a functional 60% or greater sequence identity fragment thereof, most preferably for influenza vaccination or influenza prevention without a vaccine (DOS only regimen).

12. The cyclic polypeptide, according to any preceding claim, wherein the cyclic polypeptide consists of an amino acid sequence as set out in SEQ ID No: 77, most preferably for cancer treatment.

13. The cyclic polypeptide, according to any preceding claim, wherein the cyclic polypeptide consists solely of L-amino acids, or solely of D-amino acids, or both D- and L-amino acids.

14. The cyclic polypeptide, according to any preceding claim, wherein the cyclic polypeptide consists of a *recurrentem* sequence provided herein as SEQ ID No: 85, as follows:

$X_1X_2X_3X_4X_5$

[SEQ ID No: 85]

in which X_1 is A, P, H, L, R, M, D, F, V, I, E, N, Y, S, Q or T, preferably wherein X_1 is A, P, H, L, R, M or D;
X_2 is Y, A, L, R, M, F, K, V, E, I, D, S, Q, N or T, preferably wherein X_2 is Y, A, L or R;
X_3 is L ,A, S, R, M, D, E, K, F, T, Q, C, V, P or N, preferably wherein X_3 is L, A, S or R;

X_4 is L, A, E, S, K, D, V, I, F, Q, H, C, T, P, N, R or Y, preferably wherein X_4 is L, A or E; and/or X_5 is L, R, A, E, S, K, I, P, D, F, H, Y, C, T, N, Q, V or M, preferably wherein X_5 is L, R, A or E .

15 The cyclic polypeptide, according to any preceding claim, wherein the cyclic polypeptide targets sestrin in immune cells, preferably sestrin in B cells, more preferably Natural Killer (NK) cells, and most preferably T cells (T lymphocytes).

16. The cyclic polypeptide, according to any preceding claim, wherein the cyclic polypeptide targets sestrin preferably in CD4+ and/or CD8+ T cells, more preferably sestrin in CD4+ CD27+ CD28+ cells and/or CD4+ CD27- CD28+ cells, and most preferably sestrin in CD4+ CD27- CD28- T cells (senescent T cells).

17. The cyclic polypeptide, according to any preceding claim, wherein the cyclic polypeptide induces or restores cytokine production, preferably wherein the cyclic polypeptide induces or restores the production of IFN gamma, TNF alpha and/or IL-4.

18. The cyclic polypeptide, according to any preceding claim, wherein the cyclic polypeptide prevents or reverses immune-senescence.

19. The cyclic polypeptide, according to any preceding claim, wherein the cyclic polypeptide is configured to rejuvenate the immune system preferably without a vaccine (DOS only regimen), more preferably combined with a vaccine and most preferably with an influenza vaccine.

20. The cyclic polypeptide, according to any preceding claim, wherein rejuvenating the immune system consists of: (i) restoring immune cell responsiveness to antigen stimulation most preferably in CD4+ CD27- CD28- T cells (senescent T cells); (ii) restoring telomere transfer and/or telomerase activity, and telomere elongation in immune cells most preferably in CD4+ CD27- CD28- T cells (senescent T cells) ; (iii) restoring antigen-specific proliferation and/or cytokine production in immune cells most preferably in CD4+ CD27- CD28- T cells (senescent T cells); and/or (iv) restoring antigen-specific antibody production by B cells most preferably humoral IgG.

21. Use of a cyclic polypeptide according to any one of claims 1 to 20 in the manufacture of a medicament for use in prophylaxis therapy to prevent a future infection most preferably influenza.

22. Use of a cyclic polypeptide according to any one of claims 1 to 20 in the manufacture of a medicament for treating, preventing or ameliorating a microbial infection, an age-related condition, and a T-cell mediated disease.

23. The use according to claim 22, wherein the microbial infection is preferably fungal or protist, more preferably bacterial, and most preferably viral.

24. The use according to claim 22, wherein the age-related condition is a condition associated with, caused by, or related to, the aging and/or decline of antigen responsiveness of the immune system, wherein the age-related condition is characterised by sestrin-dependent sMAC activation leading to immune-senescence.

25. The use according to claim 22, wherein the age-related condition is selected from a group consisting of cancer, preferably neuroblastoma, melanoma, liver, pancreatic, testis or pancreatic cancer, more preferably breast cancer and most preferably paediatric neuroblastoma.

26. Use of a cyclic polypeptide according to any one of claims 1 to 20 in the manufacture of a medicament for stimulating an immune response, preferably as a vaccine booster.

27. A composition comprising the cyclic polypeptide, according to any preceding claim, and a vaccine.

28. A pharmaceutical composition comprising the cyclic polypeptide, according to any preceding claim, and a pharmaceutically acceptable vehicle.

29. A nucleic acid encoding the cyclic polypeptide, according to any one of claims 1 to 27, even if the desired polypeptide would be produced upon a silent change of its nucleic acid sequence.