The disclosure provides~~, in another aspect,~~ an isolated antibody that binds to human HER3 and that binds to human HER4, wherein the antibody has one or more of the following properties:

a) the antibody binds to the amino acid sequence of SEQ ID NO:1; and/or

b) the antibody binds to the amino acid sequence SEQ ID NO:1 in activated HER3; and/or

c) the antibody binds within an amino acid sequence of PQPLVYNKLTFQLEPNPHT (SEQ ID NO:1) which is comprised in a polypeptide selected from the group consisting of:

SEQ ID NO: 13	TtSlyD-FKBP-Her3,
SEQ ID NO: 17	TtSlyDcas-Her3,
SEQ ID NO: 18	TtSlyDcys-Her3,
SEQ ID NO: 19	TgSlyDser-Her3, and
SEQ ID NO: 20	TgSlyDcys-Her3;

and/or

d) the antibody binds to the ß-hairpin region of HER3; and/or

e) the antibody inhibits the heterodimerisation of HER3/HER2 heterodimers; and/or

f) the antibody binds to HER3-ECD with a ratio of the association constant (Ka) in presence of Heregulin (Ka (+Heregulin)) and in absence of Heregulin (Ka (-Heregulin)) of 4.0 or higher (Ka (+Heregulin))/(Ka (-Heregulin)); and/or

g) the antibody binds to HER3-ECD with a ratio of the Molar Ratio MR of binding in presence of Heregulin (MR (+Heregulin)) and in absence of Heregulin (MR (-Heregulin)) of 2.0 or higher (MR (+Heregulin))/ (MR (-Heregulin)); and/or

h) the antibody specifically binds to the amino acid sequence of SEQ ID NO:2; and/or

i) the antibody binds to the amino acid sequence SEQ ID NO:2 in activated HER4; and/or

j) the antibody binds within an amino acid sequence of PQTFVYNPTTFQLEHNFNA (SEQ ID NO:2) which is comprised in a polypeptide selected from the group consisting of:

SEQ ID NO: 21	TtSlyDcas-Her4,
SEQ ID NO: 22	TtSlyDcys-Her4,

The disclosure further provides, in another aspect, the anti-HER3/HER4 antibody described herein, or the immunoconjugate comprising the anti-HER3/HER4 antibody and a cytotoxic agent, for use as a medicament. The disclosure further provides, in another aspect, the anti-HER3/HER4 antibody described herein, or the immunoconjugate comprising the anti-HER3/HER4 antibody and a cytotoxic agent, for use in treating cancer. The disclosure further provides, in another aspect, the anti-HER3/HER4 antibody described herein for use in inhibition of HER3/HER2 dimerization.

The disclosure further provides, in another aspect, use of such anti-HER3/HER4 antibody, or an immunoconjugate comprising the anti-HER3/HER4 antibody and a cytotoxic agent, in the manufacture of a medicament. Such use wherein the medicament is for treatment of cancer.Such use wherein the medicament is for the inhibition of HER3/HER2 dimerization.

The disclosure further provides a method of treating an individual having cancer comprising administering to the individual an effective amount of the anti-HER3/HER4 antibody described herein, or an immunoconjugate comprising the anti-HER3/HER4 antibody and a cytotoxic agent.

The disclosure further provides a method of inducing apoptosis in a cancer cell in an individual sufferning from cancer comprising administering to the individual an effective amount of an immunoconjugate comprising the anti-HER3/HER4 antibody described herein and a cytotoxic agent, thereby inducing apoptosis in a cancer cell in the individual.

One embodiment of the disclosure is ~~The disclosure further provides, in another aspect,~~ a polypeptide selected from the group consisting of:

i) SEQ ID NO: 13 TtSlyD-FKBP-Her3,
ii) SEQ ID NO: 17 TtSlyDcas-Her3,
iii) SEQ ID NO: 18 TtSlyDcys-Her3,
iv) SEQ ID NO: 19 TgSlyDser-Her3, and
v) SEQ ID NO: 20 TgSlyDcys-Her3,

which polypeptide comprises the amino acid sequence of SEQ ID NO:1

One embodiment of the disclosure is ~~The disclosure further provides, in another aspect,~~ a polypeptide selected from the group consisting of:

i) SEQ ID NO: 21 TtSlyDcas-Her4,
ii) SEQ ID NO: 22 TtSlyDcys-Her4,

and thereby selecting an antigen binding protein that binds within an amino acid sequence of PQPLVYNKLTFQLEPNPHT (SEQ ID NO:1) and within an amino acid sequence of PQTFVYNPTTFQLEHNFNA (SEQ ID NO:2).

2. An antigen binding protein obtained by the selection method of claim 1.

3. The method of claim 1, or the antigen binding protein of claim 2 wherein the antigen binding protein is an antibody.

4. An isolated antigen binding protein that binds to human HER3 and binds to human HER4, wherein the antigen binding protein binds within an amino acid sequence of PQPLVYNKLTFQLEPNPHT (SEQ ID NO:1) of human HER3 and binds within an amino acid sequence of PQTFVYNPTTFQLEHNFNA (SEQ ID NO:2) of human HER4.

5. The antigen binding protein of claim 4

a) wherein the antigen binding protein binds to a polypeptide of

SEQ ID NO: 18 TtSlyDcys-Her3,

and

b) wherein the antigen binding protein binds to a polypeptide of

SEQ ID NO: 22 TtSlyDcys-Her4.

6. The antigen binding protein of claims 4 or 5 wherein the antigen binding protein is an antibody.

~~7. An isolated antibody that binds to human HER3 and that binds to human HER4, wherein the antibody has one or more of the following properties:~~

~~a) the antibody binds to the amino acid sequence of SEQ ID NO:1; and/or~~

~~b) the antibody binds to the amino acid sequence SEQ ID NO:1 in activated HER3; and/or~~

~~c) the antibody binds within an amino acid sequence of PQPLVYNKLTFQLEPNPHT (SEQ ID NO:1) which is comprised in a polypeptide selected from the group consisting of:~~

SEQ ID NO: 13 TtSlyD-FKBP-Her3,

SEQ ID NO: 17 TtSlyDcas-Her3,

SEQ ID NO: 18 TtSlyDcys-Her3,

SEQ ID NO: 19 TgSlyDser-Her3, and

SEQ ID NO: 20 TgSlyDcys-Her3;
and/or

d) the antibody binds to the ß-hairpin region of HER3; and/or

e) the antibody inhibits the heterodimerisation of HER3/HER2 heterodimers; and/or

f) the antibody binds to HER3-ECD with a ratio of the association constant (Ka) in presence of Heregulin (Ka (+Heregulin)) and in absence of Heregulin (Ka (-Heregulin)) of 4.0 or higher (Ka (+Heregulin))/(Ka (-Heregulin)); and/or

g) the antibody binds to HER3-ECD with a ratio of the Molar Ratio MR of binding in presence of Heregulin (MR (+Heregulin)) and in absence of Heregulin (MR (-Heregulin)) of 2.0 or higher (MR (+Heregulin))/ (MR (-Heregulin)); and/or

h) the antibody binds to the amino acid sequence of SEQ ID NO:2; and/or

i) the antibody binds to the amino acid sequence SEQ ID NO:2 in activated HER4; and/or

j) the antibody binds within an amino acid sequence of PQTFVYNPTTFQLEHNFNA (SEQ ID NO:2) which is comprised in a polypeptide selected from the group consisting of:

SEQ ID NO: 21 TtSlyDcas-Her4,

SEQ ID NO: 22 TtSlyDcys-Her4,

SEQ ID NO: 23 TgSlyDser-Her4, and

SEQ ID NO: 24 TgSlyDcys-Her4;

and/or

k) the antibody binds to the ß-hairpin region of HER4; and/or

l) the antibody binds to HER4-ECD with a ratio of the association constant (Ka) in presence of Heregulin (Ka (+Heregulin)) and in absence of Heregulin (Ka (-Heregulin)) of 20.0 or higher (Ka (+Heregulin))/(Ka (-Heregulin)); and/or

m) the antibody binds to HER4-ECD with a ratio of the Molar Ratio MR of binding in presence of Heregulin (MR (+Heregulin)) and in absence of Heregulin (MR (-Heregulin)) of 5.0 or higher (MR (+Heregulin))/ (MR (-Heregulin)); and/or

n) the antibody shows as monovalent Fab fragment the same or higher biological activity as compared to its bivalent parent full length antibody; and/or

o) the antibody inhibits the HER3 phosporylation in MCF-7 cells; and/or

p) the antibody does not compete for binding to HER3 with Heregulin/ induces binding of Heregulin to HER3; and/or

q) the antibody inhibits the proliferation of MDA-MB-175 tumor cells; and/or

r) the antibody shows tumor growth inhibitory activity in vivo; and/or

s) the antibody binds with an affinity of a KD value $\leq 1 \times 10^{-8}$ M to HER3-ECD; and/or

t) the antibody binds with an affinity of a KD value $\leq 1 \times 10^{-8}$ M to HER4-ECD; and/or

u) the antibody binds to a polypeptide consisting of VYNKLTFQLEP (SEQ ID NO:43) and to a polypeptide consisting of VYNPTTFQLE (SEQ ID NO:44); and/or

~~v) the antibody binds to a polypeptide consisting of VYNKLTFQLEP (SEQ ID NO:43); and/or~~

~~w) the antibody binds to a polypeptide consisting of VYNPTTFQLE (SEQ ID NO:44); and/or~~

~~x) the antibody binds in a FACS assay to HER3 expressing T47D cells; and wherein the antibody shows an at least 25% higher percentage of internalization in the presence of Heregulin as compared to the percentage of internalization in the presence of Heregulin when measured after 1 h after antibody exposure.~~

87. An antibody that binds to human HER3 and that binds human HER4, wherein the antibody binds to a polypeptide with a length of 15 amino acids comprising the amino acid sequence VYNKLTFQLEP (SEQ ID NO:43) and to a polypeptide with a length of 15 amino acids comprising the amino acid sequence VYNPTTFQLE (SEQ ID NO:44).

98. The antibody of any one of claims 6 to 87, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:25; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:26, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:27.

~~109~~. The antibody of claims any one of claims 6 to 98, comprising (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:28; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:29; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:30.

~~110~~. The antibody of any one of claims 6 to 87, wherein the antibody comprises

i) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:25;

(b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:26;

(c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:27;

(d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:28;

(e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:29; and

(f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:30;

ii) or a humanized variant of the HVRs of the antibody under i) (a), (b), (d) and/or (e).

~~12~~11. The antibody of claims any one of claims 6 to ~~8~~7, or ~~11~~10, wherein the antibody comprises

i) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:38;

(b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:39;

(c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:27;

(d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:40;

(e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:41; and

(f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:30; or

ii) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:38;

(b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:39;

(c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:27;

(d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:40;

(e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:42; and

(f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:30; or

iii) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:25;

(b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:39;

(c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:27;

(d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:40;

(e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:41; and

(f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:30; or

iv) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:25;

(b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:39;

(c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:27;

(d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:40;

(e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:42; and

(f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:30.

~~13~~12. An antibody comprising :
a) a VH sequence of SEQ ID NO:33 and a VL sequence of SEQ ID NO:36; or
b) a VH sequence of SEQ ID NO:33 and a VL sequence of SEQ ID NO:37; or
c) a VH sequence of SEQ ID NO:34 and a VL sequence of SEQ ID NO:36; or
d) a VH sequence of SEQ ID NO:34 and a VL sequence of SEQ ID NO:37; or
e) a VH sequence of SEQ ID NO:35 and a VL sequence of SEQ ID NO:36; or
f) a VH sequence of SEQ ID NO:35 and a VL sequence of SEQ ID NO:37.

~~14~~13. The antibody of any one of claims 6 to ~~13~~12, which is a full length IgG1 antibody or IgG4 antibody.

~~15~~14. The antibody of any one of claims 6 to ~~13~~12, which is a Fab fragment.

~~16~~15. An immunoconjugate comprising the antibody of any one of claims 6 to ~~15~~14 and a cytotoxic agent.

~~17~~16. The antibody of any one of claims 6 to ~~15~~14, or the immunoconjugate of claim ~~16~~15, for use in treating cancer.

~~18~~17. The antibody of any one of claims 6 to ~~15~~ 14 for use in inhibition of HER3/HER2 dimerization.

~~19~~18. A pharmaceutical formulation comprising the antibody of any one of claims 6 to ~~15~~14, or the immunoconjugate of claim ~~16~~15, and a pharmaceutically acceptable carrier.

~~20~~19. The antibody of any one of claims 6 to ~~15~~14, or the immunoconjugate of claim ~~16~~15, for use as a medicament.

~~21~~20. Use of the antibody of any one of claims 6 to ~~15~~14, or the immunoconjugate of claim ~~16~~15, in the manufacture of a medicament.

~~22~~21. The use of claim ~~21~~20, wherein the medicament is for treatment of cancer.

~~23~~22. Isolated nucleic acid encoding the antibody of any one of claims 6 to ~~15~~14.

~~24~~23. A host cell comprising the nucleic acid of claim ~~23~~22.

~~25~~24. A method of producing an antibody comprising culturing the host cell of claim ~~24~~ 23 so that the antibody is produced, and recovering said antibody from said cell culture or the cell culture supernatant.

~~26. A polypeptide selected from the group consisting of:~~

~~i) SEQ ID NO: 13 TtSlyD-FKBP-Her3,~~

~~ii) SEQ ID NO: 17 TtSlyDeas-Her3,~~

~~iii) SEQ ID NO: 18 TtSlyDcys-Her3,~~

~~iv) SEQ ID NO: 19 TgSlyDser-Her3, and~~

~~v) SEQ ID NO: 20 TgSlyDcys-Her3,~~

~~which polypeptide comprises the amino acid sequence of SEQ ID NO:1~~

~~27. A polypeptide selected from the group consisting of:~~

~~i) SEQ ID NO: 21 TtSlyDeas-Her4,~~

~~ii) SEQ ID NO: 22 TtSlyDcys-Her4,~~

iii) SEQ ID NO: 23 TgSlyDser-Her4,and

iv) SEQ ID NO: 24 TgSlyDcys-Her4,

which polypeptide comprises the amino acid sequence of SEQ ID NO:2