

SUMMARY

The present inventors have surprisingly found peptides able to bind to a specific site on the N-terminal portion of IL-17A and thereby to inhibit the interaction with IL-17RA and the formation of the IL-17A/IL-17RA/IL-17RC complex.

The inhibition of said interaction blocks the IL-17A signaling pathway. The peptides according to the disclosure are therefore able to reduce TH17-related inflammation and the subsequent damage observed in inflammatory and autoimmune diseases where these cells and IL-17A exert a pivotal role.

In one aspect, the present disclosure refers to a peptide, able to inhibit IL-17A binding to IL-17RA, comprising the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 158, SEQ ID NO: 159, SEQ ID NO: 160, SEQ ID NO: 161, SEQ ID NO: 162, SEQ ID NO: 163, SEQ ID NO: 164, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 167, SEQ ID NO: 168, SEQ ID NO: 169, SEQ ID NO: 170, SEQ ID NO: 171, SEQ ID NO: 172, SEQ ID NO: 173, SEQ ID NO: 174, SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 178, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 181, SEQ ID NO: 182, SEQ ID NO: 183, SEQ ID NO: 184, SEQ ID NO: 185, SEQ ID NO: 186, SEQ ID NO: 187, SEQ ID NO: 188, SEQ ID NO: 189, SEQ ID NO: 190, SEQ ID NO: 191, SEQ ID NO: 192, SEQ ID NO: 193, SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 200, SEQ ID NO: 201, SEQ ID NO: 202, SEQ ID NO: 203, SEQ ID NO: 204, SEQ ID NO: 205, SEQ ID NO: 206, SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 210, SEQ ID NO: 211, SEQ ID NO: 212, SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 215, SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID NO: 218, SEQ ID NO: 219, SEQ ID NO: 220, SEQ ID NO: 221, SEQ ID NO: 222, SEQ ID NO: 223, SEQ ID NO: 224, SEQ ID NO: 225, SEQ ID NO: 226, SEQ ID NO: 227, SEQ ID NO: 228, SEQ ID NO: 229, SEQ ID NO: 230, SEQ ID NO: 231, SEQ ID NO: 232, SEQ ID NO: 233, SEQ ID NO: 234, SEQ ID NO: 235, SEQ ID NO: 236, SEQ ID NO: 237, SEQ ID NO: 238, SEQ ID NO: 239, SEQ ID NO: 240, SEQ ID NO: 241, SEQ ID NO: 242, SEQ ID NO: 243, SEQ ID NO: 244, SEQ ID NO: 245, SEQ ID NO: 246, SEQ ID NO: 247, SEQ ID NO: 248, SEQ ID NO: 249, SEQ ID NO: 250, SEQ ID NO: 251, SEQ ID NO: 252, SEQ ID NO: 253, SEQ ID NO: 254, SEQ ID NO: 255, SEQ ID NO: 256, or SEQ ID NO: 257.

In another aspect, the present disclosure refers to the peptide having an amino acid sequence comprising the sequence of the peptide as disclosed herein and at the C- and/or N- terminal of the peptide having the amino acid sequence of formula (III):

(III) Y_1 - Y_2 - Y_3 - Y_4 - Y_5 - Y_6 - Y_7 - Y_8 - Y_9 - Y_{10} - Y_{11} - Y_{12} - Y_{13} - Y_{14} - Y_{15} - Y_{16}

wherein:

Y_1 is A, T, V, K, R, I, L, X or G;

Y_2 is R, W, P, E, Q or A;

Y_3 is K, W, G, T, I, R or P;

Y_4 is K, T, E, W, A, R, D, G, X or F;

Y_5 is A, E, T, G, W, I, R, P or V;

Y_6 is A, W, E, R, G, P or absent;

Y_7 is K, S, W, T, F, R, V, G or absent;

Y_8 is A, Q, W, R, G or absent;

Y_9 is N, G or absent;

Y_{10} is R or absent;

Y_{11} is R or absent;

Y_{12} is M or absent;

Y_{13} is K or absent.

Y_{14} is W or absent;

Y_{15} is K or absent;

Y_{16} is K or absent.

In another aspect, the present disclosure refers to the peptide having an amino acid sequence comprising the sequence of the peptide as disclosed herein and at the C- and/or N- terminal of the peptide having an amino acid sequence $(A)_m$, wherein A is an amino acid selected from R, K, G, E, Q or A, preferably R, K, G, E or A, and m is an integer between 1 and 10.

In another aspect, the present disclosure refers to a dimer formed by two peptides, each having an amino acid sequence of one of the peptides as disclosed herein.

In another aspect, the present disclosure refers to a bioconjugate comprising the peptide as disclosed herein and a biomolecule, preferably said biomolecule being bound to the N- and/or C- terminal of said peptide.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising (A)(i) the peptide as disclosed herein, (ii) the dimer as disclosed herein, or (iii) the bioconjugate as disclosed herein, and (B) at least one pharmaceutically acceptable excipient.

In another aspect, the present disclosure refers to use of the peptide as disclosed herein, the dimer as disclosed herein or the bioconjugate as disclosed herein, in the manufacture of a medicament for treating a disease selected from rheumatoid arthritis, multiple sclerosis, Crohn's disease, systemic lupus erythematosus, asthma, Behçet's disease, hyper IgE syndrome, ankylosing spondylitis, psoriasis, psoriatic arthritis, keratoconjunctivitis sicca, vernal keratoconjunctivitis, stromal herpetic keratitis, corneal allograft rejection, corneal infections, herpes virus or Pseudomonas aeruginosa keratitis and dry eye disease, preferably psoriasis or dry eye disease.

As will be shown in the experimental section, the peptides of the disclosure have physical-chemical properties that make them particularly suitable for topical treatment of ophthalmic and dermatological diseases.

Said peptides are useful to design innovative and specific topical treatment of diseases dependent on an excessive production or activity of IL-17A.

Objects of the present disclosure are peptides able to inhibit IL-17A binding to IL-17RA, dimers and bioconjugates, pharmaceutical compositions comprising said peptides, dimers or bioconjugates and the use of the above in the prevention and/or treatment of autoimmune and inflammatory diseases depending on IL-17A.

Brief description of the figures

Figure 1 shows some dose-response curves obtained in the IL-17RA-IL17RC dimerization assay described in Example 5 of with representative IL-17A binding peptides according to the invention. The percentage of inhibition of IL-17RA/IL17RC dimerization induced by IL-17A obtained by treatment with different peptides is reported.

Figure 2 shows the activity of the IL-17A binding peptide of SEQ ID N.18 on secretion of IL6, IL-17A and IL23 by human differentiated and activated TH17 cells, measured as described in

Claims

1. A peptide, able to inhibit IL-17A binding to IL-17RA, comprising the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 158, SEQ ID NO: 159, SEQ ID NO: 160, SEQ ID NO: 161, SEQ ID NO: 162, SEQ ID NO: 163, SEQ ID NO: 164, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 167, SEQ ID NO: 168,, SEQ ID NO: 169, SEQ ID NO: 170, SEQ ID NO: 171, SEQ ID NO: 172, SEQ ID NO: 173, SEQ ID NO: 174, SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 178, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 181, SEQ ID NO: 182, SEQ ID NO: 183, SEQ ID NO: 184, SEQ ID NO: 185, SEQ ID NO: 186, SEQ ID NO: 187, SEQ ID NO: 188, SEQ ID NO: 189, SEQ ID NO: 190, SEQ ID NO: 191, SEQ ID NO: 192, SEQ ID NO: 193, SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 200, SEQ ID NO: 201, SEQ ID NO: 202, SEQ ID NO: 203, SEQ ID NO: 204, SEQ ID NO: 205, SEQ ID NO: 206, SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 210, SEQ ID NO: 211, SEQ ID NO: 212, SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 215, SEQ ID NO: 216, SEQ ID NO: 217,

SEQ ID NO: 218, SEQ ID NO: 219, SEQ ID NO: 220, SEQ ID NO: 221, SEQ ID NO: 222, SEQ ID NO: 223, SEQ ID NO: 224, SEQ ID NO: 225, SEQ ID NO: 226, SEQ ID NO: 227, SEQ ID NO: 228, SEQ ID NO: 229, SEQ ID NO: 230, SEQ ID NO: 231, SEQ ID NO: 232, SEQ ID NO: 233, SEQ ID NO: 234, SEQ ID NO: 235, SEQ ID NO: 236, SEQ ID NO: 237, SEQ ID NO: 238, SEQ ID NO: 239, SEQ ID NO: 240, SEQ ID NO: 241, SEQ ID NO: 242, SEQ ID NO: 243, SEQ ID NO: 244, SEQ ID NO: 245, SEQ ID NO: 246, SEQ ID NO: 247, SEQ ID NO: 248, SEQ ID NO: 249, SEQ ID NO: 250, SEQ ID NO: 251, SEQ ID NO: 252, SEQ ID NO: 253, SEQ ID NO: 254, SEQ ID NO: 255, SEQ ID NO: 256, or SEQ ID NO: 257.

2. The peptide of claim 1, comprising the amino acid sequence of SEQ ID NOs: 2-40, SEQ ID NOs: 111-115, or SEQ ID NO: 121.

3. The peptide of claim 1, comprising the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 7, SEQ ID NO: 11, SEQ ID NO: 14, SEQ ID NO: 38, SEQ ID NO: 111, SEQ ID NO: 113, SEQ ID NO: 115, and SEQ ID NO: 121.

4. The peptide having an amino acid sequence comprising the sequence of the peptide of any one of claims 1 to 3 and at the C- and/or N- terminal of the peptide having the amino acid sequence of formula (III):

(III) $Y_1-Y_2-Y_3-Y_4-Y_5-Y_6-Y_7-Y_8-Y_9-Y_{10}-Y_{11}-Y_{12}-Y_{13}-Y_{14}-Y_{15}-Y_{16}$

wherein:

Y_1 is A, T, V, K, R, I, L, X or G;

Y_2 is R, W, P, E, Q or A;

Y_3 is K, W, G, T, I, R or P;

Y_4 is K, T, E, W, A, R, D, G, X or F;

Y_5 is A, E, T, G, W, I, R, P or V;

Y_6 is A, W, E, R, G, P or absent;

Y_7 is K, S, W, T, F, R, V, G or absent;

Y₈ is A, Q, W, R, G or absent;

Y₉ is N, G or absent;

Y₁₀ is R or absent;

Y₁₁ is R or absent;

Y₁₂ is M or absent;

Y₁₃ is K or absent.

Y₁₄ is W or absent;

Y₁₅ is K or absent;

Y₁₆ is K or absent.

5. The peptide of claim 4, having sequence of SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33 SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40.

6. The peptide having an amino acid sequence comprising the sequence of the peptide of any one of claims 1 to 5 and at the C- and/or N- terminal of the peptide having an amino acid sequence (A)_m, wherein A is an amino acid selected from R, K, G, E, Q or A, preferably R, K, G, E or A, and m is an integer between 1 and 10.

7. The peptide of claim 6, having sequence of SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 29, or SEQ ID NO: 30.

8. The peptide of any one of claims 1 to 7, bound at the C- and/or N- terminal to a protective cap group, preferably the protective cap group bound to a C-terminal being selected from amides, aldehydes, esters, p-Nitroanilide, 7-Amino-4-methylcoumarin and the protective group cap bound to a N-terminal being selected from acetyl, formyl, pyroglutamyl, fatty acids, urea, carbamate sulfonamide, alkylamine.

9. The peptide of claim 1, comprising an amino acid sequence of SEQ ID NO: 2.

10. A dimer formed by two peptides, each having an amino acid sequence of one of the peptides of any one of claims 1 to 9.
11. The dimer of claim 10, wherein said peptides are linked by a polyethylene spacer.
12. A bioconjugate comprising the peptide of any one of claims 1 to 9 and a biomolecule, preferably said biomolecule being bound to the N- and/or C- terminal of said peptide.
13. The bioconjugate of claim 12, wherein said biomolecule is selected from capric acid, capronic acid, ascorbic acid, N-Acetyl-Glucosamine (NAG)-N-Acetylmuramic acid (NAM), NAG, NAM, hyaluronic acid, alginic acid, chitin, (GalNAc)₂, Gal-alpha1,3-GalNAc and trigalacturonic acid.
14. A pharmaceutical composition comprising (A)(i) the peptide of any one of claims 1 to 9, (ii) the dimer of claim 10 or 11, or (iii) the bioconjugate of claim 12 or 13, and (B) at least one pharmaceutically acceptable excipient.
15. Use of the peptide of any one of claims 1 to 9, the dimer of any one of claims 10 or 11 or the bioconjugate of any one of claims 12 or 13, in the manufacture of a medicament for treating a disease selected from rheumatoid arthritis, multiple sclerosis, Crohn's disease, systemic lupus erythematosus, asthma, Behçet's disease, hyper IgE syndrome, ankylosing spondylitis, psoriasis, psoriatic arthritis, keratoconjunctivitis sicca, vernal keratoconjunctivitis, stromal herpetic keratitis, corneal allograft rejection, corneal infections, herpes virus or Pseudomonas aeruginosa keratitis and dry eye disease, preferably psoriasis or dry eye disease.