

CLAIMS

1. A peptide ligand specific for EphA2 comprising a polypeptide comprising three cysteine residues, separated by two loop sequences, and a non-aromatic molecular scaffold which forms covalent bonds with the cysteine residues of the polypeptide such that two polypeptide loops are formed on the molecular scaffold, wherein the peptide ligand is a peptide ligand which comprises an amino acid sequence other than:

Ci(HyP)LVNPLCiiLHP(D-Asp)W(HArg)Ciii (SEQ ID NO: 1), wherein HyP is hydroxyproline, HArg is homoarginine and Ci, Cii and Ciii represent first, second and third cysteine residues, respectively or a pharmaceutically acceptable salt thereof.

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

3. The peptide ligand as defined in claim 1 or claim 2, 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 (such as those listed in Table 4).

4. The peptide ligand as defined in claim 1 or claim 2, wherein said loop sequences comprise three cysteine residues separated by two loop sequences both of which consist of 5 amino acids (such as those listed in Tables 3 and 4).

5. The peptide ligand as defined in claim 1 or claim 2, wherein said loop sequences comprise three cysteine residues separated by two loop sequences both of which consist of 6 amino acids (such as those listed in Tables 3 to 5 and 10).

6. The peptide ligand as defined in claim 1 or claim 2, wherein said loop sequences comprise three cysteine residues separated by two loop sequences one of which consists of 7 amino acids and the other of which consists of 3 amino acids (such as those listed in Table 4).

7. The peptide ligand as defined in claim 1 or claim 2, wherein said loop sequences comprise three cysteine residues separated by two loop sequences one of which consists of 6 amino acids and the other of which consists of 7 amino acids (such as those listed in Table 5).

8. The peptide ligand as defined in any one of claims 1 to 7, wherein the peptide ligand comprises an amino acid sequence selected from:



wherein X_1 and X_2 represent the amino acid residues between the cysteine residues listed in Tables 3 to 5 and 10 and C_i , C_{ii} and C_{iii} represent first, second and third cysteine residues, respectively or a pharmaceutically acceptable salt thereof.

9. The peptide ligand as defined in any one of claims 1 to 8, wherein the peptide ligand comprises a peptide ligand selected from Tables 3 to 5 and 10.

10. The peptide ligand as defined in any one of claims 1 to 8, wherein said loop sequences comprise three cysteine residues separated by two loop sequences both of which consist of 6 amino acids and the peptide ligand has the following amino acid sequence:



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

11. The peptide ligand as defined in claim 10, wherein said loop sequences comprise three cysteine residues separated by two loop sequences both of which consist of 6 amino acids and the peptide ligand has the following amino acid sequence:



(BCY6014; Compound 67);

wherein Sar is sarcosine, HArg is homoarginine and HyP is hydroxyproline.

12. The peptide ligand as defined in any one of claims 1 to 11, wherein the molecular scaffold is selected from 1,1',1''-(1,3,5-triazinane-1,3,5-triyl)triprop-2-en-1-one (TATA) and the peptide ligand is selected from any one of the peptide ligands listed in Tables 3, 4, 5 and 10.

13. The peptide ligand as defined in any one of claims 1 to 11, wherein the molecular scaffold is selected from 1,1',1''-(1,3,5-triazinane-1,3,5-triyl)triprop-2-en-1-one (TATA) and the peptide ligand is



(BCY6014; Compound 67);

wherein Sar is sarcosine, HArg is homoarginine and HyP is hydroxyproline.

14. The peptide ligand as defined in any one of claims 1 to 13, wherein said peptide ligand is selected from:

ACMNDWWCAMGWKCA-Sar6-K(FI) ((SEQ ID NO: 3)-Sar6-K(FI));
ACVPDRRCAYMNVCA-Sar6-K(FI) ((SEQ ID NO: 4)-Sar6-K(FI));
ACVVDGRCAVMNVCA-Sar6-K(FI) ((SEQ ID NO: 5)-Sar6-K(FI));
ACVVDSRCAYMNVCA-Sar6-K(FI) ((SEQ ID NO: 6)-Sar6-K(FI));
ACVPDSRCAYMNVCA-Sar6-K(FI) ((SEQ ID NO: 7)-Sar6-K(FI));
ACYVGKECAIRNVCA-Sar6-K(FI) ((SEQ ID NO: 8)-Sar6-K(FI));
ACYVGKECAYMNVCA-Sar6-K(FI) ((SEQ ID NO: 9)-Sar6-K(FI));
FI-G-Sar5-ACYVGKECAYMNVCA (FI-G-Sar5-(SEQ ID NO: 9));
FI-(β -Ala)-Sar10-ARDCPLVNPLCLHPGWTC (FI-(β -Ala)-Sar10-(SEQ ID NO: 10));
FI-(β -Ala)-Sar10-A(HArg)DCPLVNPLCLHPGWTC (FI-(β -Ala)-Sar10-(SEQ ID NO: 11));
Ac-CPLVNPLCLHPGWTCCLHG-Sar6-(D-K[F]) (Ac-(SEQ ID NO: 12)-Sar6-(D-K[F]));
Ac-CPLVNPLCLHPGWTC(D-His)G-Sar6-(D-K[F]) (Ac-SEQ ID NO: 13)-Sar6-(D-K[F]);
Ac-CPLVNPLCLHPGWSCRQG-Sar6-(D-K[F]) (Ac-(SEQ ID NO: 14)-Sar6-(D-K[F]));
Ac-CPLVNPLCLHPGWSC(HArg)GQ-Sar6-(D-K[F]) (Ac-(SEQ ID NO: 15)-Sar6-(D-K[F]));
ACMNDWWCAMGWKCA (SEQ ID NO: 3);
ACVPDRRCAYMNVCA (SEQ ID NO: 4);
(β -Ala)-Sar10-ACVPDRRCAYMNVCA ((β -Ala)-Sar10-(SEQ ID NO: 16));
DLRCGGDPRCAYMNVCA (SEQ ID NO: 17);
SRPCVIDSRCAYMNVCA (SEQ ID NO: 18);
ESRCSPDARCAVMNVCA (SEQ ID NO: 19);
HSGCRPDPRCAYMNVCA (SEQ ID NO: 20);
GSGCKPDSRCAYMNVCA (SEQ ID NO: 21);
ETVCLPDSRCAYMNVCA (SEQ ID NO: 22);
GQVCIVDARCAVMNVCA (SEQ ID NO: 23);
ACVPDRRCAFENVCDH (SEQ ID NO: 24);
ACVPDRRCAFMNVCDR (SEQ ID NO: 25);
ACVPDRRCAFQDVCDHE (SEQ ID NO: 26);
ACVPDRRCAFRDVCLTG (SEQ ID NO: 27);
ACYVGKECAYMNVCA (SEQ ID NO: 9);
ACQPSNHCAFMYNYCA (SEQ ID NO: 28);
ACSPTPACAVQNLCA (SEQ ID NO: 29);

ACTSCWAYPDSFCA (SEQ ID NO: 30);
 ACTKPTGFCAYPDITICA (SEQ ID NO: 31);
 ACRGEWGYCAYPDITICA (SEQ ID NO: 32);
 ACRNWGMYCAYPDITICA (SEQ ID NO: 33);
 ACPDWGKYCAYPDITICA (SEQ ID NO: 34);
 ACRVYGPYCAYPDITICA (SEQ ID NO: 35);
 ACSSCWAYPDSVCA (SEQ ID NO: 36);
 ACQSCWAYPDITYCA (SEQ ID NO: 37);
 ACGFMGLEPCETFCA (SEQ ID NO: 38);
 ACGFMGLVPCEVHCA (SEQ ID NO: 39);
 ACGFMGLEPCCEMVCA (SEQ ID NO: 40);
 ACGFMGLEPCVITYCA (SEQ ID NO: 41);
 ACGFMGLEPCELVCA (SEQ ID NO: 42);
 ACGFMGLVPCNVFCA (SEQ ID NO: 43);
 ACGFMGLEPCELFCA (SEQ ID NO: 44);
 ACGFMGLEPCELFCEMPK (SEQ ID NO: 45);
 ACGFMGLEPCELYCA (SEQ ID NO: 46);
 ACGFMGLEPCELYCAHT (SEQ ID NO: 47);
 ACGFMGLEPCEMYCA (SEQ ID NO: 48);
 ACGFMGLVPCELYCADN (SEQ ID NO: 49);
 ACPLVNPLCLTSGWKCA (SEQ ID NO: 50);
 ACPMVNPLCLHPGWICA (SEQ ID NO: 51);
 ACPLVNPLCLHPGWICA (SEQ ID NO: 52);
 ACPLVNPLCLHPGWRCA (SEQ ID NO: 53);
 ACPLVNPLCLNPGWTCA (SEQ ID NO: 54);
 ACPLVNPLCLVPGWSCA (SEQ ID NO: 55);
 ACPLVNPLCLLDGWTCA (SEQ ID NO: 56);
 ACPLVNPLCLMPGWGCA (SEQ ID NO: 57);
 ACPLVNPLCMIGNWTCA (SEQ ID NO: 58);
 ACPLVNPLCLMTGWSCA (SEQ ID NO: 59);
 ACPLVNPLCMMGGWKCA (SEQ ID NO: 60);
 ACPLVNPLCLYGSWKCA (SEQ ID NO: 61);
 ACPLVNPLCLHPGWTCA (SEQ ID NO: 62);
 ARDCPLVNPLCLHPGWTCA (SEQ ID NO: 63);
 ((β -Ala)-Sar10-A(HArg)DCPLVNPLCLHPGWTCA ((β -Ala)-Sar10-(SEQ ID NO: 11);
 Ac-ARDCPLVNPLCLHPGWTCA-Sar6-(D-K) (Ac-(SEQ ID NO: 63)-Sar6-(D-K));

Ac-A(HArg)DCPLVNPLCLHPGWTCA- Sar6-(D-K) (Ac-(SEQ ID NO: 11)-A-Sar6-(D-K));
 RPACPLVNPLCLHPGWTCA (SEQ ID NO: 64);
 RPPCPLVNPLCLHPGWTCA (SEQ ID NO: 65);
 KHSCPLVNPLCLHPGWTCA (SEQ ID NO: 66);
 ACPLVNPLCLHPGWTCLHG (SEQ ID NO: 67);
 Ac-CPLVNPLCLHPGWTCLHG (Ac-(SEQ ID NO: 12));
 (β -Ala)-Sar10-ACPLVNPLCLHPGWTCLHG ((β -Ala)-Sar10-(SEQ ID NO: 67));
 (β -Ala)-Sar10-ACPLVNPLCLHPGWTCL(D-His)G ((β -Ala)-Sar10-(SEQ ID NO: 68));
 Ac-CPLVNPLCLHPGWTCLHG-Sar6-(D-K) (Ac-(SEQ ID NO: 12)-Sar6-(D-K));
 Ac-CPLVNPLCLHPGWTCL(D-His)G-Sar6-(D-K) (Ac-(SEQ ID NO: 13)- Sar6-(D-K));
 ACPLVNPLCLHPG(2NaI)TCLHG (SEQ ID NO: 69);
 RHDCPLVNPLCLLPGWTC (SEQ ID NO: 70);
 TPRCPLVNPLCLMPGWTC (SEQ ID NO: 71);
 ACPLVNPLCLAPGWTC (SEQ ID NO: 72);
 ACPLVNPLCLAPGWTCRS (SEQ ID NO: 73);
 ACPLVNPLCLEPGWTC (SEQ ID NO: 74);
 ACPLVNPLCLEPGWTCAR (SEQ ID NO: 75);
 ACPLVNPLCLHPGWSCA (SEQ ID NO: 76);
 ACPLVNPLCLHPGWSCRQ (SEQ ID NO: 77);
 Ac-CPLVNPLCLHPGWSCRQ (Ac-(SEQ ID NO: 14));
 (β -Ala)-Sar10-ACPLVNPLCLHPGWSCRQ ((β -Ala)-Sar10-(SEQ ID NO: 77);
 (β -Ala)-Sar10-ACPLVNPLCLHPGWSC(HArg)GQ ((β -Ala)-Sar10-(SEQ ID NO: 78));
 Ac-CPLVNPLCLHPGWSCRQ-Sar6-(D-K) (Ac-(SEQ ID NO: 14)-Sar6-(D-K));
 Ac-CPLVNPLCLHPGWSC(HArg)GQ-Sar6-(D-K) (Ac-(SEQ ID NO: 15) -Sar6-(D-K));
 ACPLVNPLCLHPG(2NaI)SCRQ (SEQ ID NO: 79);
 ACPLVNPLCLTPGWTCNT (SEQ ID NO: 80);
 ACPMVNPLCLHPGWKCA (SEQ ID NO: 81);
 ACPMVNPLCLTPGWICA (SEQ ID NO: 82);
 ACPMVNPLCLHPGWTC (SEQ ID NO: 83);
 (β -Ala)-Sar10-H(D-Asp)VT-C(Aib)(1NaI)G(Aib)F(1NaI)CP(tBuGly)N(HArg)P(D-Asp)C
 ((β -Ala)-Sar10-(SEQ ID NO: 84));
 (β -Ala)-Sar10-A(HArg)DC(HyP)(Hse(Me))VNPLCLHP(D-Asp)W(HArg)C ((β -Ala)-
 Sar10-(SEQ ID NO: 85));
 (β -Ala)-Sar10-A(HArg)DC(HyP)(Hse(Me))VNPLCLHP(D-Asp)WTC ((β -Ala)-Sar10-
 (SEQ ID NO: 86));

(β -Ala)-Sar10-A(HArg)DC(HyP)LVNPLCLHP(D-Ala)WTC ((β -Ala)-Sar10-(SEQ ID NO: 87));
 (β -Ala)-Sar10-A(HArg)DCPLVNPLCLHP(D-Ala)WTC ((β -Ala)-Sar10-(SEQ ID NO: 88));
 (β -Ala)-Sar10-ARDC(HyP)LVNPLCLHPGWTC ((β -Ala)-Sar10-(SEQ ID NO: 89));
 (β -Ala)-Sar10-ARDCPLVNPLCL(D-3,3-DPA)PGWTC ((β -Ala)-Sar10-(SEQ ID NO: 90));
 (β -Ala)-Sar10-ARDCPLVNPLCLHPGWTCCLH ((β -Ala)-Sar10-(SEQ ID NO: 91))
 Ac-(SEQ ID NO: 12)-Sar6-(D-K[Ac]);
 (β -AlaSO₃H)-Sar4-(Cya)-Sar4-(Cya)-A(HArg)DCPLVNPLCLHP(D-Cya)WTC ((β -AlaSO₃H)-Sar4-(Cya)-Sar4-(Cya)-(SEQ ID NO: 92));
 (β -Ala)-Sar10-ARDCPLVNPLCLHPGWTC ((β -Ala)-Sar10-(SEQ ID NO: 10));
 A(HArg)DCPLVNPLCLHPGWTC (SEQ ID NO: 11);
 (β -Ala)-Sar5-(SEQ ID NO: 11);
 (β -AlaSO₃H)-Sar10-(SEQ ID NO: 11);
 (β -Ala)-Sar10-A(D-Arg)DC(HyP)LVNPLCL(D-3,3-DPA)P(D-Asp)W(HArg)C ((β -Ala)-Sar10-(SEQ ID NO: 93)); and
 (β -AlaSO₃H)-Sar5-(SEQ ID NO: 11);
 or a pharmaceutically acceptable salt thereof.

15. The peptide ligand as defined in any one of claims 1 to 13, wherein said peptide ligand is (β -Ala)-Sar10-A(HArg)DCPLVNPLCLHPGWTC ((β -Ala)-Sar10-(SEQ ID NO: 11)) or a pharmaceutically acceptable salt thereof.

16. The peptide ligand as defined in any one of claims 1 to 15, wherein the pharmaceutically acceptable salt is selected from a free acid or a sodium, potassium, calcium, ammonium salt.

17. The peptide ligand as defined in any one of claims 1 to 16, wherein the EphA2 is human EphA2.

18. A drug conjugate comprising a peptide ligand as defined in any one of claims 1 to 17, conjugated to one or more effector and/or functional groups.

19. The drug conjugate as defined in claim 18, wherein said functional group is a cytotoxic agent selected from DM1 or monomethyl auristatin E (MMAE).

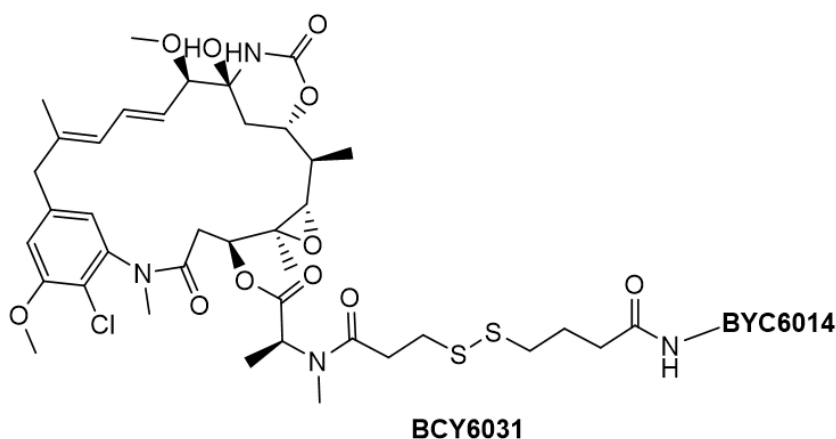
20. The drug conjugate as defined in claim 18 or claim 19, which additionally comprises a linker between said peptide ligand and said cytotoxic agent.

21. The drug conjugate as defined in claim 20, wherein said cytotoxic agent is MMAE and the linker is selected from: -Val-Cit-, -Trp-Cit-, -Val-Lys-, -D-Trp-Cit-, -Ala-Ala-Asn-, D-Ala-Phe-Lys- or -Glu-Pro-Cit-Gly-hPhe-Tyr-Leu- (SEQ ID NO: 98).

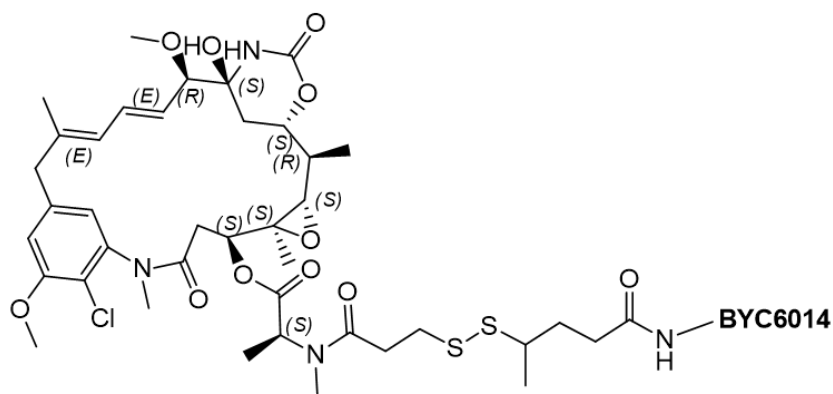
22. The drug conjugate as defined in claim 21, wherein said cytotoxic agent is MMAE and the linker is -Val-Cit-.

23. The drug conjugate as defined in claim 20, wherein said cytotoxic agent is DM1 and the linker is selected from: -S-S-, -SS(SO₃H)-, -SS-(Me)-, -(Me)-SS-(Me)-, -SS-(Me₂)- or -SS-(Me)-SO₃H-.

24. The drug conjugate as defined in any one of claims 18 to 23, which is selected from any one of BCY6031:



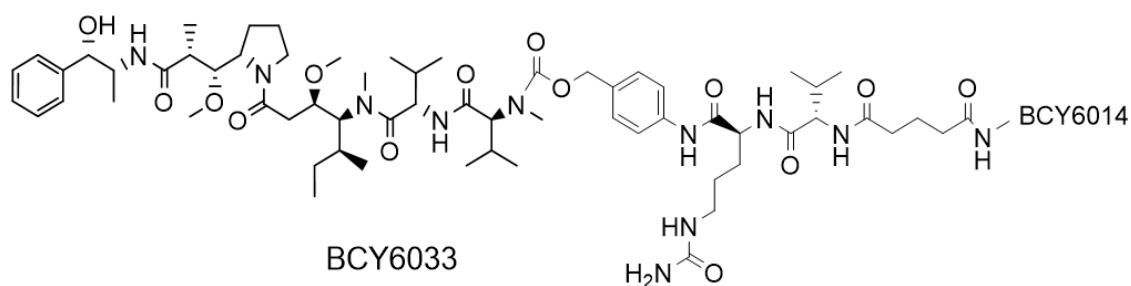
and BCY6032:



BCY6032

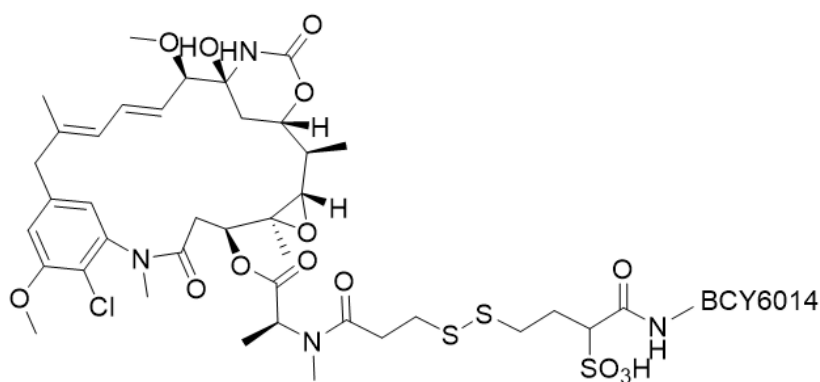
the Bicycle drug conjugates (BDCs) listed in Tables 11 or 13; or

BCY6033:



BCY6033

and BCY6082:



BCY6082

wherein BCY6014 is $(\beta\text{-Ala})\text{-Sar}_{10}\text{-A(HArg)D-C}_i\text{PLVNPLC}_{ii}\text{LHPGWTC}_{iii}$ ($(\beta\text{-Ala})\text{-Sar}_{10}\text{-(SEQ ID NO: 11)}$).

25. The drug conjugate as defined in claim 24, which is selected from any one of: BCY6031, BCY6033, and BCY6082,.

26. A pharmaceutical composition which comprises the peptide ligand of any one of claims 1 to 17 or the drug conjugate of any one of claims 18 to 25, in combination with one or more pharmaceutically acceptable excipients.
27. The drug conjugate as defined in any one of claims 18 to 25, for use in suppressing or treating a disease or disorder characterised by overexpression of EphA2 in diseased tissue.
28. The drug conjugate as defined in any one of claims 18 to 25, for use in suppressing or treating cancer.
29. The drug conjugate for use as defined in claim 28, wherein the cancer is selected from: prostate cancer, lung cancer (such as non-small cell lung carcinomas (NSCLC)), breast cancer (such as triple negative breast cancer), gastric cancer, ovarian cancer, oesophageal cancer, multiple myeloma and fibrosarcoma.
30. Use of a drug conjugate as defined in any one of claims 18 to 25 in the manufacture of a medicament for suppressing or treating cancer in a patient in need thereof, wherein said patient is identified as having an increased copy number variation (CNV) of EphA2.