

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

18 June 2020 (18.06.2020)



(10) International Publication Number

WO 2020/120978 A1

(51) International Patent Classification:

A61P 35/00 (2006.01)

C07K 7/08 (2006.01)

A61K 38/00 (2006.01)

C07K 14/54 (2006.01)

(21) International Application Number:

PCT/GB2019/053534

(22) International Filing Date:

13 December 2019 (13.12.2019)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

1820316.6

13 December 2018 (13.12.2018) GB

(71) Applicant: **BICYCLERD LIMITED** [GB/GB]; Building 900, Babraham Research Campus, Cambridge CB22 3AT (GB).

(72) Inventors: **CHEN, Liuhong**; c/o BicycleTX Limited, Building 900, Babraham Research Campus, Cambridge CB22 3AT (GB). **LANI, Rachid**; c/o BicycleTX Limited, Building 900, Babraham Research Campus, Cambridge CB22 3AT (GB). **MUDD, Gemma**; c/o BicycleTX Limited, Building 900, Babraham Research Campus, Cambridge CB22 3AT (GB). **TEUFEL, Daniel**; c/o BicycleTX Limited, Building 900, Babraham Research Campus, Cambridge CB22 3AT (GB). **WALKER, Edward**; c/o BicycleTX Limited, Building 900, Babraham Research Campus, Cambridge CB22 3AT (GB).

(74) Agent: **GIBSON, Mark** et al.; Sagittarius IP, Marlow International, Parkway, Marlow Buckinghamshire SL7 1YL (GB).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,

TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

— with sequence listing part of description (Rule 5.2(a))

(54) Title: BICYCLIC PEPTIDE LIGANDS SPECIFIC FOR IL-17

(57) Abstract: The present invention relates to polypeptides which are covalently bound to molecular scaffolds such that two or more peptide loops are subtended between attachment points to the scaffold. In particular, the invention describes peptides which are high affinity binders of IL-17. The invention also includes drug conjugates comprising said peptides, conjugated to one or more effector and/or functional groups, to pharmaceutical compositions comprising said peptide ligands and drug conjugates and to the use of said peptide ligands and drug conjugates in preventing, suppressing or treating a disease or disorder mediated by IL-17.

WO 2020/120978 A1

BICYCLIC PEPTIDE LIGANDS SPECIFIC FOR IL-17

FIELD OF THE INVENTION

The present invention relates to polypeptides which are covalently bound to molecular scaffolds such that two or more peptide loops are subtended between attachment points to the scaffold. In particular, the invention describes peptides which are high affinity binders of IL-17. The invention also includes drug conjugates comprising said peptides, conjugated to one or more effector and/or functional groups, to pharmaceutical compositions comprising said peptide ligands and drug conjugates and to the use of said peptide ligands and drug conjugates in preventing, suppressing or treating a disease or disorder mediated by IL-17.

BACKGROUND OF THE INVENTION

Cyclic peptides are able to bind with high affinity and target specificity to protein targets and hence are an attractive molecule class for the development of therapeutics. In fact, several cyclic peptides are already successfully used in the clinic, as for example the antibacterial peptide vancomycin, the immunosuppressant drug cyclosporine or the anti-cancer drug octreotide (Driggers et al. (2008), Nat Rev Drug Discov 7 (7), 608-24). Good binding properties result from a relatively large interaction surface formed between the peptide and the target as well as the reduced conformational flexibility of the cyclic structures. Typically, macrocycles bind to surfaces of several hundred square angstrom, as for example the cyclic peptide CXCR4 antagonist CVX15 (400 Å²; Wu et al. (2007), Science 330, 1066-71), a cyclic peptide with the Arg-Gly-Asp motif binding to integrin αVβ3 (355 Å²) (Xiong et al. (2002), Science 296 (5565), 151-5) or the cyclic peptide inhibitor upain-1 binding to urokinase-type plasminogen activator (603 Å²; Zhao et al. (2007), J Struct Biol 160 (1), 1-10).

Due to their cyclic configuration, peptide macrocycles are less flexible than linear peptides, leading to a smaller loss of entropy upon binding to targets and resulting in a higher binding affinity. The reduced flexibility also leads to locking target-specific conformations, increasing binding specificity compared to linear peptides. This effect has been exemplified by a potent and selective inhibitor of matrix metalloproteinase 8 (MMP-8) which lost its selectivity over other MMPs when its ring was opened (Cherney et al. (1998), J Med Chem 41 (11), 1749-51). The favorable binding properties achieved through macrocyclization are even more pronounced in multicyclic peptides having more than one peptide ring as for example in vancomycin, nisin and actinomycin.

Different research teams have previously tethered polypeptides with cysteine residues to a synthetic molecular structure (Kemp and McNamara (1985), J. Org. Chem; Timmerman et

al. (2005), ChemBioChem). Meloen and co-workers had used tris(bromomethyl)benzene and related molecules for rapid and quantitative cyclisation of multiple peptide loops onto synthetic scaffolds for structural mimicry of protein surfaces (Timmerman et al. (2005), ChemBioChem). Methods for the generation of candidate drug compounds wherein said
5 compounds are generated by linking cysteine containing polypeptides to a molecular scaffold as for example tris(bromomethyl)benzene are disclosed in WO 2004/077062 and WO 2006/078161.

Phage display-based combinatorial approaches have been developed to generate and
10 screen large libraries of bicyclic peptides to targets of interest (Heinis et al. (2009), Nat Chem Biol 5 (7), 502-7 and WO 2009/098450). Briefly, combinatorial libraries of linear peptides containing three cysteine residues and two regions of six random amino acids (Cys-(Xaa)₆-Cys-(Xaa)₆-Cys) were displayed on phage and cyclised by covalently linking the cysteine side chains to a small molecule scaffold.

SUMMARY OF THE INVENTION

According to a first aspect of the invention, there is provided a peptide ligand specific for IL-17 comprising a polypeptide comprising at least three cysteine residues, separated by at least two loop sequences, and a molecular scaffold which forms covalent bonds with the
20 cysteine residues of the polypeptide such that at least two polypeptide loops are formed on the molecular scaffold.

According to a further aspect of the invention, there is provided a drug conjugate comprising a peptide ligand as defined herein conjugated to one or more effector and/or functional groups.

According to a further aspect of the invention, there is provided a pharmaceutical composition comprising a peptide ligand or a drug conjugate as defined herein in combination with one or more pharmaceutically acceptable excipients.

According to a further aspect of the invention, there is provided a peptide ligand or drug conjugate as defined herein for use in preventing, suppressing or treating a disease or disorder mediated by IL-17.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, said loop sequences comprise 2 to 7 amino acids. In a further embodiment, said loop sequences comprise 2, 5, 6 or 7 amino acids.

In a further embodiment, said loop sequences comprise three cysteine residues separated by two loop sequences both of which consist of 5 amino acids.

5 In a further embodiment, said loop sequences comprise three cysteine residues separated by two loop sequences both of which consist of 6 amino acids.

In a further embodiment, said loop sequences comprise three cysteine residues separated by two loop sequences one of which consists of 2 amino acids and the other of which consists of 7 amino acids.

10

In one embodiment, the peptide ligand is specific for IL-17A, IL-17E or IL-17F.

In one embodiment, the peptide ligand is specific for IL-17A.

15 In one embodiment, the peptide ligand is specific for IL-17A and said loop sequences comprise three cysteine residues separated by two loop sequences both of which consist of 6 amino acids and comprises an amino acid sequence selected from:

C_iPQDLELC_{ii}TFLFGDC_{iii} (SEQ ID NO: 1);
C_iDQDELMC_{ii}FLTGHQC_{iii} (SEQ ID NO: 2);
20 C_iPENELYC_{ii}FLSSQQC_{iii} (SEQ ID NO: 3);
C_iDPDSLEC_{ii}WIFNQTC_{iii} (SEQ ID NO: 4);
C_iPDDELYC_{ii}FLTGFKC_{iii} (SEQ ID NO: 5);
C_iDDDELYC_{ii}FLTNNQC_{iii} (SEQ ID NO: 6);
C_iAEDELYC_{ii}FLTNHTC_{iii} (SEQ ID NO: 7);
25 C_iPDDELYC_{ii}FLTGQHC_{iii} (SEQ ID NO: 8);
C_iPDDELYC_{ii}FLTGVPC_{iii} (SEQ ID NO: 9);
C_iPDDELYC_{ii}FLTGQTC_{iii} (SEQ ID NO: 10);
C_iDTDPELC_{ii}RFLNLDC_{iii} (SEQ ID NO: 11);
C_iDTDVELC_{ii}KFLGLDC_{iii} (SEQ ID NO: 12);
30 C_iDTDPELC_{ii}SFLGIAC_{iii} (SEQ ID NO: 13);
C_iEGDPELC_{ii}RFLGLEC_{iii} (SEQ ID NO: 14);
C_iGTDPELC_{ii}AFLGVDC_{iii} (SEQ ID NO: 15);
C_iETDLDC_{ii}AFLNIPC_{iii} (SEQ ID NO: 16);
C_iATDPELC_{ii}RFLNLDC_{iii} (SEQ ID NO: 17);
35 C_iQTDPELC_{ii}RFLNLDC_{iii} (SEQ ID NO: 18);
C_iDHDPELC_{ii}RFLNLDC_{iii} (SEQ ID NO: 19);
C_iDADPELC_{ii}RFLNLDC_{iii} (SEQ ID NO: 20);

C_iDGDPELC_{ii}RFLNLDC_{iii} (SEQ ID NO: 21);

C_iDTDPELC_{ii}MFLNLDC_{iii} (SEQ ID NO: 22);

C_iDTDPELC_{ii}RFLGLDC_{iii} (SEQ ID NO: 23);

C_iDTDPELC_{ii}RFLRLDC_{iii} (SEQ ID NO: 24);

5 C_iDTDPELC_{ii}RFLNVDC_{iii} (SEQ ID NO: 25);

C_iDTDPELC_{ii}RFLNLKC_{iii} (SEQ ID NO: 26);

C_iDTDPELC_{ii}RFLNLPC_{iii} (SEQ ID NO: 27);

C_iDTDPELC_{ii}RFLNLTC_{iii} (SEQ ID NO: 28);

C_iNNNSELC_{ii}QFFGIEC_{iii} (SEQ ID NO: 29);

10 C_iAGDVEWC_{ii}AFWNLAC_{iii} (SEQ ID NO: 30);

C_iGDDELLC_{ii}WLGISTC_{iii} (SEQ ID NO: 31); and

wherein C_i, C_{ii} and C_{iii} represent first, second and third cysteine residues, respectively or a pharmaceutically acceptable salt thereof.

15 In a further embodiment, the peptide ligand is specific for IL-17A and said loop sequences comprise three cysteine residues separated by two loop sequences both of which consist of 6 amino acids and comprises an amino acid sequence selected from:

A-(SEQ ID NO: 1)-A (herein referred to as BCY2272);

A-(SEQ ID NO: 1)-A-[Sar₆]-K-[FI] (herein referred to as BCY2310);

20 [Mca]-G-[Sar₅]-A-(SEQ ID NO: 1)-A (herein referred to as BCY2309);

[FI]-G-[Sar₅]-A-(SEQ ID NO: 1)-A (herein referred to as BCY2311);

A-(SEQ ID NO: 2)-A (herein referred to as BCY2265);

(SEQ ID NO: 3) (herein referred to as BCY2232);

A-(SEQ ID NO: 3)-A (herein referred to as BCY2231);

25 A-(SEQ ID NO: 3)-A-[Sar₆]-K-[FI] (herein referred to as BCY2310);

A-(SEQ ID NO: 4)-A (herein referred to as BCY2230);

A-(SEQ ID NO: 5)-A (herein referred to as BCY2266);

A-(SEQ ID NO: 6)-A (herein referred to as BCY2267);

A-(SEQ ID NO: 7)-A (herein referred to as BCY2268);

30 A-(SEQ ID NO: 8)-A (herein referred to as BCY2269);

A-(SEQ ID NO: 9)-A (herein referred to as BCY2270);

A-(SEQ ID NO: 10)-A (herein referred to as BCY2271);

A-(SEQ ID NO: 11)-A (herein referred to as BCY2273);

A-(SEQ ID NO: 12)-A (herein referred to as BCY2274);

35 A-(SEQ ID NO: 13)-A (herein referred to as BCY2275);

A-(SEQ ID NO: 14)-A (herein referred to as BCY2276);

A-(SEQ ID NO: 14)-A-[Sar₆]-K-[FI] (herein referred to as BCY2315);

A-(SEQ ID NO: 15)-A (herein referred to as BCY2277);
 A-(SEQ ID NO: 16)-A (herein referred to as BCY2278);
 A-(SEQ ID NO: 17)-A (herein referred to as BCY2279);
 A-(SEQ ID NO: 18)-A (herein referred to as BCY2280);
 5 A-(SEQ ID NO: 19)-A (herein referred to as BCY2282);
 A-(SEQ ID NO: 20)-A (herein referred to as BCY2283);
 A-(SEQ ID NO: 21)-A (herein referred to as BCY2284);
 A-(SEQ ID NO: 22)-A (herein referred to as BCY2285);
 A-(SEQ ID NO: 23)-A (herein referred to as BCY2286);
 10 A-(SEQ ID NO: 24)-A (herein referred to as BCY2287);
 A-(SEQ ID NO: 25)-A (herein referred to as BCY2288);
 A-(SEQ ID NO: 26)-A (herein referred to as BCY2289);
 A-(SEQ ID NO: 27)-A (herein referred to as BCY2290);
 A-(SEQ ID NO: 28)-A (herein referred to as BCY2291);
 15 A-(SEQ ID NO: 29)-A-[Sar₆]-K-[FI] (herein referred to as BCY2318);
 A-(SEQ ID NO: 30)-A-[Sar₆]-K-[FI] (herein referred to as BCY2319); and
 A-(SEQ ID NO: 31)-A-[Sar₆]-K-[FI] (herein referred to as BCY2320);

wherein FI represents fluorescein, Sar represents sarcosine and Mca represents methoxycoumarin-4-acetic acid.

20 In one particular embodiment, the peptide ligand is selected from A-(SEQ ID NO: 1)-A (BCY2272). This peptide ligand demonstrated good IL-17A binding activity and selectivity for IL-17A over other IL-17 sub-types such as IL-17F (see data in Table 1).

25 In a further particular embodiment, the peptide ligand is selected from:

A-(SEQ ID NO: 1)-A-[Sar₆]-K-[FI] (herein referred to as BCY2310); and
 [FI]-G-[Sar₅]-A-(SEQ ID NO: 1)-A (herein referred to as BCY2311).

These peptide ligands demonstrated good IL-17A binding activity and selectivity for IL-17A over other IL-17 sub-types such as IL-17F (see data in Table 2).

30 In an alternative embodiment, the peptide ligand is specific for IL-17A and said loop sequences comprise three cysteine residues separated by two loop sequences both of which consist of 5 amino acids and comprises an amino acid sequence selected from:

C_iYEDEL C_{ii}EFLGL C_{iii} (SEQ ID NO: 32);
 35 C_iAEDEL C_{ii}EFLGL C_{iii} (SEQ ID NO: 33);
 C_iYSDEL C_{ii}EFLGL C_{iii} (SEQ ID NO: 34);
 C_iYEAEL C_{ii}EFLGL C_{iii} (SEQ ID NO: 35);

C_iYEAELC_{ii}AFLGLC_{iii} (SEQ ID NO: 36);
 C_iYEDALC_{ii}EFLGLC_{iii} (SEQ ID NO: 37);
 C_iYEDELCL_{ii}AFLGLC_{iii} (SEQ ID NO: 38);
 C_iYEDELCL_{ii}E[2Nal]LGLC_{iii} (SEQ ID NO: 39);
 5 C_iYEDELCL_{ii}EWLGLC_{iii} (SEQ ID NO: 40);
 C_iYEDELCL_{ii}EFLALC_{iii} (SEQ ID NO: 41);
 C_iYEDELCL_{ii}EFLNLC_{iii} (SEQ ID NO: 42);
 C_iYEDELCL_{ii}EWLNLC_{iii} (SEQ ID NO: 43);
 C_iSDLELC_{ii}EFLGLC_{iii} (SEQ ID NO: 44);
 10 C_iDDYQLC_{ii}EFLGLC_{iii} (SEQ ID NO: 45);
 C_iEDKELC_{ii}EFFGLC_{iii} (SEQ ID NO: 46);
 C_iPDLELC_{ii}EFLGLC_{iii} (SEQ ID NO: 47);
 C_iDDELYC_{ii}FLNASC_{iii} (SEQ ID NO: 48);
 C_iPNELYC_{ii}FVTGNC_{iii} (SEQ ID NO: 49);
 15 C_iANELYC_{ii}FVTGNC_{iii} (SEQ ID NO: 50);
 C_iPNELAC_{ii}FVTGNC_{iii} (SEQ ID NO: 51);
 C_iPNELYC_{ii}FVAGNC_{iii} (SEQ ID NO: 52);
 C_iPNELYC_{ii}FVTGAC_{iii} (SEQ ID NO: 53);
 C_iDDSLYC_{ii}FLTGDC_{iii} (SEQ ID NO: 54); and
 20 C_iDDDLFC_{ii}FLTNSC_{iii} (SEQ ID NO: 55);

wherein 2Nal represents 2-naphthylalanine, C_i, C_{ii} and C_{iii} represent first, second and third cysteine residues, respectively or a pharmaceutically acceptable salt thereof.

In a further embodiment, the peptide ligand is specific for IL-17A and said loop sequences
 25 comprise three cysteine residues separated by two loop sequences both of which consist of
 5 amino acids and comprises an amino acid sequence selected from:

A-(SEQ ID NO: 32)-A (herein referred to as BCY2235);
 Ac-(SEQ ID NO: 32) (herein referred to as BCY2236);
 Ac-(SEQ ID NO: 33) (herein referred to as BCY2237);
 30 Ac-(SEQ ID NO: 34) (herein referred to as BCY2238);
 Ac-(SEQ ID NO: 35) (herein referred to as BCY2239);
 Ac-(SEQ ID NO: 36) (herein referred to as BCY2240);
 Ac-(SEQ ID NO: 37) (herein referred to as BCY2241);
 Ac-(SEQ ID NO: 38) (herein referred to as BCY2243);
 35 Ac-(SEQ ID NO: 39) (herein referred to as BCY2244);
 Ac-(SEQ ID NO: 40) (herein referred to as BCY2246);
 Ac-(SEQ ID NO: 41) (herein referred to as BCY2248);

(SEQ ID NO: 41) (herein referred to as BCY2249);
Ac-(SEQ ID NO: 42) (herein referred to as BCY2250);
Ac-(SEQ ID NO: 43) (herein referred to as BCY2252);
A-(SEQ ID NO: 44)-A (herein referred to as BCY2258);
5 A-(SEQ ID NO: 45)-A (herein referred to as BCY2259);
A-(SEQ ID NO: 46)-A (herein referred to as BCY2260);
A-(SEQ ID NO: 47)-A (herein referred to as BCY2262);
A-(SEQ ID NO: 48)-A (herein referred to as BCY2292);
A-(SEQ ID NO: 49)-A (herein referred to as BCY2293);
10 A-(SEQ ID NO: 49)-A-[Sar₆]-K-[FI] (herein referred to as BCY2316);
Ac-(SEQ ID NO: 49) (herein referred to as BCY2294);
Ac-(SEQ ID NO: 50) (herein referred to as BCY2295);
Ac-(SEQ ID NO: 51) (herein referred to as BCY2299);
Ac-(SEQ ID NO: 52) (herein referred to as BCY2302);
15 Ac-(SEQ ID NO: 53) (herein referred to as BCY2304);
A-(SEQ ID NO: 54)-A (herein referred to as BCY2305);
A-(SEQ ID NO: 54)-A-[Sar₆]-K-[FI] (herein referred to as BCY2317); and
A-(SEQ ID NO: 55)-A (herein referred to as BCY2306);

wherein FI represents fluorescein and Sar represents sarcosine.

20 In an alternative embodiment, the peptide ligand is specific for IL-17E.

In one embodiment, the peptide ligand is specific for IL-17E and said loop sequences comprise three cysteine residues separated by two loop sequences both of which consist of
25 5 amino acids and comprises an amino acid sequence selected from:

C_iGYDY_YC_{ii}ALYD_IC_{iii} (SEQ ID NO: 56); and

C_iLWKD_NC_{ii}THWS_LC_{iii} (SEQ ID NO: 57);

wherein C_i, C_{ii} and C_{iii} represent first, second and third cysteine residues, respectively or a pharmaceutically acceptable salt thereof.

30 In a further embodiment, the peptide ligand is specific for IL-17E and said loop sequences comprise three cysteine residues separated by two loop sequences both of which consist of 5 amino acids and comprises an amino acid sequence selected from:

A-(SEQ ID NO: 56)-A (herein referred to as BCY2240); and

35 A-(SEQ ID NO: 57)-A (herein referred to as BCY2441).

In a yet further embodiment, the peptide ligand is specific for IL-17E and comprises an amino acid sequence selected from A-(SEQ ID NO: 56)-A (BCY2240). The peptide ligand of this embodiment demonstrated superior binding to IL-17E (as shown in Table 1).

5 In an alternative embodiment, the peptide ligand is specific for IL-17F.

In one embodiment, the peptide ligand is specific for IL-17F and said loop sequences comprise three cysteine residues separated by two loop sequences both of which consist of 6 amino acids and comprises an amino acid sequence which is:

10 C_iDHSDFC_{ii}WLNNFNC_{iii} (SEQ ID NO: 58);

wherein C_i, C_{ii} and C_{iii} represent first, second and third cysteine residues, respectively or a pharmaceutically acceptable salt thereof.

In a further embodiment, the peptide ligand is specific for IL-17F and said loop sequences
15 comprise three cysteine residues separated by two loop sequences both of which consist of 6 amino acids and comprises an amino acid sequence which is selected from:

A-(SEQ ID NO: 58)-A (herein referred to as BCY2203); and

A-(SEQ ID NO: 58)-A-[Sar₆]-K-[FI] (herein referred to as BCY2222);

wherein FI represents fluorescein and Sar represents sarcosine.

20

In one embodiment, the peptide ligand is specific for IL-17F and said loop sequences comprise three cysteine residues separated by two loop sequences one of which consists of 2 amino acids and the other of which consists of 7 amino acids and comprises an amino acid sequence which is:

25 C_iGQC_{ii}SFSYWLNC_{iii} (SEQ ID NO: 59);

wherein C_i, C_{ii} and C_{iii} represent first, second and third cysteine residues, respectively or a pharmaceutically acceptable salt thereof.

In a further embodiment, the peptide ligand is specific for IL-17F and said loop sequences
30 comprise three cysteine residues separated by two loop sequences one of which consists of 2 amino acids and the other of which consists of 7 amino acids and comprises an amino acid sequence which is selected from:

A-(SEQ ID NO: 59)-A (herein referred to as BCY2202); and

A-(SEQ ID NO: 59)-A-[Sar₆]-K-[FI] (herein referred to as BCY2217);

35 wherein FI represents fluorescein and Sar represents sarcosine.

In a yet further embodiment, the peptide ligand is specific for IL-17F and comprises an amino acid sequence selected from A-(SEQ ID NO: 59)-A (BCY2202). This peptide ligand demonstrated good IL-17F binding activity and selectivity for IL-17F over other IL-17 sub-types such as IL-17A (see data in Table 1).

5

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art, such as in the arts of peptide chemistry, cell culture and phage display, nucleic acid chemistry and biochemistry. Standard techniques are used for molecular biology, genetic and biochemical methods (see
10 Sambrook et al., Molecular Cloning: A Laboratory Manual, 3rd ed., 2001, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Ausubel et al., Short Protocols in Molecular Biology (1999) 4th ed., John Wiley & Sons, Inc.), which are incorporated herein by reference.

Nomenclature

15 Numbering

When referring to amino acid residue positions within the peptides of the invention, cysteine residues (C_i , C_{ii} and C_{iii}) are omitted from the numbering as they are invariant, therefore, the numbering of amino acid residues within the peptides of the invention is referred to as below:

20 $-C_i-P_1-Q_2-D_3-L_4-E_5-L_6-C_{ii}-T_7-F_8-L_9-F_{10}-G_{11}-D_{12}-C_{iii}-$ (SEQ ID NO: 1).

For the purpose of this description, all bicyclic peptides are assumed to be cyclised with TBMB (1,3,5-tris(bromomethyl)benzene) yielding a tri-substituted 1,3,5-trimethylbenzene structure. Cyclisation with TBMB occurs on C_i , C_{ii} , and C_{iii} .

25

Molecular Format

N- or C-terminal extensions to the bicycle core sequence are added to the left or right side of the sequence, separated by a hyphen. For example, an N-terminal β Ala-Sar10-Ala tail would be denoted as:

30 β Ala-Sar10-A-(SEQ ID NO: X).

Inversed Peptide Sequences

In light of the disclosure in Nair et al (2003) J Immunol 170(3), 1362-1373, it is envisaged that the peptide sequences disclosed herein would also find utility in their retro-inverso form.

35 For example, the sequence is reversed (i.e. N-terminus becomes C-terminus and vice versa) and their stereochemistry is likewise also reversed (i.e. D-amino acids become L-amino acids and vice versa).

Peptide Ligands

A peptide ligand, as referred to herein, refers to a peptide covalently bound to a molecular scaffold. Typically, such peptides comprise two or more reactive groups (i.e. cysteine residues) which are capable of forming covalent bonds to the scaffold, and a sequence subtended between said reactive groups which is referred to as the loop sequence, since it forms a loop when the peptide is bound to the scaffold. In the present case, the peptides comprise at least three cysteine residues (referred to herein as C_i, C_{ii} and C_{iii}), and form at least two loops on the scaffold.

Advantages of the Peptide Ligands

Certain bicyclic peptides of the present invention have a number of advantageous properties which enable them to be considered as suitable drug-like molecules for injection, inhalation, nasal, ocular, oral or topical administration. Such advantageous properties include:

- Species cross-reactivity. This is a typical requirement for preclinical pharmacodynamics and pharmacokinetic evaluation;
- Protease stability. Bicyclic peptide ligands should ideally demonstrate stability to plasma proteases, epithelial ("membrane-anchored") proteases, gastric and intestinal proteases, lung surface proteases, intracellular proteases and the like. Protease stability should be maintained between different species such that a bicycle lead candidate can be developed in animal models as well as administered with confidence to humans;
- Desirable solubility profile. This is a function of the proportion of charged and hydrophilic versus hydrophobic residues and intra/inter-molecular H-bonding, which is important for formulation and absorption purposes;
- An optimal plasma half-life in the circulation. Depending upon the clinical indication and treatment regimen, it may be required to develop a bicyclic peptide for short exposure in an acute illness management setting, or develop a bicyclic peptide with enhanced retention in the circulation, and is therefore optimal for the management of more chronic disease states. Other factors driving the desirable plasma half-life are requirements of sustained exposure for maximal therapeutic efficiency versus the accompanying toxicology due to sustained exposure of the agent; and

- Selectivity. Certain peptide ligands of the invention demonstrate good selectivity over other IL-17 sub-types.

Pharmaceutically Acceptable Salts

- 5 It will be appreciated that salt forms are within the scope of this invention, and references to peptide ligands include the salt forms of said ligands.

The salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods such as methods
10 described in *Pharmaceutical Salts: Properties, Selection, and Use*, P. Heinrich Stahl (Editor), Camille G. Wermuth (Editor), ISBN: 3-90639-026-8, Hardcover, 388 pages, August 2002. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with the appropriate base or acid in water or in an organic solvent, or in a mixture of the two.

15 Acid addition salts (mono- or di-salts) may be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include mono- or di-salts formed with an acid selected from the group consisting of acetic, 2,2-dichloroacetic, adipic, alginic, ascorbic (e.g. L-ascorbic), L-aspartic, benzenesulfonic, benzoic, 4-acetamidobenzoic,
20 butanoic, (+) camphoric, camphor-sulfonic, (+)-(1S)-camphor-10-sulfonic, capric, caproic, caprylic, cinnamic, citric, cyclamic, dodecylsulfuric, ethane-1,2-disulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, formic, fumaric, galactaric, gentisic, glucoheptonic, D-gluconic, glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), α -oxoglutaric, glycolic, hippuric, hydrohalic acids (e.g. hydrobromic, hydrochloric, hydriodic), isethionic, lactic (e.g. (+)-L-lactic, ($\pm$)-DL-lactic), lactobionic, maleic, malic, (-)-L-malic, malonic, ($\pm$)-DL-mandelic,
25 methanesulfonic, naphthalene-2-sulfonic, naphthalene-1,5-disulfonic, 1-hydroxy-2-naphthoic, nicotinic, nitric, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, pyruvic, L-pyroglutamic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulfuric, tannic, (+)-L-tartaric, thiocyanic, p-toluenesulfonic, undecylenic and valeric acids, as well as acylated
30 amino acids and cation exchange resins.

One particular group of salts consists of salts formed from acetic, hydrochloric, hydriodic, phosphoric, nitric, sulfuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric, benzenesulfonic, toluenesulfonic, sulfuric, methanesulfonic (mesylate), ethanesulfonic,
35 naphthalenesulfonic, valeric, propanoic, butanoic, malonic, glucuronic and lactobionic acids. One particular salt is the hydrochloride salt. Another particular salt is the acetate salt.

If the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be -COO^-), then a salt may be formed with an organic or inorganic base, generating a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Li^+ , Na^+ and K^+ , alkaline earth metal cations such as Ca^{2+} and Mg^{2+} , and other cations such as Al^{3+} or Zn^{2+} . Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+ , NH_2R_2^+ , NHR_3^+ , NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: methylamine, ethylamine, diethylamine, propylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $\text{N}(\text{CH}_3)_4^+$.

Where the peptides of the invention contain an amine function, these may form quaternary ammonium salts, for example by reaction with an alkylating agent according to methods well known to the skilled person. Such quaternary ammonium compounds are within the scope of the peptides of the invention.

Modified Derivatives

It will be appreciated that modified derivatives of the peptide ligands as defined herein are within the scope of the present invention. Examples of such suitable modified derivatives include one or more modifications selected from: N-terminal and/or C-terminal modifications; replacement of one or more amino acid residues with one or more non-natural amino acid residues (such as replacement of one or more polar amino acid residues with one or more isosteric or isoelectronic amino acids; replacement of one or more non-polar amino acid residues with other non-natural isosteric or isoelectronic amino acids); addition of a spacer group; replacement of one or more oxidation sensitive amino acid residues with one or more oxidation resistant amino acid residues; replacement of one or more amino acid residues with an alanine, replacement of one or more L-amino acid residues with one or more D-amino acid residues; N-alkylation of one or more amide bonds within the bicyclic peptide ligand; replacement of one or more peptide bonds with a surrogate bond; peptide backbone length modification; substitution of the hydrogen on the alpha-carbon of one or more amino acid residues with another chemical group, modification of amino acids such as cysteine, lysine, glutamate/aspartate and tyrosine with suitable amine, thiol, carboxylic acid and phenol-reactive reagents so as to functionalise said amino acids, and introduction or replacement of amino acids that introduce orthogonal reactivities that are suitable for functionalisation, for example azide or alkyn-group bearing amino acids that allow functionalisation with alkyn or azide-bearing moieties, respectively.

In one embodiment, the modified derivative comprises an N-terminal and/or C-terminal modification. In a further embodiment, wherein the modified derivative comprises an N-terminal modification using suitable amino-reactive chemistry, and/or C-terminal modification using suitable carboxy-reactive chemistry. In a further embodiment, said N-terminal or C-terminal modification comprises addition of an effector group, including but not limited to a cytotoxic agent, a radiochelator or a chromophore.

In a further embodiment, the modified derivative comprises an N-terminal modification. In a further embodiment, the N-terminal modification comprises an N-terminal acetyl group. In this embodiment, the N-terminal cysteine group (the group referred to herein as C_i) is capped with acetic anhydride or other appropriate reagents during peptide synthesis leading to a molecule which is N-terminally acetylated. This embodiment provides the advantage of removing a potential recognition point for aminopeptidases and avoids the potential for degradation of the bicyclic peptide.

In an alternative embodiment, the N-terminal modification comprises the addition of a molecular spacer group which facilitates the conjugation of effector groups and retention of potency of the bicyclic peptide to its target. In one embodiment, the N-terminal modification comprises addition of a G-Sar₆- group, such as an fl-G-Sar₆- group (as added to the peptide ligand of SEQ ID NO: 1).

In a further embodiment, the modified derivative comprises a C-terminal modification. In a further embodiment, the C-terminal modification comprises an amide group. In this embodiment, the C-terminal cysteine group (the group referred to herein as C_{iii}) is synthesized as an amide during peptide synthesis leading to a molecule which is C-terminally amidated. This embodiment provides the advantage of removing a potential recognition point for carboxypeptidase and reduces the potential for proteolytic degradation of the bicyclic peptide. In one embodiment, the C-terminal modification comprises addition of a -Sar₆-K group, such as a -Sar₆-K-fl group (as added to the peptide ligand of SEQ ID NOs: 2 to 17).

In one embodiment, the modified derivative comprises replacement of one or more amino acid residues with one or more non-natural amino acid residues. In this embodiment, non-natural amino acids may be selected having isosteric/isoelectronic side chains which are neither recognised by degradative proteases nor have any adverse effect upon target potency.

Alternatively, non-natural amino acids may be used having constrained amino acid side

chains, such that proteolytic hydrolysis of the nearby peptide bond is conformationally and sterically impeded. In particular, these concern proline analogues, bulky sidechains, C α -disubstituted derivatives (for example, aminoisobutyric acid, Aib), and cyclo amino acids, a simple derivative being amino-cyclopropylcarboxylic acid.

5

In one embodiment, the modified derivative comprises the addition of a spacer group. In a further embodiment, the modified derivative comprises the addition of a spacer group to the N-terminal cysteine (C_i) and/or the C-terminal cysteine (C_{iii}).

10 In one embodiment, the modified derivative comprises replacement of one or more oxidation sensitive amino acid residues with one or more oxidation resistant amino acid residues. In a further embodiment, the modified derivative comprises replacement of a tryptophan residue with a naphthylalanine or alanine residue. This embodiment provides the advantage of improving the pharmaceutical stability profile of the resultant bicyclic peptide ligand.

15

In one embodiment, the modified derivative comprises replacement of one or more charged amino acid residues with one or more hydrophobic amino acid residues. In an alternative embodiment, the modified derivative comprises replacement of one or more hydrophobic amino acid residues with one or more charged amino acid residues. The correct balance of charged versus hydrophobic amino acid residues is an important characteristic of the bicyclic peptide ligands. For example, hydrophobic amino acid residues influence the degree of plasma protein binding and thus the concentration of the free available fraction in plasma, while charged amino acid residues (in particular arginine) may influence the interaction of the peptide with the phospholipid membranes on cell surfaces. The two in combination may influence half-life, volume of distribution and exposure of the peptide drug, and can be tailored according to the clinical endpoint. In addition, the correct combination and number of charged versus hydrophobic amino acid residues may reduce irritation at the injection site (if the peptide drug has been administered subcutaneously).

25 30 In one embodiment, the modified derivative comprises replacement of one or more L-amino acid residues with one or more D-amino acid residues. This embodiment is believed to increase proteolytic stability by steric hindrance and by a propensity of D-amino acids to stabilise β -turn conformations (Tugyi et al (2005) PNAS, 102(2), 413–418).

35 In one embodiment, the modified derivative comprises removal of any amino acid residues and substitution with alanines. This embodiment provides the advantage of removing potential

proteolytic attack site(s).

It should be noted that each of the above mentioned modifications serve to deliberately improve the potency or stability of the peptide. Further potency improvements based on modifications may be achieved through the following mechanisms:

- Incorporating hydrophobic moieties that exploit the hydrophobic effect and lead to lower off rates, such that higher affinities are achieved;

- Incorporating charged groups that exploit long-range ionic interactions, leading to faster on rates and to higher affinities (see for example Schreiber et al, Rapid, electrostatically assisted association of proteins (1996), Nature Struct. Biol. 3, 427-31); and

- Incorporating additional constraint into the peptide, by for example constraining side chains of amino acids correctly such that loss in entropy is minimal upon target binding, constraining the torsional angles of the backbone such that loss in entropy is minimal upon target binding and introducing additional cyclisations in the molecule for identical reasons.

(for reviews see Gentilucci et al, Curr. Pharmaceutical Design, (2010), 16, 3185-203, and Nestor et al, Curr. Medicinal Chem (2009), 16, 4399-418).

Isotopic variations

The present invention includes all pharmaceutically acceptable (radio)isotope-labeled peptide ligands of the invention, wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature, and peptide ligands of the invention, wherein metal chelating groups are attached (termed "effector") that are capable of holding relevant (radio)isotopes, and peptide ligands of the invention, wherein certain functional groups are covalently replaced with relevant (radio)isotopes or isotopically labelled functional groups.

Examples of isotopes suitable for inclusion in the peptide ligands of the invention comprise isotopes of hydrogen, such as ^2H (D) and ^3H (T), carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I , ^{125}I and ^{131}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , sulfur, such as ^{35}S , copper, such as ^{64}Cu , gallium, such as ^{67}Ga or ^{68}Ga , yttrium, such as ^{90}Y and lutetium, such as ^{177}Lu , and Bismuth, such as ^{213}Bi .

Certain isotopically-labelled peptide ligands of the invention, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies, and to clinically assess the presence and/or absence of the IL-17 target on diseased tissues. The peptide ligands of the invention can further have valuable diagnostic properties in that they can be used for detecting or identifying the formation of a complex between a labelled compound and other molecules, peptides, proteins, enzymes or receptors. The detecting or identifying methods can use compounds that are labelled with labelling agents such as radioisotopes, enzymes, fluorescent substances, luminous substances (for example, luminol, luminol derivatives, luciferin, aequorin and luciferase), etc. The radioactive isotopes tritium, i.e. ^3H (T), and carbon-14, i.e. ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, i.e. ^2H (D), may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining target occupancy.

Isotopically-labeled compounds of peptide ligands of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Molecular scaffold

Molecular scaffolds are described in, for example, WO 2009/098450 and references cited therein, particularly WO 2004/077062 and WO 2006/078161.

As noted in the foregoing documents, the molecular scaffold may be a small molecule, such as a small organic molecule.

In one embodiment the molecular scaffold may be a macromolecule. In one embodiment the molecular scaffold is a macromolecule composed of amino acids, nucleotides or carbohydrates.

In one embodiment the molecular scaffold comprises reactive groups that are capable of reacting with functional group(s) of the polypeptide to form covalent bonds.

The molecular scaffold may comprise chemical groups which form the linkage with a peptide, such as amines, thiols, alcohols, ketones, aldehydes, nitriles, carboxylic acids, esters, alkenes, alkynes, azides, anhydrides, succinimides, maleimides, alkyl halides and acyl halides.

In one embodiment, the molecular scaffold may comprise or may consist of tris(bromomethyl)benzene, especially 1,3,5-tris(bromomethyl)benzene ('TBMB'), or a derivative thereof.

In one embodiment, the molecular scaffold is 2,4,6-tris(bromomethyl)mesitylene. This molecule is similar to 1,3,5-tris(bromomethyl)benzene but contains three additional methyl groups attached to the benzene ring. This has the advantage that the additional methyl groups may form further contacts with the polypeptide and hence add additional structural constraint.

The molecular scaffold of the invention contains chemical groups that allow functional groups of the polypeptide of the encoded library of the invention to form covalent links with the molecular scaffold. Said chemical groups are selected from a wide range of functionalities including amines, thiols, alcohols, ketones, aldehydes, nitriles, carboxylic acids, esters, alkenes, alkynes, anhydrides, succinimides, maleimides, azides, alkyl halides and acyl halides.

Scaffold reactive groups that could be used on the molecular scaffold to react with thiol groups of cysteines are alkyl halides (or also named halogenoalkanes or haloalkanes).

Examples include bromomethylbenzene (the scaffold reactive group exemplified by TBMB) or iodoacetamide. Other scaffold reactive groups that are used to selectively couple compounds to cysteines in proteins are maleimides, $\alpha\beta$ unsaturated carbonyl containing compounds and α -halomethylcarbonyl containing compounds. Examples of maleimides which may be used as molecular scaffolds in the invention include: tris-(2-maleimidoethyl)amine, tris-(2-maleimidoethyl)benzene, tris-(maleimido)benzene. An example of an $\alpha\beta$ unsaturated carbonyl containing compound is 1,1',1''-(1,3,5-triazinane-1,3,5-triyl)triprop-2-en-1-one (TATA) (Angewandte Chemie, International Edition (2014),

53(6), 1602-1606). An example of an α -halomethylcarbonyl containing compound is N,N',N''-(benzene-1,3,5-triyl)tris(2-bromoacetamide). Selenocysteine is also a natural amino acid which has a similar reactivity to cysteine and can be used for the same reactions. Thus, wherever cysteine is mentioned, it is typically acceptable to substitute selenocysteine unless the context suggests otherwise.

Effector and Functional Groups

According to a further aspect of the invention, there is provided a drug conjugate comprising a peptide ligand as defined herein conjugated to one or more effector and/or functional groups.

Effector and/or functional groups can be attached, for example, to the N and/or C termini of the polypeptide, to an amino acid within the polypeptide, or to the molecular scaffold.

Appropriate effector groups include antibodies and parts or fragments thereof. For instance, an effector group can include an antibody light chain constant region (CL), an antibody CH1 heavy chain domain, an antibody CH2 heavy chain domain, an antibody CH3 heavy chain domain, or any combination thereof, in addition to the one or more constant region domains. An effector group may also comprise a hinge region of an antibody (such a region normally being found between the CH1 and CH2 domains of an IgG molecule).

In a further embodiment of this aspect of the invention, an effector group according to the present invention is an Fc region of an IgG molecule. Advantageously, a peptide ligand-effector group according to the present invention comprises or consists of a peptide ligand Fc fusion having a $t_{1/2}$ half-life of a day or more, two days or more, 3 days or more, 4 days or more, 5 days or more, 6 days or more or 7 days or more. Most advantageously, the peptide ligand according to the present invention comprises or consists of a peptide ligand Fc fusion having a $t_{1/2}$ half-life of a day or more.

Functional groups include, in general, binding groups, drugs, reactive groups for the attachment of other entities, functional groups which aid uptake of the macrocyclic peptides into cells, and the like.

The ability of peptides to penetrate into cells will allow peptides against intracellular targets to be effective. Targets that can be accessed by peptides with the ability to penetrate into cells include transcription factors, intracellular signalling molecules such as tyrosine kinases and molecules involved in the apoptotic pathway. Functional groups which enable the

penetration of cells include peptides or chemical groups which have been added either to the peptide or the molecular scaffold. Peptides such as those derived from such as VP22, HIV-Tat, a homeobox protein of *Drosophila* (*Antennapedia*), e.g. as described in Chen and Harrison, *Biochemical Society Transactions* (2007) Volume 35, part 4, p821; Gupta et al. in *Advanced Drug Discovery Reviews* (2004) Volume 57 9637. Examples of short peptides which have been shown to be efficient at translocation through plasma membranes include the 16 amino acid penetratin peptide from *Drosophila Antennapedia* protein (Derossi et al (1994) *J Biol. Chem.* Volume 269 p10444), the 18 amino acid 'model amphipathic peptide' (Oehlke et al (1998) *Biochim Biophys Acts* Volume 1414 p127) and arginine rich regions of the HIV TAT protein. Non peptidic approaches include the use of small molecule mimics or SMOCs that can be easily attached to biomolecules (Okuyama et al (2007) *Nature Methods* Volume 4 p153). Other chemical strategies to add guanidinium groups to molecules also enhance cell penetration (Elson-Scwab et al (2007) *J Biol Chem* Volume 282 p13585). Small molecular weight molecules such as steroids may be added to the molecular scaffold to enhance uptake into cells.

One class of functional groups which may be attached to peptide ligands includes antibodies and binding fragments thereof, such as Fab, Fv or single domain fragments. In particular, antibodies which bind to proteins capable of increasing the half-life of the peptide ligand in vivo may be used.

In one embodiment, a peptide ligand-effector group according to the invention has a $t_{1/2}$ half-life selected from the group consisting of: 12 hours or more, 24 hours or more, 2 days or more, 3 days or more, 4 days or more, 5 days or more, 6 days or more, 7 days or more, 8 days or more, 9 days or more, 10 days or more, 11 days or more, 12 days or more, 13 days or more, 14 days or more, 15 days or more or 20 days or more. Advantageously a peptide ligand-effector group or composition according to the invention will have a $t_{1/2}$ half life in the range 12 to 60 hours. In a further embodiment, it will have a $t_{1/2}$ half-life of a day or more. In a further embodiment still, it will be in the range 12 to 26 hours.

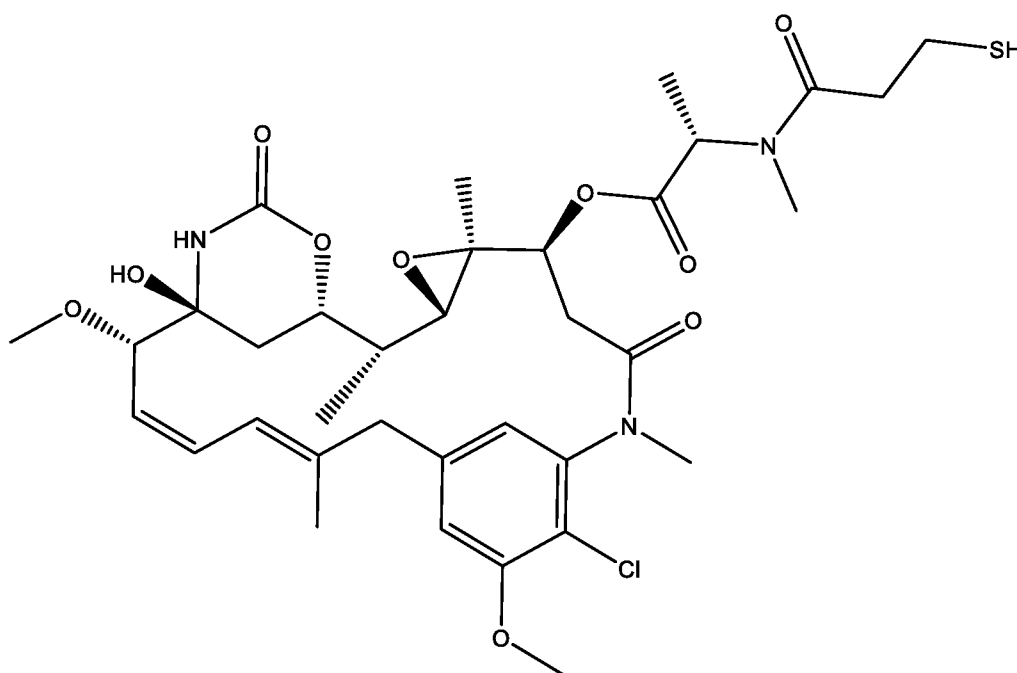
In one particular embodiment of the invention, the functional group is selected from a metal chelator, which is suitable for complexing metal radioisotopes of medicinal relevance.

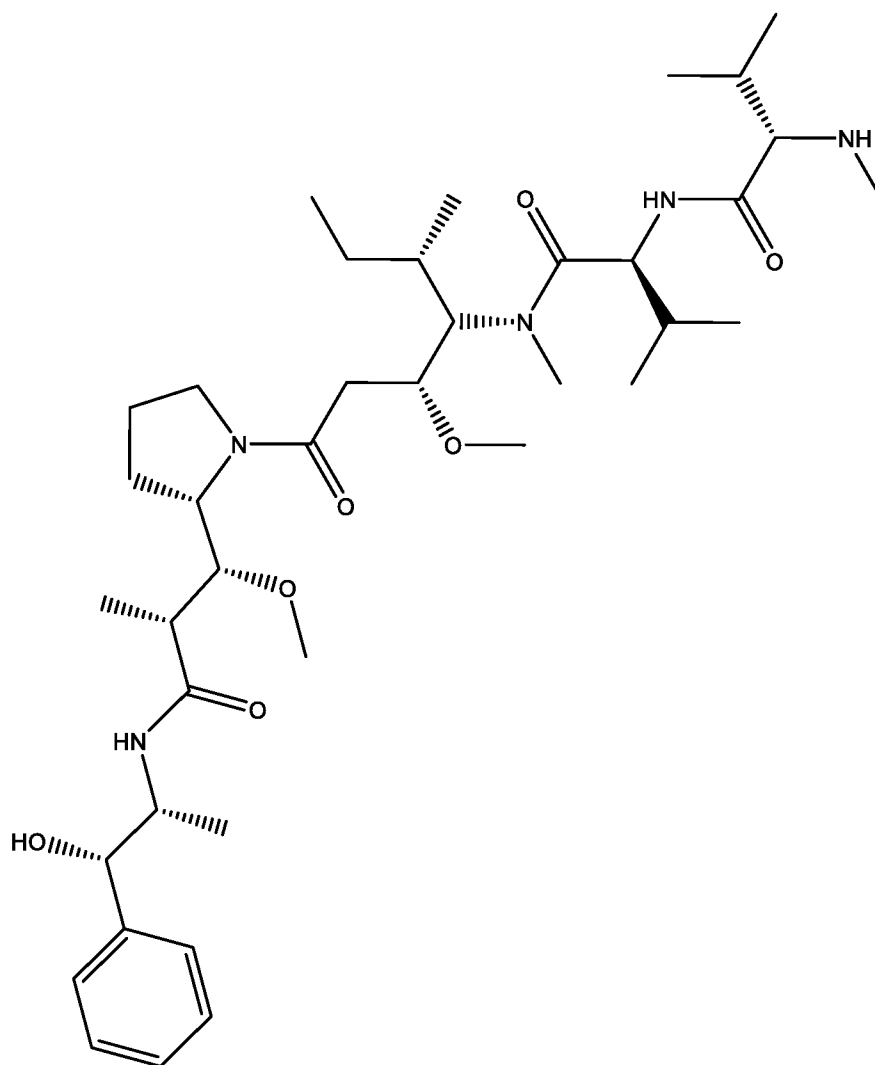
Possible effector groups also include enzymes, for instance such as carboxypeptidase G2 for use in enzyme/prodrug therapy, where the peptide ligand replaces antibodies in ADEPT.

In one particular embodiment of the invention, the functional group is selected from a drug, such as a cytotoxic agent for cancer therapy. Suitable examples include: alkylating agents such as cisplatin and carboplatin, as well as oxaliplatin, mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide; Anti-metabolites including purine analogs azathioprine and mercaptopurine or pyrimidine analogs; plant alkaloids and terpenoids including vinca alkaloids such as Vincristine, Vinblastine, Vinorelbine and Vindesine; Podophyllotoxin and its derivatives etoposide and teniposide; Taxanes, including paclitaxel, originally known as Taxol; topoisomerase inhibitors including camptothecins: irinotecan and topotecan, and type II inhibitors including amsacrine, etoposide, etoposide phosphate, and teniposide. Further agents can include antitumour antibiotics which include the immunosuppressant dactinomycin (which is used in kidney transplantations), doxorubicin, epirubicin, bleomycin, calicheamycins, and others.

In one further particular embodiment of the invention, the cytotoxic agent is selected from maytansinoids (such as DM1) or monomethyl auristatins (such as MMAE).

DM1 is a cytotoxic agent which is a thiol-containing derivative of maytansine and has the following structure:





In one embodiment, the cytotoxic agent is linked to the bicyclic peptide by a cleavable bond, such as a disulphide bond or a protease sensitive bond. In a further embodiment, the groups adjacent to the disulphide bond are modified to control the hindrance of the disulphide bond, and by this the rate of cleavage and concomitant release of cytotoxic agent.

Published work established the potential for modifying the susceptibility of the disulphide bond to reduction by introducing steric hindrance on either side of the disulphide bond (Kellogg et al (2011) Bioconjugate Chemistry, 22, 717). A greater degree of steric hindrance reduces the rate of reduction by intracellular glutathione and also extracellular (systemic) reducing agents, consequentially reducing the ease by which toxin is released, both inside and outside the cell. Thus, selection of the optimum in disulphide stability in the circulation (which minimises undesirable side effects of the toxin) versus efficient release in the intracellular milieu (which maximises the therapeutic effect) can be achieved by careful selection of the degree of hindrance on either side of the disulphide bond.

The hindrance on either side of the disulphide bond is modulated through introducing one or more methyl groups on either the targeting entity (here, the bicyclic peptide) or toxin side of the molecular construct.

- 5 In one embodiment, the cytotoxic agent and linker is selected from any combinations of those described in WO 2016/067035 (the cytotoxic agents and linkers thereof are herein incorporated by reference).

Synthesis

- 10 The peptides of the present invention may be manufactured synthetically by standard techniques followed by reaction with a molecular scaffold in vitro. When this is performed, standard chemistry may be used. This enables the rapid large scale preparation of soluble material for further downstream experiments or validation. Such methods could be accomplished using conventional chemistry such as that disclosed in Timmerman et al
15 (supra).

- Thus, the invention also relates to manufacture of polypeptides or conjugates selected as set out herein, wherein the manufacture comprises optional further steps as explained below. In one embodiment, these steps are carried out on the end product polypeptide/conjugate
20 made by chemical synthesis.

Optionally amino acid residues in the polypeptide of interest may be substituted when manufacturing a conjugate or complex.

- 25 Peptides can also be extended, to incorporate for example another loop and therefore introduce multiple specificities.

- To extend the peptide, it may simply be extended chemically at its N-terminus or C-terminus or within the loops using orthogonally protected lysines (and analogues) using standard solid
30 phase or solution phase chemistry. Standard (bio)conjugation techniques may be used to introduce an activated or activatable N- or C-terminus. Alternatively additions may be made by fragment condensation or native chemical ligation e.g. as described in (Dawson et al. 1994. Synthesis of Proteins by Native Chemical Ligation. Science 266:776-779), or by enzymes, for example using subtiligase as described in (Chang et al Proc Natl Acad Sci U S
35 A. 1994 Dec 20; 91(26):12544-8 or in Hikari et al Bioorganic & Medicinal Chemistry Letters Volume 18, Issue 22, 15 November 2008, Pages 6000-6003).

Alternatively, the peptides may be extended or modified by further conjugation through disulphide bonds. This has the additional advantage of allowing the first and second peptide to dissociate from each other once within the reducing environment of the cell. In this case, the molecular scaffold (e.g. TBMB) could be added during the chemical synthesis of the first peptide so as to react with the three cysteine groups; a further cysteine or thiol could then be appended to the N or C-terminus of the first peptide, so that this cysteine or thiol only reacted with a free cysteine or thiol of the second peptide, forming a disulfide –linked bicyclic peptide-peptide conjugate.

Similar techniques apply equally to the synthesis/coupling of two bicyclic and bispecific macrocycles, potentially creating a tetraspecific molecule.

Furthermore, addition of other functional groups or effector groups may be accomplished in the same manner, using appropriate chemistry, coupling at the N- or C-termini or via side chains. In one embodiment, the coupling is conducted in such a manner that it does not block the activity of either entity.

Pharmaceutical Compositions

According to a further aspect of the invention, there is provided a pharmaceutical composition comprising a peptide ligand or a drug conjugate as defined herein in combination with one or more pharmaceutically acceptable excipients.

Generally, the present peptide ligands will be utilised in purified form together with pharmacologically appropriate excipients or carriers. Typically, these excipients or carriers include aqueous or alcoholic/aqueous solutions, emulsions or suspensions, including saline and/or buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride and lactated Ringer's. Suitable physiologically-acceptable adjuvants, if necessary to keep a polypeptide complex in suspension, may be chosen from thickeners such as carboxymethylcellulose, polyvinylpyrrolidone, gelatin and alginates.

Intravenous vehicles include fluid and nutrient replenishers and electrolyte replenishers, such as those based on Ringer's dextrose. Preservatives and other additives, such as antimicrobials, antioxidants, chelating agents and inert gases, may also be present (Mack (1982) Remington's Pharmaceutical Sciences, 16th Edition).

The peptide ligands of the present invention may be used as separately administered compositions or in conjunction with other agents. These can include antibodies, antibody fragments and various immunotherapeutic drugs, such as cyclosporine, methotrexate, adriamycin or cisplatin and immunotoxins. Pharmaceutical compositions can include "cocktails" of various cytotoxic or other agents in conjunction with the protein ligands of the present invention, or even combinations of selected polypeptides according to the present invention having different specificities, such as polypeptides selected using different target ligands, whether or not they are pooled prior to administration.

The route of administration of pharmaceutical compositions according to the invention may be any of those commonly known to those of ordinary skill in the art. For therapy, the peptide ligands of the invention can be administered to any patient in accordance with standard techniques. The administration can be by any appropriate mode, including parenterally, intravenously, intramuscularly, intraperitoneally, transdermally, via the pulmonary route, or also, appropriately, by direct infusion with a catheter. Preferably, the pharmaceutical compositions according to the invention will be administered by inhalation. The dosage and frequency of administration will depend on the age, sex and condition of the patient, concurrent administration of other drugs, counterindications and other parameters to be taken into account by the clinician.

The peptide ligands of this invention can be lyophilised for storage and reconstituted in a suitable carrier prior to use. This technique has been shown to be effective and art-known lyophilisation and reconstitution techniques can be employed. It will be appreciated by those skilled in the art that lyophilisation and reconstitution can lead to varying degrees of activity loss and that levels may have to be adjusted upward to compensate.

The compositions containing the present peptide ligands or a cocktail thereof can be administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, an adequate amount to accomplish at least partial inhibition, suppression, modulation, killing, or some other measurable parameter, of a population of selected cells is defined as a "therapeutically-effective dose". Amounts needed to achieve this dosage will depend upon the severity of the disease and the general state of the patient's own immune system, but generally range from 0.005 to 5.0 mg of selected peptide ligand per kilogram of body weight, with doses of 0.05 to 2.0 mg/kg/dose being more commonly used. For prophylactic applications, compositions containing the present peptide ligands or cocktails thereof may also be administered in similar or slightly lower dosages.

A composition containing a peptide ligand according to the present invention may be utilised in prophylactic and therapeutic settings to aid in the alteration, inactivation, killing or removal of a select target cell population in a mammal. In addition, the peptide ligands described herein may be used extracorporeally or in vitro selectively to kill, deplete or otherwise effectively remove a target cell population from a heterogeneous collection of cells. Blood from a mammal may be combined extracorporeally with the selected peptide ligands whereby the undesired cells are killed or otherwise removed from the blood for return to the mammal in accordance with standard techniques.

10 Therapeutic Uses

The bicyclic peptides of the invention have specific utility as IL-17 binding agents, such as IL-17A, IL-17E and IL-17F.

Interleukin-17 (IL-17), also known as IL-17A and CTLA-8, is a pro-inflammatory cytokine that stimulates secretion of various other cytokines in a variety of cell types. For example, IL-17 can induce IL-6, IL-8, G-CSF, TNF- α , IL-1 β , PGE2, and IFN- γ , as well as numerous chemokines and other effectors (see Gaffen, SL (2004) Arthritis Research & Therapy 6, 240-247).

IL-17 is expressed by TH17 cells, which are involved in the pathology of inflammation and autoimmunity. It is also expressed by CD8+ T cells, $\gamma\delta$ cells, NK cells, NKT cells, macrophages and dendritic cells. IL-17 and Th17 are linked to pathogenesis of diverse autoimmune and inflammatory diseases, but are essential to host defence against many microbes, particularly extracellular bacteria and fungi. Human IL-17A is a glycoprotein with a Mw of 17,000 daltons (Spriggs et al (1997) J Clin Immunol, 17, 366-369). IL-17 can form homodimers or heterodimers with its family member, IL-17F. IL-17 binds to both IL-17 RA and IL-17 RC to mediate signaling. IL-17, signaling through its receptor, activates the NF-KB transcription factor, as well as various MAPKs (see Gaffen, SL (2009) Nature Rev Immunol 9, 556-567).

IL-17 can act in cooperation with other inflammatory cytokines such as TNF- α , IFN- γ , and IL-1 β to mediate pro-inflammatory effects (see Gaffen, SL (2004) Arthritis Research & Therapy 6, 240-247). Increased levels of IL-17 have been implicated in numerous diseases, including rheumatoid arthritis (RA), bone erosion, intraperitoneal abscesses, inflammatory bowel disease, allograft rejection, psoriasis, angiogenesis, atherosclerosis, asthma, and multiple sclerosis (see Gaffen, SL (2004) supra and US 2008/0269467). IL-17 was found in higher serum concentrations in patients with systemic lupus erythematosus (SLE) and was recently

determined to act either alone or in synergy with B-cell activating factor (BAFF) to control B-cell survival, proliferation, and differentiation into immunoglobulin producing cells (Doreau et al (2009) *Nature Immunology* 7, 778-7859). IL-17 has also been associated with ocular surface disorders, such as dry eye (WO 2010/062858 and WO 2011/163452). IL-17 has also
5 been implicated in playing a role in ankylosing spondylitis (Appel et al (2011) *Arthritis Research and Therapy*, 13, R95) and psoriatic arthritis (McInnes et al (2011) *Arthritis & Rheumatism* 63(10),779).

IL-17 and IL-17-producing TH17 cells have recently been implicated in certain cancers (Ji
10 and Zhang (2010) *Cancer Immunol Immunother* 59, 979-987). For example, IL-17-expressing TH17 cells were shown to be involved in multiple myeloma (Prabhala et al (2010) *Blood*, online DOI 10.1182/blood-2009-10-246660), and to correlate with poor prognosis in patients with HCC (Zhang et al (2009) *J Hepatology* 50, 980-89. Also, IL-17 was found to be expressed by breast-cancer-associated macrophages (Zhu et al (2008) *Breast Cancer*
15 *Research* 10, R95). However, the role of IL-17 in cancer, in many cases, has been unclear. In particular, IL-17 and IL-17-producing TH17 cells have been identified as having both a positive and a negative role in tumor immunity, sometimes in the same type of cancer (Ji and Zhang (2010) *Cancer Immunol Immunother* 59, 979-987).

20 IL-17A binds to the IL-17 receptor (RA/RC complex). IL-17A can exist as a homodimer or a heterodimer along with IL-17F. IL-17A has restricted expression (lymphocytes, neutrophils and eosinophils). IL-17A has been implicated in airway inflammation and psoriasis.

IL-17E (also known as IL-25) binds to the IL-17 receptor (RA/RB complex). IL-17E has been
25 implicated in airway inflammation and recruits eosinophils to lung tissue. IL-17E is more distantly related to IL-17A (17%). IL-17E has very low expression (Th2, eosinophils, mast cells and macrophages).

IL-17F binds to the IL-17 receptor (RA/RC complex) with a lower affinity than IL-17A. It has a
30 similar expression pattern to IL-17A. IL-17F is implicated in airway inflammation and psoriasis. IL-17F is most closely related to IL-17A (44-55%) and can exist as a homodimer or a heterodimer along with IL-17A.

Polypeptide ligands selected according to the method of the present invention may be
35 employed in in vivo therapeutic and prophylactic applications, in vitro and in vivo diagnostic applications, in vitro assay and reagent applications, and the like. Ligands having selected levels of specificity are useful in applications which involve testing in non-human animals,

where cross-reactivity is desirable, or in diagnostic applications, where cross-reactivity with homologues or paralogues needs to be carefully controlled. In some applications, such as vaccine applications, the ability to elicit an immune response to predetermined ranges of antigens can be exploited to tailor a vaccine to specific diseases and pathogens.

5

Substantially pure peptide ligands of at least 90 to 95% homogeneity are preferred for administration to a mammal, and 98 to 99% or more homogeneity is most preferred for pharmaceutical uses, especially when the mammal is a human. Once purified, partially or to homogeneity as desired, the selected polypeptides may be used diagnostically or therapeutically (including extracorporeally) or in developing and performing assay procedures, immunofluorescent stainings and the like (Lefkovite and Pernis, (1979 and 1981) Immunological Methods, Volumes I and II, Academic Press, NY).

10

According to a further aspect of the invention, there is provided a peptide ligand or a drug conjugate as defined herein, for use in preventing, suppressing or treating a disease or disorder mediated by IL-17.

15

According to a further aspect of the invention, there is provided a method of preventing, suppressing or treating a disease or disorder mediated by IL-17, which comprises administering to a patient in need thereof an effector group and drug conjugate of the peptide ligand as defined herein.

20

In one embodiment, the IL-17 is mammalian IL-17. In a further embodiment, the mammalian IL-17 is human IL-17.

25

In one embodiment, the disease or disorder mediated by IL-17 is selected from inflammatory disorders and cancer. In a further embodiment, the disease or disorder mediated by IL-17 is selected from: rheumatoid arthritis (RA), bone erosion, intraperitoneal abscesses, inflammatory bowel disease, allograft rejection, psoriasis, angiogenesis, atherosclerosis, asthma, multiple sclerosis, systemic lupus erythematosus (SLE), ocular surface disorders (such as dry eye), ankylosing spondylitis, psoriatic arthritis, cancer (such as multiple myeloma and breast cancer).

30

In a further embodiment, the disease or disorder mediated by IL-17 is selected from cancer.

35

Examples of cancers (and their benign counterparts) which may be treated (or inhibited) include, but are not limited to tumours of epithelial origin (adenomas and carcinomas of

various types including adenocarcinomas, squamous carcinomas, transitional cell carcinomas and other carcinomas) such as carcinomas of the bladder and urinary tract, breast, gastrointestinal tract (including the esophagus, stomach (gastric), small intestine, colon, rectum and anus), liver (hepatocellular carcinoma), gall bladder and biliary system, exocrine pancreas, kidney, lung (for example adenocarcinomas, small cell lung carcinomas, non-small cell lung carcinomas, bronchioalveolar carcinomas and mesotheliomas), head and neck (for example cancers of the tongue, buccal cavity, larynx, pharynx, nasopharynx, tonsil, salivary glands, nasal cavity and paranasal sinuses), ovary, fallopian tubes, peritoneum, vagina, vulva, penis, cervix, myometrium, endometrium, thyroid (for example thyroid follicular carcinoma), adrenal, prostate, skin and adnexae (for example melanoma, basal cell carcinoma, squamous cell carcinoma, keratoacanthoma, dysplastic naevus); haematological malignancies (i.e. leukemias, lymphomas) and premalignant haematological disorders and disorders of borderline malignancy including haematological malignancies and related conditions of lymphoid lineage (for example acute lymphocytic leukemia [ALL], chronic lymphocytic leukemia [CLL], B-cell lymphomas such as diffuse large B-cell lymphoma [DLBCL], follicular lymphoma, Burkitt's lymphoma, mantle cell lymphoma, T-cell lymphomas and leukaemias, natural killer [NK] cell lymphomas, Hodgkin's lymphomas, hairy cell leukaemia, monoclonal gammopathy of uncertain significance, plasmacytoma, multiple myeloma, and post-transplant lymphoproliferative disorders), and haematological malignancies and related conditions of myeloid lineage (for example acute myelogenous leukemia [AML], chronic myelogenous leukemia [CML], chronic myelomonocytic leukemia [CMML], hypereosinophilic syndrome, myeloproliferative disorders such as polycythaemia vera, essential thrombocythaemia and primary myelofibrosis, myeloproliferative syndrome, myelodysplastic syndrome, and promyelocytic leukemia); tumours of mesenchymal origin, for example sarcomas of soft tissue, bone or cartilage such as osteosarcomas, fibrosarcomas, chondrosarcomas, rhabdomyosarcomas, leiomyosarcomas, liposarcomas, angiosarcomas, Kaposi's sarcoma, Ewing's sarcoma, synovial sarcomas, epithelioid sarcomas, gastrointestinal stromal tumours, benign and malignant histiocytomas, and dermatofibrosarcoma protuberans; tumours of the central or peripheral nervous system (for example astrocytomas, gliomas and glioblastomas, meningiomas, ependymomas, pineal tumours and schwannomas); endocrine tumours (for example pituitary tumours, adrenal tumours, islet cell tumours, parathyroid tumours, carcinoid tumours and medullary carcinoma of the thyroid); ocular and adnexal tumours (for example retinoblastoma); germ cell and trophoblastic tumours (for example teratomas, seminomas, dysgerminomas, hydatidiform moles and choriocarcinomas); and paediatric and embryonal tumours (for example medulloblastoma, neuroblastoma, Wilms tumour, and

primitive neuroectodermal tumours); or syndromes, congenital or otherwise, which leave the patient susceptible to malignancy (for example Xeroderma Pigmentosum).

In one embodiment, the disease or disorder mediated by IL-17 is a disease or disorder mediated by IL-17A. In a further embodiment, the peptide ligand is specific for IL-17A as defined herein and the disease or disorder mediated by IL-17 is a disease or disorder mediated by IL-17A. In a further embodiment, the disease or disorder mediated by IL-17A is selected from airway inflammatory disease and psoriasis.

In one embodiment, the disease or disorder mediated by IL-17 is a disease or disorder mediated by IL-17E. In a further embodiment, the peptide ligand is specific for IL-17E as defined herein and the disease or disorder mediated by IL-17 is a disease or disorder mediated by IL-17E. In a further embodiment, the disease or disorder mediated by IL-17A is selected from airway inflammatory disease.

In one embodiment, the disease or disorder mediated by IL-17 is a disease or disorder mediated by IL-17F. In a further embodiment, the peptide ligand is specific for IL-17F as defined herein and the disease or disorder mediated by IL-17 is a disease or disorder mediated by IL-17F. In a further embodiment, the disease or disorder mediated by IL-17F is selected from airway inflammatory disease and psoriasis.

References herein to the term "prevention" involves administration of the protective composition prior to the induction of the disease. "Suppression" refers to administration of the composition after an inductive event, but prior to the clinical appearance of the disease. "Treatment" involves administration of the protective composition after disease symptoms become manifest.

Animal model systems which can be used to screen the effectiveness of the peptide ligands in protecting against or treating the disease are available. The use of animal model systems is facilitated by the present invention, which allows the development of polypeptide ligands which can cross react with human and animal targets, to allow the use of animal models.

The invention is further described below with reference to the following examples.

Examples

Materials and Methods

5 Peptide Synthesis

Peptide synthesis was based on Fmoc chemistry, using a Symphony peptide synthesiser manufactured by Peptide Instruments and a Syro II synthesiser by MultiSynTech. Standard Fmoc-amino acids were employed (Sigma, Merck), with appropriate side chain protecting groups: where applicable standard coupling conditions were used in each case, followed by
10 deprotection using standard methodology. Peptides were purified using HPLC and following isolation they were modified with 1,3,5-tris(bromomethyl)benzene (TBMB, Sigma). For this, linear peptide was diluted with H₂O up to ~35 mL, ~500 µL of 100 mM TBMB in acetonitrile was added, and the reaction was initiated with 5 mL of 1 M NH₄HCO₃ in H₂O. The reaction was allowed to proceed for ~30 -60 min at RT, and lyophilised once the reaction had
15 completed (judged by MALDI). Following lyophilisation, the modified peptide was purified as above, while replacing the Luna C8 with a Gemini C18 column (Phenomenex), and changing the acid to 0.1% trifluoroacetic acid. Pure fractions containing the correct TMB-modified material were pooled, lyophilised and kept at -20°C for storage.

20 All amino acids, unless noted otherwise, were used in the L- configurations.

BIOLOGICAL DATA

IL-17A, IL-17E and IL-17F Human and Mouse Binding Assays

25 IL-17A, IL-17E and IL-17F binding was determined using an analogous method to that described in WO 2011/141823.

Selected peptide ligands of the invention were tested in the above mentioned IL-17A, IL-17E and IL-17F human and mouse binding assays and the results are shown in Tables 1 and 2:

30

Table 1: Human Binding Assay Data for Peptide Ligands of the Invention

Peptide Ligand	hIL17-A Binding K _d (nM)	hIL17-E Binding K _d (nM)	hIL17-F Binding K _d (nM)
BCY2271	20	> 1000	nt

BCY2265	336	nt	nt
BCY2232	398	nt	nt
BCY2203	702	240	nt
BCY2202	> 5000	373	nt
BCY2240	nt	nt	198
BCY2441	nt	nt	392

nt = not tested

Table 2: Human and Mouse Binding Assay Data for Peptide Ligands of the Invention

5

Peptide Ligand	Species	Target	Kd (nM)	Mean	n
BCY2307	Human	IL17A dimer	453.6 ± 122.45	437.7	5
	Mouse	IL17A dimer	>1000		2
BCY2309	Human	IL17A dimer	335.5 ± 71.54	333.5	2
	Mouse	IL17A dimer	>1000 n=1		1
BCY2310	Human	IL17A dimer	26.65 ± 0.29	26.6	2
	Mouse	IL17A dimer	110 n=1		1
	Human	IL17F dimer	>1000 n=1		1
	Human	IL17A/F dimer	>1000 n=1		1
BCY2311	Human	IL17A dimer	25.89 ± 6.19	24.7	8
	Mouse	IL17A dimer	>650		3
	Human	IL17F dimer	>1000 n=1		1

	Human	IL17A/F dimer	>1000 n=1		1
BCY2315	Human	IL17A dimer	5.63 $\pm$ 0.73	5.6	3
	Mouse	IL17A dimer	>650 n=1		1
BCY2316	Human	IL17A dimer	372 n=1		1
	Mouse	IL17A dimer	>650 n=1		1
BCY2317	Human	IL17A dimer	181 n=1		1
	Mouse	IL17A dimer	>650 n=1		1
BCY2318	Human	IL17A dimer	538 n=1		1
	Mouse	IL17A dimer	>1000 n=1		1
BCY2319	Human	IL17A dimer	657 n=1		1
	Mouse	IL17A dimer	158 n=1		1
BCY2320	Human	IL17A dimer	282 n=1		1
	Mouse	IL17A dimer	>650 n=1		1
BCY2222	Human	IL17A dimer	702 n=1		
	Human	IL17F dimer	229 n=1		
BCY2217	Human	IL17F dimer	401 n=1		

Human Fluorescence Polarisation (FP) Competition Assay

Affinity determination by fluorescence polarization (FP) competition. Bicycles were screened to determine affinity (K_i) in a fluorescence polarisation assay where in competition with a

bicycle labelled with fluorescein (referred to as tracer) with a known affinity for IL-17A. Peptides were diluted to an appropriate concentration in assay buffer (PBS + 0.01% Tween20, adjusted to pH7.4 using NaOH (1M)) with a maximum of 1% DMSO, then serially diluted 1 in 2 into assay buffer. Into black 384-well low volume plates, 5µL of diluted peptide was added to the plate followed by 10µL of IL-17A (75nM) then 10µL tracer added to a final concentration of 1nM. Measurements were conducted on a BMG PHERAstar FS equipped with an “FP 485 520 520” optic module which excites at 485nm and detects parallel and perpendicular emission at 520nm. The PHERAstar FS was set at 25°C with 200 flashes per well and a positioning delay of 0.1 second, with each well measured at 5 to 10 minute intervals for 60 minutes. The gain used for measurements was determined at the point of experiment on a tracer alone well. Data analysis was performed in Dotmatics where mP values were fit to the Cheng Prusoff equation in order to generate a Ki value.

Selected peptide ligands of the invention were tested in the above mentioned human FP competition assay and the results are shown in Table 3:

Table 3: Competition Assay Data for Peptide Ligands of the Invention

Peptide Ligand	Target	Ki Result (nM)	Ki Mean	n	Tracer
BCY2235	IL17A dimer	134.38 ± 38.27	130.4	4	BCY2311
BCY2230	IL17A dimer	633 n=1		1	BCY2311
BCY2231	IL17A dimer	1500 n=1		1	BCY2311
BCY2236	IL17A dimer	57.4 ± 21.95	56.3	2	BCY2311
BCY2237	IL17A dimer	110 n=1			BCY2311
BCY2238	IL17A dimer	62.9 n=1		1	BCY2311
BCY2239	IL17A dimer	33.22 ± 7.45	32.3	5	BCY2311
BCY2240	IL17A dimer	26.95 ± 6.8	25.7	6	BCY2311
BCY2241	IL17A dimer	278 n=1		1	BCY2311
BCY2243	IL17A dimer	40.5 ± 10.55	39.8	3	BCY2315

	IL17A dimer	30.4 n=1		1	BCY2311
BCY2244	IL17A dimer	1800 n=1		1	BCY2315
BCY2246	IL17A dimer	549.5 $\pm$ 130.34	545.5	2	BCY2315
BCY2248	IL17A dimer	60.6 n=1		1	BCY2315
	IL17A dimer	241 n=1		1	BCY2311
BCY2249	IL17A dimer	65.05 $\pm$ 4.41	65	2	BCY2315
BCY2250	IL17A dimer	113.3 n=1		1	BCY2315
BCY2252	IL17A dimer	1750 $\pm$ 881.98	1691.2	2	BCY2315
BCY2258	IL17A dimer	409.67 $\pm$ 134.82	399.1	3	BCY2311
BCY2259	IL17A dimer	600.67 $\pm$ 84.08	597.5	3	BCY2311
BCY2260	IL17A dimer	276.5 $\pm$ 79.29	267.6	4	BCY2311
BCY2262	IL17A dimer	213 n=1		1	BCY2311
BCY2265	IL17A dimer	822.5 $\pm$ 700.69	740.7	2	BCY2311
BCY2266	IL17A dimer	165 n=1		1	BCY2311
BCY2267	IL17A dimer	118 n=1		1	BCY2311
BCY2268	IL17A dimer	188 n=1		1	BCY2311
BCY2269	IL17A dimer	78.65 $\pm$ 13.23	78.4	2	BCY2311
BCY2270	IL17A dimer	38.7 n=1		1	BCY2315
	IL17A dimer	68.75 $\pm$ 25.77	67.5	2	BCY2311
BCY2271	IL17A dimer	90.1 $\pm$ 6.47	90	2	BCY2311
BCY2272	IL17A dimer	280.8 $\pm$ 116.98	254.9	5	BCY2311

BCY2273	IL17A dimer	34.2 n=1		1	BCY2315
	IL17A dimer	85.22 $\pm$ 11.61	84.3	5	BCY2311
BCY2274	IL17A dimer	35.8 n=1		1	BCY2315
	IL17A dimer	51.45 $\pm$ 15.39	50.8	2	BCY2311
BCY2275	IL17A dimer	29.1 n=1		1	BCY2315
	IL17A dimer	38.4 $\pm$ 6.27	38.3	2	BCY2311
BCY2276	IL17A dimer	24.4 n=1		1	BCY2315
	IL17A dimer	46.1 $\pm$ 15.68	45.4	2	BCY2311
BCY2277	IL17A dimer	84.6 $\pm$ 10	84.4	2	BCY2311
BCY2278	IL17A dimer	547 n=1		1	BCY2311
BCY2279	IL17A dimer	244 n=1		1	BCY2311
BCY2280	IL17A dimer	112 n=1		1	BCY2311
BCY2282	IL17A dimer	43.5 n=1		1	BCY2311
BCY2283	IL17A dimer	88.5 $\pm$ 12.94	88.3	2	BCY2311
BCY2284	IL17A dimer	261 n=1		1	BCY2311
BCY2285	IL17A dimer	576 n=1		1	BCY2311
BCY2286	IL17A dimer	15.7 $\pm$ 7.25	15.3	2	BCY2315
	IL17A dimer	25.03 $\pm$ 13.14	23.3	3	BCY2311
BCY2287	IL17A dimer	81.9 n=1		1	BCY2311
BCY2288	IL17A dimer	153.3 n=1		1	BCY2311
BCY2289	IL17A dimer	108 n=1		1	BCY2311
BCY2290	IL17A dimer	95.2 n=1		1	BCY2311
BCY2291	IL17A dimer	73.3 n=1		1	BCY2311
BCY2292	IL17A dimer	571 n=1		1	BCY2311
BCY2293	IL17A dimer	280.67 $\pm$ 62.46	276.9	3	BCY2311
BCY2294	IL17A dimer	1026 $\pm$ 221.48	1019.8	2	BCY2311
BCY2295	IL17A dimer	694.5 $\pm$ 24.5	694.4	2	BCY2311

BCY2299	IL17A dimer	3350 ± 98	3349.6	2	BCY2311
BCY2302	IL17A dimer	1915 ± 754.59	1875.9	2	BCY2311
BCY2304	IL17A dimer	366.5 ± 63.7	365.1	2	BCY2311
BCY2305	IL17A dimer	240 n=1		1	BCY2311
BCY2306	IL17A dimer	1100 n=1		1	BCY2311

CLAIMS

1. A peptide ligand specific for IL-17 comprising a polypeptide comprising at least three cysteine residues, separated by at least two loop sequences, and a molecular scaffold which forms covalent bonds with the cysteine residues of the polypeptide such that at least two polypeptide loops are formed on the molecular scaffold.

2. The peptide ligand as defined in claim 1, wherein said loop sequences comprise 2 to 7 amino acids.

3. The peptide ligand as defined in claim 1 or claim 2, wherein said loop sequences comprise 2, 5, 6 or 7 amino acids.

4. The peptide ligand as defined in any one of claims 1 to 3, wherein said loop sequences comprise three cysteine residues separated by two loop sequences both of which consist of 5 amino acids.

5. The peptide ligand as defined in any one of claims 1 to 3, wherein said loop sequences comprise three cysteine residues separated by two loop sequences both of which consist of 6 amino acids.

6. The peptide ligand as defined in any one of claims 1 to 3, wherein said loop sequences comprise three cysteine residues separated by two loop sequences one of which consists of 2 amino acids and the other of which consists of 7 amino acids.

7. The peptide ligand as defined in any one of claims 1 to 6, wherein the peptide ligand is specific for IL-17A, IL-17E or IL-17F.

8. The peptide ligand as defined in claim 7, which is specific for IL-17A and said loop sequences comprise three cysteine residues separated by two loop sequences both of which consist of 6 amino acids and comprises an amino acid sequence selected from:

C_iPQDLELC_{ii}TFLFGDC_{iii} (SEQ ID NO: 1);

C_iDQDELMC_{ii}FLTGHQC_{iii} (SEQ ID NO: 2);

C_iPENELYC_{ii}FLSSQQC_{iii} (SEQ ID NO: 3);

C_iDPDSLEC_{ii}WIFNQTC_{iii} (SEQ ID NO: 4);

C_iPDDELYC_{ii}FLTGFKC_{iii} (SEQ ID NO: 5);

C_iDDDELYC_{ii}FLTNNQC_{iii} (SEQ ID NO: 6);

- C_iAEDELYC_{ii}FLTNHTC_{iii} (SEQ ID NO: 7);
 C_iPDDELYC_{ii}FLTGQHC_{iii} (SEQ ID NO: 8);
 C_iPDDELYC_{ii}FLTGVPC_{iii} (SEQ ID NO: 9);
 C_iPDDELYC_{ii}FLTGQTC_{iii} (SEQ ID NO: 10);
 5 C_iDTDPELC_{ii}RFLNLDC_{iii} (SEQ ID NO: 11);
 C_iDTDVELC_{ii}KFLGLDC_{iii} (SEQ ID NO: 12);
 C_iDTDPELC_{ii}SFLGIAC_{iii} (SEQ ID NO: 13);
 C_iEGDPELC_{ii}RFLGLEC_{iii} (SEQ ID NO: 14);
 C_iGTDPPELC_{ii}AFLGVDC_{iii} (SEQ ID NO: 15);
 10 C_iETDL DLC_{ii}AFLNIPC_{iii} (SEQ ID NO: 16);
 C_iATDPELC_{ii}RFLNLDC_{iii} (SEQ ID NO: 17);
 C_iQTDPELC_{ii}RFLNLDC_{iii} (SEQ ID NO: 18);
 C_iDHDPELC_{ii}RFLNLDC_{iii} (SEQ ID NO: 19);
 C_iDADPELC_{ii}RFLNLDC_{iii} (SEQ ID NO: 20);
 15 C_iDGDPELC_{ii}RFLNLDC_{iii} (SEQ ID NO: 21);
 C_iDTDPELC_{ii}MFLNLDC_{iii} (SEQ ID NO: 22);
 C_iDTDPELC_{ii}RFLGLDC_{iii} (SEQ ID NO: 23);
 C_iDTDPELC_{ii}RFLRLDC_{iii} (SEQ ID NO: 24);
 C_iDTDPELC_{ii}RFLNVDC_{iii} (SEQ ID NO: 25);
 20 C_iDTDPELC_{ii}RFLNLKC_{iii} (SEQ ID NO: 26);
 C_iDTDPELC_{ii}RFLNLPC_{iii} (SEQ ID NO: 27);
 C_iDTDPELC_{ii}RFLNLTC_{iii} (SEQ ID NO: 28);
 C_iNNNSELC_{ii}QFFGIEC_{iii} (SEQ ID NO: 29);
 C_iAGDVEWC_{ii}AFWNLAC_{iii} (SEQ ID NO: 30);
 25 C_iGDDELLC_{ii}WLGISTC_{iii} (SEQ ID NO: 31); and

wherein C_i, C_{ii} and C_{iii} represent first, second and third cysteine residues, respectively
 or a pharmaceutically acceptable salt thereof; such as:

- A-(SEQ ID NO: 1)-A (herein referred to as BCY2272);
 A-(SEQ ID NO: 1)-A-[Sar₆]-K-[FI] (herein referred to as BCY2310);
 30 [Mca]-G-[Sar₅]-A-(SEQ ID NO: 1)-A (herein referred to as BCY2309);
 [FI]-G-[Sar₅]-A-(SEQ ID NO: 1)-A (herein referred to as BCY2311);
 A-(SEQ ID NO: 2)-A (herein referred to as BCY2265);
 (SEQ ID NO: 3) (herein referred to as BCY2232);
 A-(SEQ ID NO: 3)-A (herein referred to as BCY2231);
 35 A-(SEQ ID NO: 3)-A-[Sar₆]-K-[FI] (herein referred to as BCY2310);
 A-(SEQ ID NO: 4)-A (herein referred to as BCY2230);
 A-(SEQ ID NO: 5)-A (herein referred to as BCY2266);

A-(SEQ ID NO: 6)-A (herein referred to as BCY2267);
 A-(SEQ ID NO: 7)-A (herein referred to as BCY2268);
 A-(SEQ ID NO: 8)-A (herein referred to as BCY2269);
 A-(SEQ ID NO: 9)-A (herein referred to as BCY2270);
 5 A-(SEQ ID NO: 10)-A (herein referred to as BCY2271);
 A-(SEQ ID NO: 11)-A (herein referred to as BCY2273);
 A-(SEQ ID NO: 12)-A (herein referred to as BCY2274);
 A-(SEQ ID NO: 13)-A (herein referred to as BCY2275);
 A-(SEQ ID NO: 14)-A (herein referred to as BCY2276);
 10 A-(SEQ ID NO: 14)-A-[Sar₆]-K-[FI] (herein referred to as BCY2315);
 A-(SEQ ID NO: 15)-A (herein referred to as BCY2277);
 A-(SEQ ID NO: 16)-A (herein referred to as BCY2278);
 A-(SEQ ID NO: 17)-A (herein referred to as BCY2279);
 A-(SEQ ID NO: 18)-A (herein referred to as BCY2280);
 15 A-(SEQ ID NO: 19)-A (herein referred to as BCY2282);
 A-(SEQ ID NO: 20)-A (herein referred to as BCY2283);
 A-(SEQ ID NO: 21)-A (herein referred to as BCY2284);
 A-(SEQ ID NO: 22)-A (herein referred to as BCY2285);
 A-(SEQ ID NO: 23)-A (herein referred to as BCY2286);
 20 A-(SEQ ID NO: 24)-A (herein referred to as BCY2287);
 A-(SEQ ID NO: 25)-A (herein referred to as BCY2288);
 A-(SEQ ID NO: 26)-A (herein referred to as BCY2289);
 A-(SEQ ID NO: 27)-A (herein referred to as BCY2290);
 A-(SEQ ID NO: 28)-A (herein referred to as BCY2291);
 25 A-(SEQ ID NO: 29)-A-[Sar₆]-K-[FI] (herein referred to as BCY2318);
 A-(SEQ ID NO: 30)-A-[Sar₆]-K-[FI] (herein referred to as BCY2319); and
 A-(SEQ ID NO: 31)-A-[Sar₆]-K-[FI] (herein referred to as BCY2320);

wherein FI represents fluorescein, Sar represents sarcosine and Mca represents methoxycoumarin-4-acetic acid; in particular:

30 A-(SEQ ID NO: 1)-A (BCY2272);
 A-(SEQ ID NO: 1)-A-[Sar₆]-K-[FI] (herein referred to as BCY2310); and
 [FI]-G-[Sar₅]-A-(SEQ ID NO: 1)-A (herein referred to as BCY2311).

9. The peptide ligand as defined in claim 7, which is specific for IL-17A and said loop
 35 sequences comprise three cysteine residues separated by two loop sequences both of
 which consist of 5 amino acids and comprises an amino acid sequence selected from:

C_iYEDEL_{C_{ii}}EFLGLC_{iii} (SEQ ID NO: 32);

C_iAEDEL C_{ii}EFLGL C_{iii} (SEQ ID NO: 33);
 C_iYSDEL C_{ii}EFLGL C_{iii} (SEQ ID NO: 34);
 C_iYEAEL C_{ii}EFLGL C_{iii} (SEQ ID NO: 35);
 C_iYEAEL C_{ii}AFLGL C_{iii} (SEQ ID NO: 36);
 5 C_iYEDAL C_{ii}EFLGL C_{iii} (SEQ ID NO: 37);
 C_iYEDEL C_{ii}AFLGL C_{iii} (SEQ ID NO: 38);
 C_iYEDEL C_{ii}E[2Nal]LGL C_{iii} (SEQ ID NO: 39);
 C_iYEDEL C_{ii}EWLGL C_{iii} (SEQ ID NO: 40);
 C_iYEDEL C_{ii}EFLAL C_{iii} (SEQ ID NO: 41);
 10 C_iYEDEL C_{ii}EFLNL C_{iii} (SEQ ID NO: 42);
 C_iYEDEL C_{ii}EWLNL C_{iii} (SEQ ID NO: 43);
 C_iSDLEL C_{ii}EFLGL C_{iii} (SEQ ID NO: 44);
 C_iDDYQL C_{ii}EFLGL C_{iii} (SEQ ID NO: 45);
 C_iEDKEL C_{ii}EFFGL C_{iii} (SEQ ID NO: 46);
 15 C_iPDLEL C_{ii}EFLGL C_{iii} (SEQ ID NO: 47);
 C_iDDELY C_{ii}FLNASC_{iii} (SEQ ID NO: 48);
 C_iPNELY C_{ii}FVTGNC_{iii} (SEQ ID NO: 49);
 C_iANELY C_{ii}FVTGNC_{iii} (SEQ ID NO: 50);
 C_iPNELAC_{ii}FVTGNC_{iii} (SEQ ID NO: 51);
 20 C_iPNELY C_{ii}FVAGNC_{iii} (SEQ ID NO: 52);
 C_iPNELY C_{ii}FVTGAC_{iii} (SEQ ID NO: 53);
 C_iDDSLY C_{ii}FLTGDC_{iii} (SEQ ID NO: 54); and
 C_iDDDLFC_{ii}FLTNSC_{iii} (SEQ ID NO: 55);

wherein 2Nal represents 2-naphthylalanine, C_i, C_{ii} and C_{iii} represent first, second and third
 25 cysteine residues, respectively or a pharmaceutically acceptable salt thereof; such as:

A-(SEQ ID NO: 32)-A (herein referred to as BCY2235);
 Ac-(SEQ ID NO: 32) (herein referred to as BCY2236);
 Ac-(SEQ ID NO: 33) (herein referred to as BCY2237);
 Ac-(SEQ ID NO: 34) (herein referred to as BCY2238);
 30 Ac-(SEQ ID NO: 35) (herein referred to as BCY2239);
 Ac-(SEQ ID NO: 36) (herein referred to as BCY2240);
 Ac-(SEQ ID NO: 37) (herein referred to as BCY2241);
 Ac-(SEQ ID NO: 38) (herein referred to as BCY2243);
 Ac-(SEQ ID NO: 39) (herein referred to as BCY2244);
 35 Ac-(SEQ ID NO: 40) (herein referred to as BCY2246);
 Ac-(SEQ ID NO: 41) (herein referred to as BCY2248);
 (SEQ ID NO: 41) (herein referred to as BCY2249);

Ac-(SEQ ID NO: 42) (herein referred to as BCY2250);
 Ac-(SEQ ID NO: 43) (herein referred to as BCY2252);
 A-(SEQ ID NO: 44)-A (herein referred to as BCY2258);
 A-(SEQ ID NO: 45)-A (herein referred to as BCY2259);
 5 A-(SEQ ID NO: 46)-A (herein referred to as BCY2260);
 A-(SEQ ID NO: 47)-A (herein referred to as BCY2262);
 A-(SEQ ID NO: 48)-A (herein referred to as BCY2292);
 A-(SEQ ID NO: 49)-A (herein referred to as BCY2293);
 A-(SEQ ID NO: 49)-A-[Sar₆]-K-[FI] (herein referred to as BCY2316);
 10 Ac-(SEQ ID NO: 49) (herein referred to as BCY2294);
 Ac-(SEQ ID NO: 50) (herein referred to as BCY2295);
 Ac-(SEQ ID NO: 51) (herein referred to as BCY2299);
 Ac-(SEQ ID NO: 52) (herein referred to as BCY2302);
 Ac-(SEQ ID NO: 53) (herein referred to as BCY2304);
 15 A-(SEQ ID NO: 54)-A (herein referred to as BCY2305);
 A-(SEQ ID NO: 54)-A-[Sar₆]-K-[FI] (herein referred to as BCY2317); and
 A-(SEQ ID NO: 55)-A (herein referred to as BCY2306);

wherein FI represents fluorescein and Sar represents sarcosine.

10. The peptide ligand as defined in claim 7, which is specific for IL-17E and said loop sequences comprise three cysteine residues separated by two loop sequences both of which consist of 5 amino acids and comprises an amino acid sequence selected from:

C_iGYDY_YC_{ii}ALYD_IC_{iii} (SEQ ID NO: 56); and

C_iLWKDNC_{ii}THWSLC_{iii} (SEQ ID NO: 57);

25 wherein C_i, C_{ii} and C_{iii} represent first, second and third cysteine residues, respectively or a pharmaceutically acceptable salt thereof; such as:

A-(SEQ ID NO: 56)-A (herein referred to as BCY2240); and

A-(SEQ ID NO: 57)-A (herein referred to as BCY2441); in particular:

A-(SEQ ID NO: 56)-A (BCY2240).

11. The peptide ligand as defined in claim 7, which is specific for IL-17F and said loop sequences comprise three cysteine residues separated by two loop sequences both of which consist of 6 amino acids and comprises an amino acid sequence which is:

C_iDHSD_FIC_{ii}WLNN_FNC_{iii} (SEQ ID NO: 58);

35 wherein C_i, C_{ii} and C_{iii} represent first, second and third cysteine residues, respectively or a pharmaceutically acceptable salt thereof; such as:

A-(SEQ ID NO: 58)-A (herein referred to as BCY2203); and

A-(SEQ ID NO: 58)-A-[Sar₆]-K-[FI] (herein referred to as BCY2222);
wherein FI represents fluorescein and Sar represents sarcosine.

12. The peptide ligand as defined in claim 7, which is specific for IL-17F and said loop sequences comprise three cysteine residues separated by two loop sequences one of which consists of 2 amino acids and the other of which consists of 7 amino acids and comprises an amino acid sequence which is:

C_iGQC_{ii}SFSYWLNC_{iii} (SEQ ID NO: 59);

wherein C_i, C_{ii} and C_{iii} represent first, second and third cysteine residues, respectively

or a pharmaceutically acceptable salt thereof; such as:

A-(SEQ ID NO: 59)-A (herein referred to as BCY2202); and

A-(SEQ ID NO: 59)-A-[Sar₆]-K-[FI] (herein referred to as BCY2217);

wherein FI represents fluorescein and Sar represents sarcosine; in particular:

A-(SEQ ID NO: 59)-A (BCY2202).

13. The peptide ligand as defined in any one of claims 1 to 12, wherein the pharmaceutically acceptable salt is selected from the free acid or the sodium, potassium, calcium, ammonium salt.

14. The peptide ligand as defined in any one of claims 1 to 13, wherein the IL-17 is human IL-17.

15. A drug conjugate comprising a peptide ligand as defined in any one of claims 1 to 14, conjugated to one or more effector and/or functional groups.

16. A pharmaceutical composition which comprises the peptide ligand of any one of claims 1 to 14 or the drug conjugate of claim 15, in combination with one or more pharmaceutically acceptable excipients.

17. The peptide ligand as defined in any one of claims 1 to 14 or the drug conjugate as defined in claim 15, for use in preventing, suppressing or treating a disease or disorder mediated by IL-17.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2019/053534

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P35/00 A61K38/00 C07K7/08 C07K14/54
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61P A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KALE SANGRAM S ET AL: "Cyclization of peptides with two chemical bridges affords large scaffold diversities", NATURE CHEMISTRY, NATURE PUBLISHING GROUP UK, LONDON, vol. 10, no. 7, 30 April 2018 (2018-04-30), pages 715-723, XP036530421, ISSN: 1755-4330, DOI: 10.1038/S41557-018-0042-7 [retrieved on 2018-04-30]	1-7,16
Y	Abstract; Fig. 6 ----- -/--	1-17



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

2 March 2020

Date of mailing of the international search report

11/03/2020

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

López García, F

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2019/053534

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHRISTIAN HEINIS ET AL: "Phage-encoded combinatorial chemical libraries based on bicyclic peptides", NATURE CHEMICAL BIOLOGY, vol. 5, no. 7, 31 May 2009 (2009-05-31), pages 502-507, XP55562241, Basingstoke ISSN: 1552-4450, DOI: 10.1038/nchembio.184 cited in the application the whole document	1-14,16, 17
Y	----- SHIYU CHEN ET AL: "Peptide Ligands Stabilized by Small Molecules", ANGEWANDTE CHEMIE, INTERNATIONAL EDITION, vol. 53, no. 6, 3 February 2014 (2014-02-03), pages 1602-1606, XP55356354, DE ISSN: 1433-7851, DOI: 10.1002/anie.201309459 cited in the application the whole document	1-14,16, 17
Y	----- WO 2016/067035 A1 (BICYCLE THERAPEUTICS LTD [GB]) 6 May 2016 (2016-05-06) cited in the application Abstract; p. 23	1-17
E	----- WO 2019/243350 A1 (BICYCLETX LTD [GB]) 26 December 2019 (2019-12-26) the whole document -----	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2019/053534

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016067035	A1	06-05-2016	
		AU 2015340300 A1	11-05-2017
		BR 112017008575 A2	26-12-2017
		CA 2965754 A1	06-05-2016
		CN 107148425 A	08-09-2017
		EP 3215518 A1	13-09-2017
		JP 2018502825 A	01-02-2018
		KR 20170073611 A	28-06-2017
		RU 2017118326 A	29-11-2018
		RU 2019138346 A	13-12-2019
		SG 11201702845Q A	30-05-2017
		US 2018280525 A1	04-10-2018
		WO 2016067035 A1	06-05-2016

WO 2019243350	A1	26-12-2019	NONE
