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(54) Title:

ANTIBODIES DIRECTED TO HER-3 AND USES THEREOF

(57) Abstract:

ANTIBODIES DIRECTED TO HER-3 AND USES THEREOF
Abstract The present invention relates to binding proteins that bind to HER-3 and polynucleotides encoding the same. Expression vectors and host cells comprising the same for the production of the binding protein of the invention are also provided. In addition, the invention provides compositions and methods for diagnosing and treating diseases associated with HER-3 mediated signal transduction and/or its ligand heregulin. No suitable figure

ANTIBODIES DIRECTED TO HER-3 AND USES THEREOF

5

Abstract

10 The present invention relates to binding proteins that bind to HER-3 and polynucleotides encoding the same. Expression vectors and host cells comprising the same for the production of the binding protein of the invention are also provided. In addition, the invention provides compositions and methods for diagnosing and treating diseases associated with HER-3 mediated signal transduction and/or its ligand heregulin.

No suitable figure

Antibodies directed to HER-3 and uses thereof

DESCRIPTION

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to binding proteins including antibodies and binding fragments thereof that bind to HER-3 and polynucleotides encoding the same. Expression vectors and host cells comprising the same for the production of the binding protein of the invention are also provided. In addition, the invention provides compositions and methods for diagnosing and treating diseases associated with HER-3 mediated signal transduction and/or its ligand heregulin.

2. Background of the Technology

The human epidermal growth factor receptor 3 (HER-3, also known as ErbB3) is a receptor protein tyrosine kinase and belongs to the epidermal growth factor receptor (EGFR) subfamily of receptor protein tyrosine kinases, which also includes HER-1 (also known as EGFR), HER-2, and HER-4 (Plowman *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 87 (1990), 4905-4909; Kraus *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 86 (1989), 9193-9197; and Kraus *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 90 (1993), 2900-2904). Like the prototypical epidermal growth factor receptor, the transmembrane receptor HER-3 consists of an extracellular ligand-binding domain (ECD), a dimerization domain within the ECD, a transmembrane domain, an intracellular protein tyrosine kinase domain (TKD) and a C-terminal phosphorylation domain.

The ligand Heregulin (HRG) binds to the extracellular domain of HER-3 and activates the receptor-mediated signaling pathway by promoting dimerization with other human epidermal growth factor receptor (HER)

family members and transphosphorylation of its intracellular domain. Dimer formation between HER family members expands the signaling potential of HER-3 and is a means not only for signal diversification but also signal amplification. For example the HER-2/HER-3 heterodimer induces one of the most important mitogenic signals among HER family members.

HER-3 has been found to be overexpressed in several types of cancer such as breast, gastrointestinal and pancreatic cancers. Interestingly a correlation between the expression of HER-2/HER-3 and the progression from a non-invasive to an invasive stage has been shown (Alimandi *et al.*, *Oncogene* 10,1813-1821; deFazio *et al.*, *Cancer* 87, 487-498; Naidu *et al.*, *Br. J. Cancer* 78, 1385-1390). Accordingly, agents that interfere with HER-3 mediated signaling are desirable. Murine or chimeric HER-3 antibodies have been reported, such as in US5968511, US5480968 and WO03013602.

A humanized monoclonal antibody against HER-2, Herceptin®, has recently been shown to interfere with HER-2 mediated signaling and is therapeutically effective in humans (Fendly *et al.*, *Hybridoma* 6, 359-370; Hudziak *et al.*, *Mol. Cell. Biol.* 9, 1165-1172; Stebbing *et al.*, *Cancer Treat. Rev.* 26, 287-290). Herceptin® has been shown to act through two different mechanisms, i.e. the engagement of the effector cells of the immune system as well as a direct cytotoxic, apoptosis inducing effect.

However, only patients with highly amplified HER-2 respond significantly to Herceptin® therapy, thus limiting the number of patients suitable for therapy. In addition the development of resistance to drugs or a change in the expression or epitope sequence of HER-2 on tumor cells may render even those approachable patients unreactive with the antibody and therefore abrogating its therapeutic benefits. Therefore more drugs for target based therapies approaching further members of the HER family, such as HER-3, are needed.

BRIEF DESCRIPTION OF THE DRAWING FIGURES

Fig. 1 shows the extent of HER-3 expression in a panel of human cancer cell lines and demonstrates that HER-3 is expressed in a variety of human cancers.

Fig. 2 shows the results of the FACS analysis of HER-3 antibody binding to either Rat1 cells stably expressing the different members of the HER family or only empty vector.

Fig. 3 shows antibody binding competition bins mapped to HER3 domains.

Fig. 4. show the results of the indirect FACS Scatchard antibody affinity analysis performed with anti-HER-3 antibodies of the invention. The analysis indicates that the anti-HER-3 antibodies of the invention possess high affinities and strong binding constants for HER-3 expressed on the cell surface

Fig. 5 shows the accelerated endocytosis of HER-3 induced by anti-HER-3 antibodies of the invention.

Figs. 6 a-e show the results of a ligand competition assay performed with anti-HER-3 antibodies of the invention. The results demonstrate that the antibodies of the invention specifically reduce binding of [¹²⁵I]-α-HRG/[¹²⁵I]-β-HRG to cells expressing endogenous HER-3.

Fig. 7a shows the results of a HER-3 phosphotyrosine ELISA performed with anti-HER-3 antibodies of the invention. Antibodies according to the present invention were able to inhibit β-HRG-mediated HER-3 activation as indicated by increased receptor tyrosine phosphorylation. Furthermore fig. 7b shows representative results of this experiment with titrated antibody.

Fig. 8 shows the result of a p42/p44 MAP-Kinase ELISA performed with

anti-HER-3 antibodies of the invention. Antibodies according to the present invention were able to reduce β -HRG-mediated p42/p44 MAP-Kinase activation as indicated by increased MAP-Kinase phosphorylation.

5 **Fig. 9** shows the result of a phospho-AKT ELISA performed with anti-HER-3 antibodies of the invention. Antibodies according to the present invention were able to reduce β -HRG-mediated AKT activation as indicated by AKT phosphorylation.

10 **Fig. 10** shows the inhibition of MCF7 cell proliferation by human anti-HER-3 antibodies of the invention. Antibodies according to the present invention inhibit HRG-induced cell growth in human cancer cells.

15 **Fig. 11** shows the transmigration of MCF7 cells inhibited by human anti-HER-3 antibodies of the invention.

Figs. 12a-i shows the inhibition of the anchorage independent cell growth by human HER-3 antibodies of the invention.

20 **Fig. 13** shows the inhibition of xenograft growth of T47D human breast cancer cells by a human anti-HER-3 antibody of the invention.

Fig. 14 shows the reduction of BxPC3 human pancreas cancer cells in mice after administration of anti Her3 (U1-59 and U1-53) or anti EGFR (Erbixux) antibodies.

25

Fig. 15 shows the reduction of xenograft growth of BxPC3 human pancreas cancer cells by a human anti-HER-3 antibody of the invention and in combination with anti EGFR (Erbixux) antibodies.

30 **Fig. 16** demonstrates that antibodies of the invention delay human melanoma (HT144) cell growth in nu/nu mice.

Fig. 17 shows the reduction of xenograft growth of HT-29 human colon carcinoma cells by human HER-3 antibodies of the invention (U1-53, U1-59 and U1-7).

5 Fig. 18 shows the reduction of xenograft growth of Calu-3 human lung cancer cells by human anti-HER-3 antibodies of the invention (U1-59, U1-53 and U1-7).

Fig. 19 shows the reduction of xenograft growth of BxPC-3 human pancreas cancer cells by human anti-HER-3 antibodies of the invention (U1-7, U1-59 and U1-53).

Fig. 20 demonstrates that an antibody of the invention (U1-59) causes suppression of HER-3 in BxPC3 human pancreas cancer xenografts.

15

SUMMARY OF THE INVENTION

A first aspect of the present invention relates to an isolated binding protein that binds to HER-3.

20

In one embodiment of the present invention, an isolated binding protein of the invention comprises a heavy chain amino acid sequence comprising at least one of the CDR's selected from the group consisting of: (a) CDRH1's as shown in SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30, 34, 36, 40, 42, 46, 50, 54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170, 174, 178, 182, 186, 190, 194, 198, 202, 206, 210, 214, 218, 222, 226 and 230, (b) CDRH2's as shown in SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30, 34, 36, 40, 42, 46, 50, 54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170, 174, 178, 182, 186, 190, 194, 198, 202, 206, 210, 214, 218, 222, 226 and 230, and (c) CDRH3's as shown in SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30, 34, 36, 40, 42, 46, 50, 54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100,

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104, 108, 112, 116, 120, 122, 126, 130, 134, 138, 142, 146, 150, 154, 158,
162, 166, 170, 174, 178, 182, 186, 190, 194, 198, 202, 206, 210, 214, 218,
222, 226 and 230, and/or a light chain amino acid sequence comprising at
least one of the CDR's selected from the group consisting of: (d) CDRL1's
5 as shown in SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 38, 44, 48, 52, 56, 58,
64, 68, 72, 76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132,
136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192,
196, 200, 204, 208, 212, 216, 220, 224, 228 and 232, (e) CDRL2's as shown
in SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 38, 44, 48, 52, 56, 58, 64, 68,
10 72, 76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132, 136, 140,
144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200,
204, 208, 212, 216, 220, 224, 228 and 232, and (f) CDRL3's as shown in
SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 38, 44, 48, 52, 56, 58, 64, 68, 72,
76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132, 136, 140,
15 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200,
204, 208, 212, 216, 220, 224, 228 and 232.

In another embodiment of the present invention, an isolated binding protein
of the invention comprises a heavy chain amino acid sequence selected
20 from the group consisting of SEQ ID Nos: 2, 6, 10, 14, 18, 22, 26, 30, 34, 36,
40, 42, 46, 50, 54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100, 104, 108,
112, 116, 120, 122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166,
170, 174, 178, 182, 186, 190, 194, 198, 202, 206, 210, 214, 218, 222, 226
and 230, and/or a light chain amino acid sequence selected from the group
25 consisting of SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 38, 44, 48, 52, 56, 58,
64, 68, 72, 76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132,
136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192,
196, 200, 204, 208, 212, 216, 220, 224, 228 and 232.

30 In yet another embodiment of the present invention, an isolated binding
protein of the invention comprises a heavy chain amino acid sequence and a
light chain amino acid sequence as shown in SEQ ID NOs: 2 and 4, 6 and 8,
10 and 12, 14 and 16, 18 and 20, 22 and 24, 26 and 28, 30 and 32, 36 and

38, 42 and 44, 46 and 48, 50 and 52, 54 and 56, 60 and 58, 62 and 64, 66 and 68, 70 and 72, 74 and 76, 78 and 82, 80 and 82, 84 and 86, 88 and 90, 92 and 94, 96 and 98, 100 and 102, 104 and 106, 108 and 110, 112 and 114, 116 and 118, 122 and 124, 126 and 128, 130 and 132, 134 and 136, 5 138 and 140, 142 and 144, 146 and 148, 150 and 152, 154 and 156, 158 and 160, 162 and 164, 166 and 168, 170 and 172, 174 and 176, 178 and 180, 182 and 184, 186 and 188, 190 and 192, 194 and 196, 198 and 200, 202 and 204, 206 and 208, 210 and 212, 214 and 216, 218 and 220, 222 and 224, 226 and 228, 230 and 232, or a heavy chain amino acid sequence as shown in SEQ ID NOs: 34, 40, 60, 62 or 120, or a light chain amino acid 10 sequence as shown in SEQ ID NOs: 58 or 64.

According to the present invention, an isolated binding protein that is capable of binding to HER-3 interacts with at least one epitope in the extracellular 15 part of HER-3. The epitopes are preferably located in domain L1 (aa 19-184) which is the amino terminal domain, in domain S1 (aa 185-327) and S2 (aa 500-632) which are the two Cysteine-rich domains, or in domain L2 (328-499) which is flanked by the two Cysteine-rich domains. The epitopes may also be located in combinations of domains such as but not limited to an 20 epitope comprised by parts of L1 and S1. Further preferred is an isolated binding protein that binds to a three-dimensional structure formed by amino acid residues 1-160, 161-358, 359-575, 1-358 and/or 359-604 of mature HER-3, particularly of mature human HER-3.

25 Preferably, an isolated binding protein of the invention is a scaffold protein having an antibody like binding activity or an antibody, e.g. an anti-HER-3 antibody. In particular, the anti-HER-3 antibody is selected from the group consisting of U1-1 antibody, U1-2 antibody, U1-3 antibody, U1-4 antibody, U1-5 antibody, U1-6 antibody, U1-7 antibody, U1-8 antibody, U1-9 antibody, 30 U1-10 antibody, U1-11 antibody, U1-12 antibody, U1-13 antibody, U1-14 antibody, U1-15 antibody, U1-16 antibody, U1-17 antibody, U1-18 antibody, U1-19 antibody, U1-20 antibody, U1-21 antibody, U1-22 antibody, U1-23 antibody, U1-24 antibody, U1-25 antibody, U1-26 antibody, U1-27 antibody,

U1-28 antibody, U1-29 antibody, U1-30 antibody, U1-31 antibody, U1-32 antibody, U1-33 antibody, U1-34 antibody, U1-35 antibody, U1-36 antibody, U1-37 antibody, U1-38 antibody, U1-39 antibody, U1-40 antibody, U1-41 antibody, U1-42 antibody, U1-43 antibody, U1-44 antibody, U1-45 antibody,
5 U1-46 antibody, U1-47 antibody, U1-48 antibody, U1-49 antibody, U1-50 antibody, U1-51 antibody, U1-52 antibody, U1-53 antibody, U1-55.1 antibody, U1-55 antibody, U1-57.1 antibody, U1-57 antibody, U1-58 antibody, U1-59 antibody, U1-61.1 antibody, U1-61 antibody, U1-62 antibody or an antibody having at least one heavy or light chain of one of
10 said antibodies. Especially preferred are the antibodies U1-49 (SEQ ID NO: 42/44), U1-53 (SEQ ID NO: 54/56) and U1-59 (SEQ ID NO: 70/72) or an antibody having at least one heavy or light chain of one of said antibodies.

In addition, further embodiments of the present invention provide an isolated
15 binding protein coupled to a labelling group or effector group. Preferably, such an binding protein is useful for the treatment of hyperproliferative diseases, particularly oncological diseases such as breast cancer, gastrointestinal cancer, pancreatic cancer, prostate cancer, ovarian cancer, stomach cancer, endometrial cancer, salivary gland cancer, lung cancer, kidney cancer, colon
20 cancer, colorectal cancer, thyroid cancer, bladder cancer, glioma, melanoma, testis cancer, soft tissue sarcoma, head and neck cancer, or other HER-3 expressing or overexpressing cancers, and the formation of tumor metastases.

Other aspects of the present invention relate to an isolated nucleic acid
25 molecule encoding a binding protein of the invention, a vector having a nucleic acid molecule encoding the binding protein of the invention, and a host cell, e.g. a CHO cell, an NS/O myeloma cell, transformed with such nucleic acid molecule or vector.

30 A further aspect of the present invention relates to a method for producing a binding protein of the invention by preparing said binding protein from a host cell that secretes the binding protein. Preferably, the binding protein of the invention is prepared from a hybridoma cell line that secretes a binding

protein or a CHO or other cell type transformed with a nucleic acid molecule encoding a binding protein of the invention.

Another aspect of the present invention relates to a method for producing a
5 binding protein of the invention by preparing said binding protein from a
tissue, product or secretion of an animal, plant or fungus transgenic for a
nucleic acid molecule or nucleic acid molecules encoding the binding protein
of the invention. Preferably, a binding protein of the invention is prepared
from the tissue, product or secretion of a transgenic animal such as cow,
10 sheep, rabbit, chicken or other mammalian or avian species, a transgenic
plant such as corn, tobacco or other plant, or a transgenic fungus such as
Aspergillus, *Pichia* or other fungal species.

Another aspect of the present invention pertains to a pharmaceutical
15 composition comprising as an active agent at least one binding protein of
the invention in admixture with pharmaceutically acceptable carriers,
diluent and/or adjuvants. In another preferred embodiment of the present
invention, the pharmaceutical composition of the invention additionally
contains at least one other active agent, e.g. at least one antineoplastic
20 agent. Yet another aspect of the present invention pertains to the use of at
least one binding protein of the invention, and optionally at least one other
active agent, e.g. at least one antineoplastic agent, in admixture with
pharmaceutically acceptable carriers, diluent and/or adjuvants for the
preparation of a pharmaceutical composition. The pharmaceutical
25 composition is suitable for diagnosing, preventing or treating a
hyperproliferative disease, particularly an oncological disease such as breast
cancer, gastrointestinal cancer, pancreas cancer, prostate cancer, ovarian
cancer, stomach cancer, endometrial cancer, salivary gland cancer, lung
cancer, kidney cancer, colon cancer, colorectal cancer, thyroid cancer,
30 bladder cancer, glioma, melanoma or other HER-3 expressing or
overexpressing cancers, and the formation of tumor metastases.

Moreover, the present invention relates in a further aspect to a method for

diagnosing diseases or conditions associated with the expression of HER-3, comprising contacting a sample with at least one binding protein of the invention, and detecting the presence of HER-3. Preferred diseases or conditions include the hyperproliferative diseases mentioned above.

5

Still another aspect of the present invention is a method for preventing or treating diseases or conditions associated with the expression of HER-3 in a patient in need thereof, comprising administering to the patient an effective amount of at least one binding protein of the invention and optionally at least one other active agent, e.g. at least one neoplastic agent. Preferably, the patient is a mammalian patient, more preferably a human patient. Preferred diseases or conditions associated with the expression of HER-3 are the hyperproliferative diseases mentioned above.

15 A further aspect of the present invention relates to a kit for the diagnosis, prevention or treatment diseases or conditions associated with the expression of HER-3, comprising at least one binding protein, and/or nucleic acid molecule and/or vector of the invention. Optionally, the kit of the invention can further comprise at least one other active agent, e.g. at least one anti neoplastic agent. Preferably, the diseases or conditions associated with the expression of HER-3 are the hyperproliferative diseases mentioned above.

20

DETAILED DESCRIPTION

25

A first aspect of the present invention relates to an isolated binding protein that binds to HER-3.

30

In one embodiment of the present invention, the isolated binding protein of the invention comprises a heavy chain amino acid sequence comprising at least one of the CDR's selected from the group consisting of: (a) CDRH1's as shown in SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30, 34, 36, 40, 42, 46, 50, 54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120,

122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170, 174, 178,
182, 186, 190, 194, 198, 202, 206, 210, 214, 218, 222, 226 and 230, (b)
CDRH2's as shown in SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30, 34, 36, 40,
42, 46, 50, 54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100, 104, 108, 112,
5 116, 120, 122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170,
174, 178, 182, 186, 190, 194, 198, 202, 206, 210, 214, 218, 222, 226 and
230, and (c) CDRH3's as shown in SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26,
30, 34, 36, 40, 42, 46, 50, 54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100,
104, 108, 112, 116, 120, 122, 126, 130, 134, 138, 142, 146, 150, 154, 158,
10 162, 166, 170, 174, 178, 182, 186, 190, 194, 198, 202, 206, 210, 214, 218,
222, 226 and 230, and/or a light chain amino acid sequence comprising at
least one of the CDR's selected from the group consisting of: (d) CDRL1's
as shown in SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 38, 44, 48, 52, 56, 58,
64, 68, 72, 76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132,
15 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192,
196, 200, 204, 208, 212, 216, 220, 224, 228 and 232, (e) CDRL2's as shown
in SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 38, 44, 48, 52, 56, 58, 64, 68,
72, 76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132, 136, 140,
144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200,
20 204, 208, 212, 216, 220, 224, 228 and 232, and (f) CDRL3's as shown in
SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 38, 44, 48, 52, 56, 58, 64, 68, 72,
76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132, 136, 140,
144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200,
204, 208, 212, 216, 220, 224, 228 and 232.

25 In another embodiment of the present invention, the isolated binding protein
of the invention comprises a heavy chain amino acid sequence selected
from the group consisting of SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30, 34,
36, 40, 42, 46, 50, 54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100, 104,
30 108, 112, 116, 120, 122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162,
166, 170, 174, 178, 182, 186, 190, 194, 198, 202, 206, 210, 214, 218, 222,
226 and 230, and/or a light chain amino acid sequence selected from the
group consisting of SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 38, 44, 48, 52,

56, 58, 64, 68, 72, 76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 216, 220, 224, 228 and 232.

5 In yet another embodiment of the present invention, the isolated binding protein of the invention comprises a heavy chain amino acid sequence and a light chain amino acid sequence as shown in SEQ ID NOs: 2 and 4, 6 and 8, 10 and 12, 14 and 16, 18 and 20, 22 and 24, 26 and 28, 30 and 32, 36 and 38, 42 and 44, 46 and 48, 50 and 52, 54 and 56, 60 and 58, 62 and 64, 66
10 and 68, 70 and 72, 74 and 76, 78 and 82, 80 and 82, 84 and 86, 88 and 90, 92 and 94, 96 and 98, 100 and 102, 104 and 106, 108 and 110, 112 and 114, 116 and 118, 122 and 124, 126 and 128, 130 and 132, 134 and 136, 138 and 140, 142 and 144, 146 and 148, 150 and 152, 154 and 156, 158 and 160, 162 and 164, 166 and 168, 170 and 172, 174 and 176, 178 and
15 180, 182 and 184, 186 and 188, 190 and 192, 194 and 196, 198 and 200, 202 and 204, 206 and 208, 210 and 212, 214 and 216, 218 and 220, 222 and 224, 226 and 228, 230 and 232, or a heavy chain amino acid sequence as shown in SEQ ID NOs: 34, 40, 60, 62 or 120, or a light chain amino acid sequence as shown in SEQ ID NOs: 58 or 64.

20 In accordance with the present invention, it is to be understood, that the amino acid sequence of the binding protein of the invention is not limited to the twenty conventional amino acids (See *Immunology - A Synthesis* (2nd Edition, E.S. Golub and D.R. Gren, Eds., Sinauer Associates, Sunderland, Mass. (1991)), which is incorporated herein by reference). For example, the
25 amino acids may include stereoisomers (e.g. D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as α,α -disubstituted amino acids, N-alkyl amino acids, lactic acid, and other unconventional amino acids. Examples of unconventional amino acids, which may also be
30 suitable components for the binding protein of the invention, include: 4-hydroxyproline, γ -carboxyglutamate, ϵ -N,N,N-trimethyllysine, ϵ -N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ -N-methylarginine, and other similar

amino acids and imino acids, e.g. 4-hydroxyproline.

Furthermore, in accordance with the present invention, minor variations in the amino acid sequences shown in SEQ ID NOs: 1-232 are contemplated as being encompassed by the present invention, providing that the variations in the amino acid sequence maintain at least 75 %, more preferably at least 80 %, 90 %, 95 %, and most preferably 99 % of the sequences shown in SEQ ID NOs: 1-232. The variations may occur within the framework regions (i.e. outside the CDRs), within the CDRs, or within the framework regions and the CDRs. Preferred variations in the amino acid sequences shown in SEQ ID NOs: 1-232, i.e. deletions, insertions and/or replacements of at least one amino acid, occur near boundaries of functional domains. Structural and functional domains can be identified by comparison of the nucleotide and/or amino acid sequence data to public or proprietary sequence databases. Computerized comparison methods can be used to identify sequence motifs or predicted protein conformation domains that occur in other binding proteins of known structure and/or function. Methods to identify protein sequences that fold into a known three-dimensional structure are known. See e.g. Bowie *et al.*, *Science* 253, 164 (1991); *Proteins, Structures and Molecular Principles* (Creighton, Ed., W. H. Freeman and Company, New York (1984)); *Introduction to Protein Structure* (C. Branden and J. Tooze, eds., Garland Publishing, New York, N.Y. (1991)); and Thornton *et al.*, *Nature* 354, 105 (1991), which are all incorporated herein by reference. Thus, those of skill in the art can recognize sequence motifs and structural conformations that may be used to define structural and functional domains in accordance with the invention.

Especially preferred variations in the amino acid sequences shown in SEQ ID NOs: 1-174 and 1-232 are those that lead to a reduced susceptibility to proteolysis or oxidation, alter glycosylation patterns or alter binding affinities or confer or modify other physicochemical or functional properties of the binding protein. In particular, conservative amino acid replacements are contemplated. Conservative replacements are those that take place within a

family of amino acids that are related in their side chains. Preferred amino acid families are the following: acidic family = aspartate, glutamate; basic family = lysine, arginine, histidine; non-polar family = alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan; and uncharged polar family = glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine. More preferred families are: aliphatic-hydroxy family = serine and threonine; amide-containing family = asparagine and glutamine; aliphatic family = alanine, valine, leucine and isoleucine; and aromatic family = phenylalanine, tryptophan, and tyrosine. For example, it is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid will not have a major effect on the binding or properties of the resulting binding protein, especially if the replacement does not involve an amino acid within a framework site. However, all other possible amino acid replacements are also encompassed by the present invention. Whether an amino acid change results in a functional binding protein, i.e. in a binding protein that binds to HER-3 and reduces signal transduction of HER family members, can readily be determined by assaying the specific activity of the resulting binding protein in ELISA or FACS for binding to HER-3 or in vitro or in vivo functional assay.

According to the present invention, the binding protein of the invention interacts with at least one epitope in the extracellular part of HER-3. The epitopes are preferably located in domain L1 (aa 19-184), which is the amino terminal domain, in domain S1 (aa 185-327) and S2 (aa 500-632), which are the two Cysteine-rich domains, in domain L2 (328-499), which is flanked by the two Cysteine-rich domains or in a combination of HER-3 domains. The epitopes may also be located in combinations of domains such as but not limited to an epitope comprised by parts of L1 and S1. Moreover, the binding protein of the invention is further characterized in that its binding to HER-3 reduces HER-3-mediated signal transduction. In accordance with the present invention, a reduction of HER-3-mediated signal

transduction may, e.g. be caused by a downregulation of HER-3 resulting in an at least partial disappearance of HER-3 molecules from the cell surface or by a stabilization of HER-3 on the cell surface in a substantially inactive form, i.e. a form which exhibits a lower signal transduction compared to the non-stabilized form. Alternatively, a reduction of HER-3-mediated signal transduction may also be caused by influencing, e.g. decreasing or inhibiting, the binding of a ligand or another member of the HER family to HER-3, of GRB2 to HER-2 or of GRB2 to SHC, by inhibiting receptor tyrosine phosphorylation, AKT phosphorylation, PYK2 tyrosine phosphorylation or ERK2 phosphorylation, or by decreasing tumor invasiveness. Alternatively, a reduction of HER-3 mediated signal transduction may also be caused by influencing, e.g., decreasing or inhibiting, the formation of HER-3 containing dimers with other HER family members. One example among others may be the decreasing or inhibiting of the HER3-EGFR protein complex formation.

Preferably, the binding protein of the invention is a scaffold protein having an antibody like binding activity or an antibody, i.e. an anti-HER-3 antibody.

Within the context of the present invention, the term "scaffold protein", as used herein, means a polypeptide or protein with exposed surface areas in which amino acid insertions, substitutions or deletions are highly tolerable. Examples of scaffold proteins that can be used in accordance with the present invention are protein A from *Staphylococcus aureus*, the bilin binding protein from *Pteris brassicae* or other lipocalins, ankyrin repeat proteins, and human fibronectin (reviewed in Binz and Plückthun, *Curr Opin Biotechnol*, 16, 459-69). Engineering of a scaffold protein can be regarded as grafting or integrating an affinity function onto or into the structural framework of a stably folded protein. Affinity function means a protein binding affinity according to the present invention. A scaffold can be structurally separable from the amino acid sequences conferring binding specificity. In general, proteins appearing suitable for the development of such artificial affinity reagents may be obtained by rational, or most commonly, combinatorial protein engineering techniques such as panning

against HER-3, either purified protein or protein displayed on the cell surface, for binding agents in an artificial scaffold library displayed in vitro, skills which are known in the art (Skerra, J. Mol. Recog., 2000; Binz and Plückthun, 2005). In addition, a scaffold protein having an antibody like binding activity can be derived from an acceptor polypeptide containing the scaffold domain, which can be grafted with binding domains of a donor polypeptide to confer the binding specificity of the donor polypeptide onto the scaffold domain containing the acceptor polypeptide. Said inserted binding domains may be, for example, the complementarity determining region (CDR) of an antibody, in particular an anti-HER-3 antibody. Insertion can be accomplished by various methods known to those skilled in the art including, for example, polypeptide synthesis, nucleic acid synthesis of an encoding amino acid as well by various forms of recombinant methods well known to those skilled in the art.

Moreover, the term "antibody" or "anti-HER-3 antibody", as used herein, means a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a humanized antibody (Jones *et al.*, *Nature* 321 (1986), 522-525; Riechmann *et al.*, *Nature* 332 (1988), 323-329; and Presta, *Curr. Op. Struct. Biol.* 2 (1992), 593-596), a chimeric antibody (Morrison *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 81 (1984), 6851-6855), a multispecific antibody (e.g. a bispecific antibody) formed from at least two antibodies, or an antibody fragment thereof. The term "antibody fragment" comprises any portion of the afore-mentioned antibodies, preferably their antigen binding or variable regions. Examples of antibody fragments include Fab fragments, Fab' fragments, F(ab')₂ fragments, Fv fragments, diabodies (Hollinger *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 90 (1993), 6444-6448), single chain antibody molecules (Plückthun in: *The Pharmacology of Monoclonal Antibodies* 113, Rosenberg and Moore, EDS, Springer Verlag, N.Y. (1994), 269-315) and other fragments as long as they exhibit the desired capability of binding to HER-3.

In addition, the term "antibody" or "anti-HER-3 antibody", as used herein, may include antibody-like molecules that contain engineered sub-domains of

antibodies or naturally occurring antibody variants. These antibody-like molecules may be single-domain antibodies such as VH-only or VL-only domains derived either from natural sources such as camelids (Muyldermans et al., *Reviews in Molecular Biotechnology* 74, 277-302) or through in vitro display of libraries from humans, camelids or other species (Holt et al., *Trends Biotechnol.*, 21, 484-90).

In accordance with the present invention, the "Fv fragment" is the minimum antibody fragment that contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDR's of each variable domain interact to define an antigen-binding site on the surface of the V_H - V_L dimer. Collectively, the six CDR's confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDR's specific for an antigen) has the ability to recognize and bind the antigen, although usually at a lower affinity than the entire binding site. The "Fab fragment" also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. The "Fab fragment" differs from the "Fab' fragment" by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. The "F(ab')₂ fragment" originally is produced as a pair of "Fab' fragments" which have hinge cysteines between them. Methods of preparing such antibody fragments, such as papain or pepsin digestion, are known to those skilled in the art.

In a preferred embodiment of the present invention, the anti-HER-3 antibody of the invention is of the IgA-, IgD-, IgE, IgG- or IgM-type, preferably of the IgG- or IgM-type including, but not limited to, the IgG1-, IgG2-, IgG3-, IgG4-, IgM1- and IgM2-type. In most preferred embodiments, the antibody is of the IgG1-, IgG2- or IgG4- type.

In another preferred embodiment of the present invention, the anti-HER-3

antibody of the invention is an anti-HER-3 antibody directed against the extracellular domain (ECD) of HER-3.

In certain respects, e.g. in connection with the generation of antibodies as therapeutic candidates against HER-3, it may be desirable that the anti-HER-3 antibody of the invention is capable of fixing complement and participating in complement-dependent cytotoxicity (CDC). There are a number of isotypes of antibodies that are capable of the same including without limitations the following: murine IgM, murine IgG2a, murine IgG2b, murine IgG3, human IgM, human IgG1, human IgG3, and human IgA. It will be appreciated that antibodies that are generated need not initially possess such an isotype but, rather the antibody as generated can possess any isotype and the antibody can be isotype switched by appending the molecularly cloned V region genes or cDNA to molecularly cloned constant region genes or cDNAs in appropriate expression vectors using conventional molecular biological techniques that are well known in the art and then expressing the antibodies in host cells using techniques known in the art. The isotype-switched antibody may also possess an Fc region that has been molecularly engineered to possess superior CDC over naturally occurring variants (Idusogie et al., *J Immunol.*, 166, 2571-2575) and expressed recombinantly in host cells using techniques known in the art. Such techniques include the use of direct recombinant techniques (see e.g. U.S. Patent No. 4,816,397), cell-cell fusion techniques (see e.g. U.S. Patent Nos. 5,916,771 and 6,207,418), among others. In the cell-cell fusion technique, a myeloma or other cell line such as CHO is prepared that possesses a heavy chain with any desired isotype and another myeloma or other cell line such as CHO is prepared that possesses the light chain. Such cells can, thereafter, be fused and a cell line expressing an intact antibody can be isolated. By way of example, a human anti-HER-3 IgG4 antibody, that possesses the desired binding to the HER-3 antigen, could be readily isotype switched to generate a human IgM, human IgG1 or human IgG3 isotype, while still possessing the same variable region (which defines the antibody's specificity and some of its affinity). Such molecule might then be

capable of fixing complement and participating in CDC.

Moreover, it may also be desirable for the anti-HER-3 antibody of the invention to be capable of binding to Fc receptors on effector cells, such as monocytes and natural killer (NK) cells, and participate in antibody-dependent cellular cytotoxicity (ADCC). There are a number of isotypes of antibodies that are capable of the same, including without limitations the following: murine IgG2a, murine IgG2b, murine IgG3, human IgG1 and human IgG3. It will be appreciated that antibodies that are generated need not initially possess such an isotype but, rather the antibody as generated can possess any isotype and the antibody can be isotype switched by appending the molecularly cloned V region genes or cDNA to molecularly cloned constant region genes or cDNAs in appropriate expression vectors using conventional molecular biological techniques that are well known in the art and then expressing the antibodies in host cells using techniques known in the art. The isotype-switched antibody may also possess an Fc region that has been molecularly engineered to possess superior ADCC over naturally occurring variants (Shields et al. *J Biol Chem.*, 276, 6591-6604) and expressed recombinantly in host cells using techniques known in the art. Such techniques include the use of direct recombinant techniques (see e.g. U.S. Patent No. 4,816,397), cell-cell fusion techniques (see e.g. U.S. Patent Nos. 5,916,771 and 6,207,418), among others. In the cell-cell fusion technique, a myeloma or other cell line such as CHO is prepared that possesses a heavy chain with any desired isotype and another myeloma or other cell line such as CHO is prepared that possesses the light chain. Such cells can, thereafter, be fused and a cell line expressing an intact antibody can be isolated. By way of example, a human anti-HER-3 IgG4 antibody, that possesses the desired binding to the HER-3 antigen, could be readily isotype switched to generate a human IgG1 or human IgG3 isotype, while still possessing the same variable region (which defines the antibody's specificity and some of its affinity). Such molecule might then be capable of binding to FcγR on effectors cells and participating in ADCC.

Furthermore, according to the present invention, it is appreciated that the anti-HER-3 antibody of the invention is a fully human or humanized antibody. Human antibodies avoid certain of the problems associated with xenogeneic antibodies, for example antibodies that possess murine or rat variable and/or constant regions. The presence of xenogeneic-derived proteins such murine or rat derived proteins can lead to the generation of an immune response against the antibody by a patient, subsequently leading to the rapid clearance of the antibodies, loss of therapeutic utility through neutralization of the antibody and/or severe, even life-threatening, allergic reactions.

Preferably, the anti-HER-3 antibody of the invention is selected from the group consisting of U1-1 antibody, U1-2 antibody, U1-3 antibody, U1-4 antibody, U1-5 antibody, U1-6 antibody, U1-7 antibody, U1-8 antibody, U1-9 antibody, U1-10 antibody, U1-11 antibody, U1-12 antibody, U1-13 antibody, U1-14 antibody, U1-15 antibody, U1-16 antibody, U1-17 antibody, U1-18 antibody, U1-19 antibody, U1-20 antibody, U1-21 antibody, U1-22 antibody, U1-23 antibody, U1-24 antibody, U1-25 antibody, U1-26 antibody, U1-27 antibody, U1-28 antibody, U1-29 antibody, U1-30 antibody, U1-31 antibody, U1-32 antibody, U1-33 antibody, U1-34 antibody, U1-35 antibody, U1-36 antibody, U1-37 antibody, U1-38 antibody, U1-39 antibody, U1-40 antibody, U1-41 antibody, U1-42 antibody, U1-43 antibody, U1-44 antibody, U1-45 antibody, U1-46 antibody, U1-47 antibody, U1-48 antibody, U1-49 antibody, U1-50 antibody, U1-51 antibody, U1-52 antibody, U1-53 antibody, U1-55.1 antibody, U1-55 antibody, U1-57.1 antibody, U1-57 antibody, U1-58 antibody, U1-59 antibody, U1-61.1 antibody, U1-61 antibody, U1-62 antibody.

In a preferred embodiment of the present invention, a binding protein of the invention is coupled to a labelling group. Such a binding protein is particularly suitable for diagnostic applications. As used herein, the term "labelling group" refers to a detectable marker, e.g. a radiolabelled amino acid or biotinyl moiety that can be detected by marked avidin (e.g. streptavidin bound to a fluorescent marker or enzymatic activity that can be detected by optical or

colorimetric methods). Various methods for labelling polypeptides and glycoproteins, such as antibodies, are known in the art and may be used in performing the present invention. Examples of suitable labelling groups include, but are not limited to, the following: radioisotopes or radionuclides (e.g. ^3H , ^{14}C , ^{15}N , ^{35}S , ^{90}Y , ^{99}Tc , ^{111}In , ^{125}I , ^{131}I); fluorescent groups (e.g. FITC, rhodamine, lanthanide phosphors), enzymatic groups (e.g. horseradish peroxidase, β -galactosidase, luciferase, alkaline phosphatase), chemiluminescent groups, biotinyl groups, or predetermined polypeptide epitopes recognized by a secondary reporter (e.g. leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In certain respects, it may be desirable that the labelling groups are attached by spacer arms of various lengths to reduce potential steric hindrance.

Alternatively, a binding protein of the invention may be coupled to an effector group in another preferred embodiment of the invention. Such a binding protein is especially suitable for therapeutic applications. As used herein, the term "effector group" refers to a cytotoxic group such as a radioisotope or radionuclide, a toxin, a therapeutic group or other effector group known in the art. Examples for suitable effector groups are radioisotopes or radionuclides (e.g. ^3H , ^{14}C , ^{15}N , ^{35}S , ^{90}Y , ^{99}Tc , ^{111}In , ^{125}I , ^{131}I), calicheamicin, dolastatin analogs such as auristatins, and chemotherapeutic agents such as geldanamycin and maytansine derivatives, including DM1. In certain respects, it may be desirable that the effector groups are attached by spacer arms of various lengths to reduce potential steric hindrance.

A second aspect of the present invention relates to a process for preparing an isolated binding protein of the invention, comprising the step of preparing the binding protein from a host cell that secretes the binding protein. Host cells, that may be used according to the present invention, are hybridomas; eukaryotic cells such as mammalian cells, e.g. hamster, rabbit, rat, pig, mouse or other animal cells, plant cells, fungal cells, e.g. *Saccharomyces cerevisiae*, *Pichia pastoris*; prokaryotic cells such as *E. coli*;

and other cells used in the art for the production of binding proteins. Various methods for preparing and isolating binding proteins, such as scaffold proteins or antibodies, from host cells are known in the art and may be used in performing the present invention. Moreover, methods for preparing binding protein fragments, e.g. scaffold protein fragments or antibody fragments, such as papain or pepsin digestion, modern cloning techniques, techniques for preparing single chain antibody molecules (Plückthun in: *The Pharmacology of Monoclonal Antibodies* 113, Rosenberg and Moore, EDS, Springer Verlag, N.Y. (1994), 269-315) and diabodies (Hollinger *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 90 (1993), 6444-6448), are also known to those skilled in the art and may be used in performing the present invention.

In a preferred embodiment of the present invention, a binding protein of the invention is prepared from a hybridoma that secretes the binding protein. See e.g. Köhler *et al.*, *Nature* 256 (1975), 495.

In a further preferred embodiment of the present invention, a binding protein of the invention is prepared recombinantly by optimizing and/or amplifying expression of the binding protein in a host cell and isolating the binding protein from said host cell. To this end, the host cells are transformed or transfected with DNA encoding a binding protein or a vector containing DNA encoding the binding protein and cultured under appropriate conditions to produce the binding protein of the invention. See e.g. U.S. Patent No. 4,816,567. Preferred host cells may be CHO cells, NS/O myeloma cells, human embryonic kidney 293 cells, *E. coli* and *Saccharomyces cerevisiae*.

With regard to binding proteins that are antibodies, these antibodies may be prepared from animals genetically engineered to make fully human antibodies or from an antibody display library made in bacteriophage, yeast, ribosome or *E. coli*. See e.g. Clackson *et al.*, *Nature* 352 (1991), 624-628, Marks *et al.*, *J. Mol. Biol.* 222 (1991), 581-597, Feldhaus and Siegel *J Immunol Methods*. 290, 69-80, Groves and Osbourn, *Expert Opin Biol Ther.*, 5, 125-135 and Jostock and Dubel, *Comb Chem High Throughput Screen.* 8,

127-133.

Human antibodies avoid some of the problems associated with antibodies that possess murine or rat variable and/or constant regions. The presence of such murine or rat derived proteins can lead to the rapid clearance of the antibodies or can lead to the generation of an immune response against the antibody by a patient. In order to avoid the utilization of murine or rat derived antibodies, fully human antibodies can be generated through the introduction of functional human antibody loci into a rodent, other mammal or animal so that the rodent, other mammal or animal produces fully human antibodies.

One method for generating fully human antibodies is through the use of XENOMOUSE® strains of mice that have been engineered to contain 245 kb and 190 kb-sized germline configuration fragments of the human heavy chain locus and kappa light chain locus. Other XenoMouse strains of mice contain 980 kb and 800 kb-sized germline configuration fragments of the human heavy chain locus and kappa light chain locus. Still other XenoMouse strains of mice contain 980 kb and 800 kb-sized germline configuration fragments of the human heavy chain locus and kappa light chain locus plus a 740 kb-sized germline configured complete human lambda light chain locus. See Mendez *et al. Nature Genetics* 15:146-156 (1997) and Green and Jakobovits *J. Exp. Med.* 188:483-495 (1998). The XENOMOUSE® strains are available from Abgenix, Inc. (Fremont, CA).

The production of the XENOMOUSE® mice is further discussed and delineated in U.S. Patent Application Serial Nos. 07/466,008, filed January 12, 1990, 07/610,515, filed November 8, 1990, 07/919,297, filed July 24, 1992, 07/922,649, filed July 30, 1992, filed 08/031,801, filed March 15, 1993, 08/112,848, filed August 27, 1993, 08/234,145, filed April 28, 1994, 08/376,279, filed January 20, 1995, 08/430, 938, April 27, 1995, 08/464,584, filed June 5, 1995, 08/464,582, filed June 5, 1995, 08/463,191, filed June 5, 1995, 08/462,837, filed June 5, 1995, 08/486,853, filed June 5, 1995,

08/486,857, filed June 5, 1995, 08/486,859, filed June 5, 1995, 08/462,513, filed June 5, 1995, 08/724,752, filed October 2, 1996, and 08/759,620, filed December 3, 1996, U.S. Patent Publication 2003/0217373, filed November 20, 2002, and U.S. Patent Nos. 6,833,268, 6,162,963, 6,150,584, 6,114,598, 6,075,181, and 5,939,598 and Japanese Patent Nos. 3 068 180 B2, 3 068 506 B2, and 3 068 507 B2. See also European Patent No., EP 0 463 151 B1, grant published June 12, 1996, International Patent Application No., WO 94/02602, published February 3, 1994, International Patent Application No., WO 96/34096, published October 31, 1996, WO 98/24893, published June 11, 1998, WO 00/76310, published December 21, 2000. The disclosures of each of the above-cited patents, applications, and references are hereby incorporated by reference in their entirety.

In an alternative approach, others, including GenPharm International, Inc., have utilized a "minilocus" approach. In the minilocus approach, an exogenous Ig locus is mimicked through the inclusion of pieces (individual genes) from the Ig locus. Thus, one or more V_H genes, one or more D_H genes, one or more J_H genes, a mu constant region, and a second constant region (preferably a gamma constant region) are formed into a construct for insertion into an animal. This approach is described in U.S. Patent No. 5,545,807 to Surani *et al.* and U.S. Patent Nos. 5,545,806, 5,625,825, 5,625,126, 5,633,425, 5,661,016, 5,770,429, 5,789,650, 5,814,318, 5,877,397, 5,874,299, and 6,255,458 each to Lonberg and Kay, U.S. Patent No. 5,591,669 and 6,023,010 to Krimpenfort and Berns, U.S. Patent Nos. 5,612,205, 5,721,367, and 5,789,215 to Berns *et al.*, and U.S. Patent No. 5,643,763 to Choi and Dunn, and GenPharm International U.S. Patent Application Serial Nos. 07/574,748, filed August 29, 1990, 07/575,962, filed August 31, 1990, 07/810,279, filed December 17, 1991, 07/853,408, filed March 18, 1992, 07/904,068, filed June 23, 1992, 07/990,860, filed December 16, 1992, 08/053,131, filed April 26, 1993, 08/096,762, filed July 22, 1993, 08/155,301, filed November 18, 1993, 08/161,739, filed December 3, 1993, 08/165,699, filed December 10, 1993, 08/209,741, filed March 9, 1994, the disclosures of which are hereby incorporated by reference. See

also European Patent No. 0 546 073 B1, International Patent Application Nos. WO 92/03918, WO 92/22645, WO 92/22647, WO 92/22670, WO 93/12227, WO 94/00569, WO 94/25585, WO 96/14436, WO 97/13852, and WO 98/24884 and U.S. Patent No. 5,981,175, the disclosures of which are hereby incorporated by reference in their entirety. See further Taylor *et al.*, 1992, Chen *et al.*, 1993, Tuaillon *et al.*, 1993, Choi *et al.*, 1993, Lonberg *et al.*, (1994), Taylor *et al.*, (1994), and Tuaillon *et al.*, (1995), Fishwild *et al.*, (1996), the disclosures of which are hereby incorporated by reference in their entirety.

Kirin has also demonstrated the generation of human antibodies from mice in which, through microcell fusion, large pieces of chromosomes, or entire chromosomes, have been introduced. See European Patent Application Nos. 773 288 and 843 961, the disclosures of which are hereby incorporated by reference. Additionally, KMTM mice, which are the result of cross-breeding of Kirin's Tc mice with Medarex's minilocus (Humab) mice have been generated. These mice possess the HC transchromosome of the Kirin mice and the kappa chain transgene of the Medarex mice (Ishida *et al.*, Cloning Stem Cells, (2002) 4:91-102).

Human antibodies can also be derived by *in vitro* methods. Suitable examples include, but are not limited to, phage display (as commercialized by Cambridge Antibody Technology, Morphosys, Dyax, Biosite/Medarex, Xoma, Symphogen, Alexion (formerly Proliferon), Affimed) ribosome display (as commercialized by Cambridge Antibody Technology), yeast display, and the like.

Antibodies, as described herein, were prepared through the utilization of the XENOMOUSE[®] technology, as described below. Such mice, then, are capable of producing human immunoglobulin molecules and antibodies and are deficient in the production of murine immunoglobulin molecules and antibodies. Technologies utilized for achieving the same are disclosed in the patents, applications, and references disclosed in the background

section herein. In particular, however, a preferred embodiment of transgenic production of mice and antibodies therefrom is disclosed in U.S. Patent Application Serial No. 08/759,620, filed December 3, 1996 and International Patent Application Nos. WO 98/24893, published June 11, 1998 and WO 00/76310, published December 21, 2000, the disclosures of which are hereby incorporated by reference. See also Mendez *et al. Nature Genetics* 15:146-156 (1997), the disclosure of which is hereby incorporated by reference.

Through the use of such technology, fully human monoclonal antibodies to a variety of antigens have been produced. Essentially, XENOMOUSE® lines of mice are immunized with an antigen of interest (e.g. HER-3), lymphatic cells (such as B-cells) are recovered from the mice that expressed antibodies, and the recovered cell lines are fused with a myeloid-type cell line to prepare immortal hybridoma cell lines. These hybridoma cell lines are screened and selected to identify hybridoma cell lines that produced antibodies specific to the antigen of interest. Provided herein are methods for the production of multiple hybridoma cell lines that produce antibodies specific to HER-3. Further, provided herein are characterization of the antibodies produced by such cell lines, including nucleotide and amino acid sequence analyses of the heavy and light chains of such antibodies.

In general, antibodies produced by the fused hybridomas were human IgG1 heavy chains with fully human kappa light chains. Antibodies described herein possess human IgG4 heavy chains as well as IgG1 heavy chains. Antibodies can also be of other human isotypes, including IgG2 or IgG3. The antibodies possessed high affinities, typically possessing a K_D of from about 10^{-5} through about 10^{-13} M or below, when measured by solid phase and cell-based techniques.

Another aspect of the present invention relates to an isolated nucleic acid molecule encoding a binding protein of the invention. Within the context of the present invention, the term "isolated nucleic acid molecule", as used

herein, means a polynucleotide of genomic, cDNA, or synthetic origin or some combination thereof, which by virtue of its origin, the "isolated nucleic acid molecule" (1) is not associated with all or a portion of a polynucleotide in which the "isolated polynucleotide" is found in nature, (2) is operably
5 linked to a polynucleotide which it is not linked to in nature, or (3) does not occur in nature as part of a larger sequence. Further, the term "nucleic acid molecule", as referred to herein, means a polymeric form of nucleotides of at least 10 bases in length, either ribonucleotides or deoxynucleotides or a modified form of either type of nucleotide, such as nucleotides with modified
10 or substituted sugar groups and the like. The term also includes single and double stranded forms of DNA.

In a one embodiment of the present invention, a nucleic acid molecule of the invention is operably linked to a control sequence. The term "control
15 sequence", as used herein, refers to polynucleotide sequences that are necessary to effect the expression and processing of coding sequences to which they are ligated. The nature of such control sequences differs depending upon the host organism. In prokaryotes, such control sequences generally include promoters, ribosomal binding sites, and transcription
20 termination sequences. In eukaryotes, generally, such control sequences include promoters and transcription termination sequences. In accordance with the present invention, the term "control sequence" is intended to include, at a minimum, all components whose presence is essential for expression and processing, and can also include additional components
25 whose presence is advantageous, for example, leader sequences and fusion partner sequences. Furthermore, the term "operably linked", as used herein, refers to positions of components so described which are in a relationship permitting them to function in their intended manner. Moreover, according to the present invention, an expression control sequence operably linked to a
30 coding sequence is ligated in such a way that expression of the coding sequence is achieved under conditions compatible with the expression control sequence.

A further aspect of the present invention is a vector comprising a nucleic acid molecule that encodes a binding protein of the invention. The nucleic acid molecule can be operably linked to a control sequence. Furthermore, the vector may additionally contain a replication origin or a selection marker gene. Examples of vectors that may be used in accordance with the present invention are e.g. plasmids, cosmids, phages, viruses, etc.

Another aspect of the present invention relates to a host cell transformed with a nucleic acid molecule or vector of the invention. Transformation could be done by any known method for introducing polynucleotides into a host cell, including for example packaging the polynucleotide in a virus (or into a viral vector) and transducing a host cell with the virus (or vector) or by transfection procedures known in the art, as exemplified by U.S. Patent Nos. 4,399,216, 4,912,040, 4,740,461, and 4,959,455, which patents are hereby incorporated herein by reference. Particularly, methods for introducing heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei. Examples of host cells that may be used according to the present invention are hybridomas eukaryotic cells such as mammalian cells, e.g. hamster, rabbit, rat, pig, mouse or other animal cells; plant cells and fungal cells, e.g. corn, tobacco, *Saccharomyces cerevisiae*, *Pichia pastoris*; prokaryotic cells such as *E. coli*; and other cells used in the art for the production of antibodies. Especially mammalian cell lines available as hosts for expression are well known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g. Hep G2), and a number of other cell lines.

Yet another aspect of the present invention is a pharmaceutical composition

comprising as an active agent at least one binding protein of the invention and pharmaceutically acceptable carriers, diluents and/or adjuvants. The term "pharmaceutical composition", as used herein, refers to a chemical compound or composition capable of inducing a desired therapeutic effect when properly administered to a patient (*The McGraw-Hill Dictionary of Chemical Terms*, Parker, S., Ed., McGraw-Hill, San Francisco (1985), incorporated herein by reference). In accordance with the present invention, the potency of the pharmaceutical composition of the invention is based on the binding of the at least one binding protein to HER-3. Preferably, this binding leads to a reduction of the HER-3-mediated signal transduction.

Furthermore, the term "carriers", when used herein, includes carriers, excipients, or stabilizers that are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution or a liposome (a small vesicle composed of various types of lipids, phospholipids and/or surfactants which is useful for delivery of a drug to a mammal). Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, polyethylene glycol (PEG), and PLURONICS™.

In a one embodiment of the present invention, the at least one binding protein of the invention contained in the pharmaceutical composition is coupled to an effector, such as calicheamicin, Auristatin-PE, a radioisotope or a toxic chemotherapeutic agent such as geldanamycin and maytansine. In particular, these binding protein conjugates are useful in targeting cells, e.g.

cancer cells, expressing HER-3 for elimination.

Moreover, linking binding proteins of the invention to radioisotopes e.g. provides advantages to tumor treatments. Unlike chemotherapy and other forms of cancer treatment, radioimmunotherapy or the administration of a radioisotope-binding protein combination directly targets the cancer cells with minimal damage to surrounding normal, healthy tissue. With this "magic bullet", the patient can be treated with much smaller quantities of radioisotopes than other forms of treatment available today. Preferred radioisotopes include yttrium⁹⁰ (⁹⁰Y), indium¹¹¹ (¹¹¹In), ¹³¹I, ^{99m}Tc, radiosilver-111, radiosilver-199, and Bismuth²¹³. The linkage of radioisotopes to binding proteins of the invention may e.g. be performed with conventional bifunctional chelates. Since silver is monovalent, for radiosilver-111 and radiosilver-199 linkage, sulphur-based linkers may be used (Hazra *et al.*, *Cell Biophys.* 24-25, 1-7 (1994)). Linkage of silver radioisotopes may involve reducing the immunoglobulin with ascorbic acid. Furthermore, tiuxetan is an MX-DTPA linker chelator attached to ibritumomab to form ibritumomab tiuxetan (Zevalin) (Witzig, T.E, *Cancer Chemother. Pharmacol.* 48 Suppl 1, 91-5 (2001). Ibritumomab tiuxetan can react with radioisotypes such as indium¹¹¹ (¹¹¹In) or ⁹⁰Y to form ¹¹¹In-ibritumomab tiuxetan and ⁹⁰Y-ibritumomab tiuxetan, respectively.

Furthermore, a binding protein of the invention, particularly when used to treat cancer, may be conjugated with toxic chemotherapeutic drugs such as calicheamicin (Hamann *et al.*, *Bioconjug. Chem.* 13(1), 40-6 (2002), geldanamycin (Mandler *et al.*, *J. Natl. Cancer Inst.*, 92(19), 1549-51 (2000)) and maytansine, for example, the maytansinoid drug, DM1 (Liu *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 93:8618-8623 (1996)). Different linkers that release the drugs under acidic or reducing conditions or upon exposure to specific proteases may be employed with this technology. According to the present invention, a binding protein of the invention may be conjugated as described in the art.

Auristatin-PE, e.g. is an antimicrotubule agent that is a structural modification of the marine, shell-less mollusk peptide constituent dolastatin 10. Auristatin-PE has both anti-tumor activity and anti-tumor vascular activity (Otani *et al.*, *Jpn. J. Cancer Res.* 91(8), 837-44 (2000)). For example, 5 auristatin-PE inhibits cell growth and induces cell cycle arrest and apoptosis in pancreatic cancer cell lines (Li *et al.*, *Int. J. Mol. Med.* 3(6), 647-53 (1999)). Accordingly, to specifically target the anti-tumor activity and anti-tumor vascular activities of auristatin-PE to particular tumors, auristatin-PE may be conjugated to the binding protein of the invention.

10 In a one embodiment of the present invention, the pharmaceutical composition comprises at least one further active agent. Examples for further active agents, which may be used in accordance with the present invention, are antibodies or low molecular weight inhibitors of other receptor protein kinases, such as 15 EGFR, HER-2, HER-4, IGFR-1, or c-met, receptor ligands such as vascular endothelial factor (VEGF), cytotoxic agents, such as doxorubicin, cis-platin or carboplatin, cytokines or antineoplastic agents. Many antineoplastic agents are presently known in the art. In one embodiment, the antineoplastic agent is selected from the group of therapeutic proteins including, but not limited to, 20 antibodies or immunomodulatory proteins. In another embodiment the antineoplastic agent is selected from the group of small molecule inhibitors or chemotherapeutic agents consisting of mitotic inhibitors, kinase inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, histone 25 deacetylase inhibitors, anti-survival agents, biological response modifiers, anti-hormones, e.g. anti-androgens, and anti-angiogenesis agents. When the anti-neoplastic agent is radiation, treatment can be achieved either with an internal (brachytherapy BT) or external (external beam radiation therapy: EBRT) source.

30 The pharmaceutical composition of the present invention is especially suitable for the diagnosis, prevention or treatment of a hyperproliferative disease. The hyperproliferative disease may be, e.g., associated with

increased HER family signal transduction. Particularly, the disease can be associated with increased HER-3 phosphorylation and/or increased complex formation between HER-3 and other members of the HER family and/or increased PI₃ kinase activity and/or increased c-jun terminal kinase activity and/or AKT activity and/or increased ERK2 activity and/or PYK2 activity. Preferably, the hyperproliferative disease is selected from the group consisting of breast cancer, gastrointestinal cancer, pancreatic cancer, prostate cancer, ovarian cancer, stomach cancer, endometrial cancer, salivary gland cancer, lung cancer, kidney cancer, colon cancer, colorectal cancer, thyroid cancer, bladder cancer, glioma, melanoma or other HER-3 expressing or overexpressing cancers, and the formation of tumor metastases.

In accordance with the present invention, the term "prevention or treatment", when used herein, refers to both therapeutic treatment and prophylactic or preventative measures, wherein the patient in need is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of prevention or treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented. The patient in need of prevention or treatment is a mammalian patient, i.e. any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Preferably, the patient in need of treatment is a human patient.

According to the present invention, the pharmaceutical composition of the invention may be formulated by mixing the active agent(s) with physiologically acceptable carriers, diluents and /or adjuvants, and optionally other agents that are usually incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. The pharmaceutical composition of the invention may be formulated e.g. in the form of lyophilized formulations, aqueous solutions, dispersions or solid preparations, such as tablets, dragees or capsules. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's

Pharmaceutical Sciences (18th ed, Mack Publishing Company, Easton, PA (1990)), particularly Chapter 87 by Block, Lawrence, therein. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as Lipofectin™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. Any of the foregoing mixtures may be appropriate in treatments and therapies in accordance with the present invention, provided that the active agent in the formulation is not inactivated by the formulation and the formulation is physiologically compatible and tolerable with the route of administration. See also Baldrick P., "Pharmaceutical excipient development: the need for preclinical guidance.", *Regul. Toxicol. Pharmacol.* 32(2), 210-218 (2000); Wang W., "Lyophilization and development of solid protein pharmaceuticals.", *Int. J. Pharm.* 203(1-2), 1-60 (2000); Charman W.N., "Lipids, lipophilic drugs, and oral drug delivery-some emerging concepts.", *J. Pharm. Sci.* 89(8), 967-978 (2000); Powell *et al.*, "Compendium of excipients for parenteral formulations", *PDA J. Pharm. Sci. Technol.* 52, 238-311 (1998); and the citations therein for additional information related to formulations, excipients and carriers well known to pharmaceutical chemists.

Another aspect of the present invention pertains to the use of at least one isolated binding protein of the invention, and optionally at least one other active agent, e.g. at least one anti-neoplastic agent as described above, in admixture with pharmaceutically acceptable carriers, diluents and/or adjuvants, for the manufacture of a pharmaceutical composition for the diagnosis, prevention or treatment of a hyperproliferative disease. Preferably, the pharmaceutical composition is a pharmaceutical composition as described above and the hyperproliferative disease is a hyperproliferative disease as mentioned above.

Yet another aspect of the present invention is concerned with a method for

diagnosing diseases or conditions associated with the expression of HER-3, comprising contacting a sample with a binding protein of the invention, and detecting the presence of HER-3 in the sample. The sample may be a cell that shows expression of HER-3, such as a tumor cell, a blood sample or another suitable sample. In a preferred embodiment of the present invention, the diseases or conditions associated with the expression of HER-3 are the hyperproliferative diseases defined above.

According to the present invention, the method may, e.g., be used for the detection of HER-3 antigen in a cell, for the determination of HER-3 antigen concentration in patients suffering from a hyperproliferative disease as mentioned above or for the staging of said hyperproliferative disease in a patient. In order to stage the progression of a hyperproliferative disease in a subject under study, or to characterize the response of the subject to a course of therapy, a sample of blood can, e.g., be taken from the subject and the concentration of the HER-3 antigen present in the sample is determined. The concentration so obtained is used to identify in which range of concentrations the value falls. The range so identified correlates with a stage of progression or a stage of therapy identified in the various populations of diagnosed subjects, thereby providing a stage in the subject under study. A biopsy of the disease, e.g. cancer, tissue obtained from the patient may also be used assess the amount of HER-3 antigen present. The amount of HER-3 antigen present in the disease tissue may be assessed by immunohistochemistry, ELISA or antibody arrays using HER3 antibodies of the invention. Other parameters of diagnostic interest are the dimerization state as well as the dimerization partners of the HER3 protein and the activation state of it and its partners. Protein analytical methods to determine those parameters are well known in the art and are among others western blot and immunoprecipitation techniques, FACS analysis, chemical crosslinking, bioluminescence resonance energy transfer (BRET), fluorescence resonance energy transfer (FRET) and the like (e.g. Price et al, Methods in Molecular Biology, 218: 255-268 (2002) or the eTag technology (WO0503707, WO04091384, WO04011900).

Furthermore, the present invention relates in another aspect to a method for preventing or treating diseases or conditions associated with the expression of HER-3 in a patient, comprising administering to a patient in need thereof an effective amount of at least one binding protein of the invention. Preferably, the diseases or conditions associated with the expression of HER-3 are the hyperproliferative diseases defined above. The patient in need of prevention or treatment is a mammalian patient, i.e. any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Preferably, the patient in need is a human patient.

In a preferred embodiment of the present invention, the method for preventing or treating a hyperproliferative disease in a patient in need thereof comprises administering to the patient an effective amount of at least one binding protein of the invention and additionally at least one other active agent, e.g., at least one antineoplastic agent as mentioned above. Preferably, the method is for inhibiting abnormal cell growth, migration or invasion.

In addition to classical modes of administration of potential binding protein therapeutics, e.g. via the above mentioned formulations, newly developed modalities of administration may also be useful according to the present invention. For example, local administration of ¹³¹I-labeled monoclonal antibody for treatment of primary brain tumors after surgical resection has been reported. Additionally, direct stereotactic intracerebral injection of monoclonal antibodies and their fragments is also being studied clinically and pre-clinically. Intracarotid hyperosmolar perfusion is an experimental strategy to target primary brain malignancy with drug conjugated human monoclonal antibodies.

Depending on the type and severity of the condition to be treated, about 1 µg/kg to 15 mg/kg of the at least one binding protein of the invention may be

administered to a patient in need thereof, e.g. by one or more separate administrations or by continuous infusion. A typical daily dosage might range from about 1 µg/kg to about 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer,
5 depending on the condition to be treated, the treatment is sustained until a desired suppression of disease symptoms occurs.

The dose of the at least one antineoplastic agent administered depends on a variety of factors. These are, for example, the nature of the agent, the tumor
10 type or the route of administration. It should be emphasized that the present invention is not limited to any dose.

Finally, the present invention relates in a further aspect to a kit for the diagnosis, prevention or treatment of hyperproliferative diseases associated
15 with HER-3 mediated signal transduction, comprising the at least one binding protein and/or nucleic acid molecule and/or vector of the invention. In addition, the kit of the invention can further comprise at least one other active agent, e.g. at least one other antineoplastic agent as mentioned above.

20

Further, the present invention shall be explained by the following Examples and the accompanying drawing figures.

EXAMPLES

25

The following examples, including the experiments conducted and results achieved, are provided for illustrative purposes only and are not to be construed as limiting upon the present invention.

30

EXAMPLE 1: HER-3 antigen and cell line preparation

In the present study, recombinant HER-3 proteins were prepared. The extracellular domain of HER-3 (ECD) cDNA was cloned by polymerase chain

reaction (PCR) from pcDNA3-HER-3 (expression vector with full length human HER-3, C.Wallasch et al., *EMBO J.* 14, 4267-4275) with primers based on the sequence of HER-3 (Genebank AccNr. NM_001982).

- 5 The primers used for the amplification of HER-3 were as follows:

Forward primer: 5'-CGGGATCCATGTCCTAGCCTAGGGGC-3' (SEQ ID NO: 233)

- 10 Reverse primer:

5'-GCTCTAGATTAATGATGATGATGATGATGTTGTCCTAAACAGTCTTG-3' (SEQ ID NO: 234)

- 15 The PCR product was digested with BamH1 and XbaI and ligated into pcDNA3 (Invitrogen) digested with BamH1 and XbaI. Plasmids were transfected into HEK293 cells using a CaPO₄ method. The HER-3-HIS fusion protein was purified from harvested conditioned media via Ni-NTA affinity chromatography.

- 20 Rat1 HER-3 cells were generated by retroviral gene transfer. Briefly, GP+E 86 cells (3×10^5) were seeded on a 60 mm culture disc and transfected with 2 µg/ml pLXSN vector or pLXSN-HER-3 cDNA (C. Wallasch, PhD Thesis, Max-Planck Institute of Biochemistry, Martinsried, Germany) using the calcium phosphate method. After 24h medium was replaced by fresh medium and
25 the GP+E 86 cells were incubated for 4-8 hrs. Subconfluent Rat1 cells (2×10^5 cells per 6 cm dish) were then incubated with supernatants of GP+E 86 cells releasing high titer pLXSN or pLXSN-HER-3, p virus ($>1 \times 10^6$ G418 c.f.u./ml; m.o.i. of 10) for 4-12 h in the presence of Polybrene (4 mg/ml; Aldrich). After changing the medium, selection of Rat1 cells with G418
30 was started. Usually, stable clones were picked after selection for 21 days.

EXAMPLE 2: HER-3 expression in human cancer cell lines

Receptor tyrosine kinases, as for example HER-3, play a crucial role in the initiation and progression of hyperproliferative diseases such as the transition from benign hyperplastic cell growth towards a malignant carcinoma. Since HER-3 expression varies between tumor cells and normal tissue an analysis of HER-3 expression is a critical factor for identification of patient subgroups that would benefit from treatment with binding proteins of the invention. Thus, HER-3 expression was quantified in a panel of human cancer cell lines to elucidate the role of HER-3 in human cancer formation. Cancer cell lines were grown as recommended by the ATCC. In detail, 10⁵ cells were harvested with 10 mM EDTA in PBS, washed once with FACS buffer (PBS, 3 % FCS, 0.4 % azide) and seeded on a 96-well round bottom plate. The cells were spun for 3 min at 1000 rpm to remove supernatant and then resuspended with α -HER-3 antibody 2D1D12 (WO03013602) (3 μ g/ml). Cell suspensions were incubated on ice for 1 hr, washed twice with FACS buffer and resuspended with secondary antibody (100 μ l/well) donkey-anti-human-PE (Jackson) diluted 1:50 in FACS buffer. The cell suspensions were incubated on ice and in the dark for 30 min, washed twice with FACS buffer and analyzed (FACS, Beckman Coulter). Fig. 1 shows representative results of the analysis and demonstrates that HER-3 is expressed in a variety of human cancers.

EXAMPLE 3: Immunization and titering

The HER-3 ECD protein, that was prepared as described in Example 1 and C32 cells (Human melanoma; ATCC #CRL-1585) were used as an antigen. Monoclonal antibodies against HER-3 were developed by sequentially immunizing XenoMouse[®] mice (XenoMouse[®] strains: XMG1 and XMG4, Abgenix, Inc. Fremont, CA). XenoMouse[®] animals were immunized via footpad route for all injections. The total volume of each injection was 50 μ l per mouse, 25 μ l per footpad.

For cohort #1 (10 XMG1 mice), the initial immunization was with 10 μ g of

HER-3 ECD protein admixed 1:1 (v/v) with TITERMAX GOLD® (Sigma, Oakville, ON) per mouse. The subsequent five boosts were made with 10 µg of HER-3 ECD protein admixed 1:1 (v/v) with 100 µg alum gel (Sigma, Oakville, ON) in pyrogen-free D-PBS. The sixth boost consisted of 10 µg of HER-3 ECD protein admixed 1:1 (v/v) with TITERMAX GOLD®. The seventh injection consisted of 10 µg of HER-3 ECD protein admixed 1:1 v/v with 100 µg alum gel. A final boost was made with 10 µg HER-3 ECD protein in pyrogen-free DPBS, without adjuvant. The XenoMouse® mice were immunized on days 0, 4, 7, 11, 15, 20, 24, and 29 for this protocol and fusions were performed on day 33. The two bleeds were made through Retro-Orbital Bleed procedure on day 13 after the fourth boost, on day 19 after the sixth boost. There was no cohort #2.

For Cohort #3 (10 XMG1 mice) and Cohort #4 (10 XMG4 mice), the first injection was with 10⁷ C32 cells in pyrogen-free Dulbecco's PBS (DPBS) admixed 1:1 (v/v) with TITERMAX GOLD® per mouse. The next four boosts were with 10⁷ C32 cells in pyrogen-free DPBS, admixed with 25 µg of Adju-Phos and 10 µg CpG per mouse. The sixth boost was with 10⁷ C32 cells in pyrogen-free DPBS, admixed 1:1 (v/v) with TITERMAX GOLD® per mouse. The seventh, eighth, ninth boosts were with 10⁷ C32 cells in pyrogen-free DPBS, admixed with 25 µg of Adju-Phos and 10 µg CpG per mouse. From tenth to fourteen boosts were 5 µg of HER-3 ECD protein in pyrogen-free DPBS, admixed with 25 µg of Adju-Phos and 10 µg CpG per mouse. A final boost consisted of 5 µg of HER-3 ECD protein in pyrogen-free DPBS, without adjuvant. Both Cohort #3 and #4, the XenoMouse® mice were immunized on days 0, 3, 7, 11, 14, 17, 21, 24, 28, 33, 35, 38, 42 and 45 for this protocol and fusions were performed on day 49. The three bleeds were made through Retro-Orbital Bleed procedure on day 12 after the fourth boost, on day 19 after the sixth boost and on day 40 after twelfth boost.

Selection of animals for harvest by titer

For cohort #1, anti-HER-3 antibody titers in the serum from immunized

XenoMouse® mice were determined by ELISA against HER-3 ECD protein. The specific titer of each XenoMouse® animal was determined from the optical density at 650 nm and is shown in Table 1 below. The titer value is the reciprocal of the greatest dilution of sera with an OD reading two-fold
5 that of background. Therefore, the higher the number, the greater was the humoral immune response to HER-3 ECD.

TABLE 1

Cohort #1, XMG1

Mouse ID	After 4 inj.	After 6 inj.
P3421	8,000	11,000
P3422	850	2,600
P3423	2,700	5,200
P3424	3,200	9,100
P3425	5,400	2,500
P3426	700	1,500
P3427	5,800	7,000
P3428	3,900	4,300
P3429	2,200	2,500
P34210	600	850
NC	250	175
PC	377,000	311,000
NC	mAb IL-8, D39.2.1	
PC	xHER-3-2D1D12	

5

For cohort #3 and #4, anti-HER-3 antibody titers in the serum from immunized XenoMouse® mice were determined by FACS using Rat1/HER-3 cells (antigen positive cell line) cells and Rat1/pLSXN cells (antigen negative cell line). Data are presented as geometric mean (GeoMean) fluorescent intensity of cell anti-HER-3 cell staining by serial dilutions of serum samples.

10

TABLE 2

Cohort #3, XMG1

5

Mouse ID	Sample dilution	After 6 inj.		After 12 inj.	
		pos cells GeoMean	neg cells GeoMean	pos cells GeoMean	neg cells GeoMean
Q832-1	1:50	9	10	11	10
	1:250	6	9	6	6
	1:1250	6	7	4	4
Q832-2	1:50	8	10	29	42
	1:250	7	8	11	11
	1:1250	5	6	6	5
Q832-3	1:50	7	12	11	9
	1:250	5	7	5	5
	1:1250	5	5	4	4
Q832-4	1:50	6	10	9	9
	1:250	6	6	5	5
	1:1250	5	5	4	4
Q832-5	1:50	11	11	17	13
	1:250	10	9	7	6
	1:1250	6	8	5	4
Q832-6	1:50	7	11	15	14
	1:250	7	7	7	6
	1:1250	5	6	6	4
Q832-7	1:50	8	11	7	15
	1:250	6	7	5	5
	1:1250	5	5	4	4
Q832-8	1:50	7	8	11	20
	1:250	6	6	7	8
	1:1250	5	5	5	4
Q832-9	1:50	7	12	15	16
	1:250	6	8	6	5
	1:1250	6	6	4	4
Q832-10	1:50	8	13	34	38
	1:250	6	8	9	8
	1:1250	6	6	5	4

TABLE 3

Cohort #4, XMG4

Mouse ID	Sample dilution	After 6 inj.		After 12 inj.	
		pos cells GeoMean	neg cells GeoMean	pos cells GeoMean	neg cells GeoMean
Q856-1	1:50	4	6	91	44
	1:250	4	5	32	18
	1:1250	4	4	19	10
Q856-2	1:50	4	8	148	54
	1:250	4	5	89	23
	1:1250	4	4	42	9
Q856-3	1:50	4	5	72	14
	1:250	4	4	28	6
	1:1250	4	4	18	4
Q856-4	1:50	4	5	11	49
	1:250	4	5	10	17
	1:1250	4	4	8	7
Q856-5	1:50	4	4	74	20
	1:250	4	4	30	14
	1:1250	4	4	16	6
Q856-6	1:50	4	5	86	21
	1:250	4	4	32	10
	1:1250	4	4	16	5
Q856-7	1:50	5	6	74	32
	1:250	4	5	32	14
	1:1250	4	4	16	6
Q856-8	1:50	4	5	106	14
	1:250	4	4	45	6
	1:1250	4	4	22	4
Q856-9	1:50	5	6	53	22
	1:250	4	4	17	11
	1:1250	4	4	11	5
Q856-10	1:50	4	5	72	53
	1:250	4	4	26	17
	1:1250	4	4	15	7

EXAMPLE 4: Recovery of lymphocytes. B-Cell isolations, fusions and generation of hybridomas

Immunized mice were sacrificed and the lymph nodes were harvested and pooled from each cohort. The lymphoid cells were dissociated by grinding in DMEM to release the cells from the tissues, and the cells were suspended in DMEM. The cells were counted, and 0.9 ml DMEM per 100 million lymphocytes was added to the cell pellet to resuspend the cells gently but completely. Using 100 μ l of CD90+ magnetic beads per 100 million cells, the cells were labeled by incubating the cells with the magnetic beads at 4 °C for 15 min. The magnetically-labeled cell suspension containing up to 10^8 positive cells (or up to 2×10^8 total cells) was loaded onto a LS+ column and the column washed with DMEM. The total effluent was collected as the CD90-negative fraction (most of these cells were expected to be B cells).

The fusion was performed by mixing washed enriched B cells from above and nonsecretory myeloma P3X63Ag8.653 cells purchased from ATCC (Cat. No. CRL 1580) (Kearney et al, J. Immunol. 123, 1979, 1548-1550) at a ratio of 1:1. The cell mixture was gently pelleted by centrifugation at 800 g. After complete removal of the supernatant, the cells were treated with 2 to 4 ml of pronase solution (CalBiochem, Cat. No. 53702; 0.5 mg/ml in PBS) for no more than 2 min. Then 3 to 5 ml of FBS was added to stop the enzyme activity and the suspension was adjusted to 40 ml total volume using electro cell fusion solution, ECFS (0.3 M sucrose, Sigma, Cat. No. S7903, 0.1 mM magnesium acetate, Sigma, Cat. No. M2545, 0.1 mM calcium acetate, Sigma, Cat. No. C4705). The supernatant was removed after centrifugation and the cells were resuspended in 40 ml ECFS. This wash step was repeated and the cells again were resuspended in ECFS to a concentration of 2×10^6 cells/ml.

Electro-cell fusion was performed using a fusion generator, model ECM2001, Genetronic, Inc., San Diego, CA. The fusion chamber size used was 2.0 ml, using the following instrument settings: Alignment condition:

voltage: 50 V, time: 50 sec; membrane breaking at: voltage: 3000 V, time: 30 μ sec; post-fusion holding time: 3 sec.

After ECF, the cell suspensions were carefully removed from the fusion chamber under sterile conditions and transferred into a sterile tube containing the same volume of Hybridoma Culture Medium (DMEM (JRH Biosciences), 15 % FBS (Hyclone), supplemented with L-glutamine, pen/strep, OPI (oxaloacetate, pyruvate, bovine insulin) (all from Sigma) and IL-6 (Boehringer Mannheim). The cells were incubated for 15 to 30 min at 37 °C, and then centrifuged at 400 g for five min. The cells were gently resuspended in a small volume of Hybridoma Selection Medium (Hybridoma Culture Medium supplemented with 0.5x HA (Sigma, Cat. No. A9666)), and the volume was adjusted appropriately with more Hybridoma Selection Medium, based on a final plating of 5×10^6 B cells total per 96-well plate and 200 μ l per well. The cells were mixed gently and pipetted into 96-well plates and allowed to grow. On day 7 or 10, one-half the medium was removed, and the cells were re-fed with Hybridoma Selection Medium.

EXAMPLE 5: Selection of candidate antibodies by ELISA

After 14 days of culture, primary screening of hybridoma supernatants from the cohort #1 (mice in cohort one were split arbitrarily into fusion #1 and #2) for HER-3-specific antibodies was performed by ELISA using purified his-tagged HER-3 ECD and counter-screening against an irrelevant his-tagged protein by ELISA using goat anti-huIgGFC-HRP (Caltag Inc., Cat. No. H10507, using concentration was 1:2000 dilution) to detect human IgG binding to HER-3 ECD immobilized on ELISA plates. The old culture supernatants from the positive hybridoma cells growth wells based on primary screen were removed and the HER-3 positive hybridoma cells were suspended with fresh hybridoma culture medium and were transferred to 24-well plates. After 2 days in culture, these supernatants were ready for a secondary confirmation screen. In the secondary confirmation screen for HER-3 specific fully human IgGk antibodies, the positives in the first

screening were screened by ELISA with two sets of detective antibodies: goat anti-huIgG-Fc-HRP (Caltag Inc., Cat. No. H10507, using concentration was 1:2000 dilution) for human gamma chain detection and goat anti-huIg kappa-HRP (Southern Biotechnology, Cat. No. 2060-05) for human kappa light chain detection. There were 91 fully human IgG/kappa HER-3 specific monoclonal antibodies that were generated from cohort #1.

EXAMPLE 6: Selection of candidate antibodies by FMAT/FACS

After 14 days of culture, hybridoma supernatants from the cohort #3 and #4 (fusion #3 and #4) were screened for HER-3-specific monoclonal antibodies by FMAT. In the primary screen, hybridoma supernatants at 1:10 final dilution were incubated with Rat1-Her3 cells expressing human HER-3 and 400 ng/ml Cy5-conjugated Goat F(ab')₂ anti-human IgG, Fc-specific antibody (Jackson ImmunoResearch, Cat. No. 109-176-098) at room temperature for 6 hr. The binding of antibodies and detection antibodies complex to cells were measured by FMAT (Applied Biosystems). Non-specific binding of antibodies to the cells was determined by their binding to parental Rat1 cells. A total of 420 hybridomas producing HER-3-specific antibodies were selected from primary screen of fusion #3. The supernatants from these expanded cultures were tested again using the same FMAT protocol and 262 of them were confirmed to bind to HER-3 expressing cells specifically. A total of 193 hybridomas producing HER-3 specific antibodies were selected from primary screen of fusion #4. The supernatants from these expanded cultures were tested by FACS and 138 of them were confirmed to bind to HER-3 expressing cells specifically. In the FACS confirmation assay, Rat1-Xher3 cells and parental Rat1 cells (as negative control) were incubated with hybridoma supernatants at 1:2 dilution for 1 hr at 40C in PBS containing 2 % FBS. Following washing with PBS, the binding of antibodies to the cells were detected by 2.5 µg/ml Cy5-conjugated Goat F(ab')₂ anti-human IgG, Fc-specific antibody (JIR#109-176-098) and 5 µg/ml PE-conjugated Goat F(ab')₂ anti-human kappa-specific antibody (SB# 2063-09). After removing the unbound antibodies by washing with PBS, the

cells were fixed by cytofix (BD# 51-2090KZ) at 1:4 dilution and analyzed by FACSCalibur.

EXAMPLE 7: Selection of hybridomas for cloning

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Antibodies from cohorts 1 and 2 were selected for hybridoma cloning based on specificity for HER-3 over HER1 (EGFR), HER-2 and HER-4 in ELISA using purified recombinant extra-cellular domains available from, for example R&D Biosystems, and FACS-based analysis of human tumor cell
10 lines expressing different HER family members, and a > 5-time increase in mean fluorescent intensity in FACS staining for HER-3 positive cells over background. Based on these criteria, a total of 23 hybridoma lines were selected for cloning by limiting dilution cell plating.

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Antibodies from cohorts 3 and 4 were selected for hybridoma cloning based on specificity for HER-3 over HER-1 (EGFR), HER-2 and HER-4 plus three other criteria. The first criterion was an ELISA screen for antibodies with epitopes contained within the L2 domain of HER-3 (see Example "Structural Analysis of anti-HER-3 Antibodies in the Invention").

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The second criterion was neutralization of binding of biotinylated heregulin-alpha to HER-3 expressing cells in a FACS based assay. SKBR-3 cells were harvested, washed in culture medium, pelleted via centrifugation and resuspended in culture medium. Resuspended cells were aliquoted into 96-
25 well plates. The plates were centrifuged to pellet the cells. Test antibodies in exhaust hybridoma supernatants were added at 25µl/well and incubated for 1 hr on ice to allow antibody binding. Fifty µl of a 10 nM heregulin-alpha (R&D Biosystems, Minneapolis, MN) solution was added to each well for a final concentration of 5 nM and incubated on ice for 1.5 hr. Cells were
30 washed in 150 µl PBS, pelleted by centrifugation and the supernatant removed. Cells were resuspended in 50 µl of goat anti-HRG-alpha polyclonal antibody at 10 µg/ml and incubated for 45 min of ice. Cells were washed in 200 µl PBS, pelleted by centrifugation and the supernatant

removed. Fifty μ l of a solution of rabbit Cy5-labeled anti-goat polyclonal antibody at 5 μ g/ml plus 7AAD at 10 μ g/ml was added and incubated on ice for 15 min. Cells were washed in 200 μ l PBS, pelleted by centrifugation and the supernatant removed. The cells were resuspended in 100 μ l of FACS buffer and read in the FACS. Test HER-3 antibodies that reduced binding of heregulin-alpha were those that had lowest fluorescence intensity. As positive controls, 1:5 serial dilutions from 10,000 ng/ml to 16 ng/ml of a mouse HER-3 mAb (105.5) or the human IgG1 HER-3 mAb, U1-49 was used. Negative controls were heregulin-alpha alone, cells alone, goat anti-hereregulin-alpha polyclonal antibody alone and rabbit Cy5-labeled anti-goat polyclonal antibody alone.

The third criterion was relative ranking for affinity and/or higher relative mean fluorescence intensity in FACS using HER-3 expressing cell lines. Relative ranking for affinity was performed by normalizing HER-3-specific antibody concentrations and plotting versus data from limiting antigen ELISA as follows.

Normalization of antigen specific antibody concentrations using high antigen ELISA

Using an ELISA method, supernatants for concentration of antigen specific antibody were normalized. Using two anti-HER-3 human IgG1 antibodies from cohort 1 of known concentration titrated in parallel, a standard curve was generated and the amount of antigen specific antibody in the test hybridoma supernatants from cohorts 3 and 4 were compared to the standard. In this way, the concentration of human HER3 IgG antibody in each hybridoma culture was estimated.

Neutravidin plates were made by coating neutravidin @ 8 μ g/ml in 1XPBS/0.05% sodium azide on Costar 3368 medium binding plates at 50 μ l/well with overnight incubation at 4° C. The next day the plates were blocked with 1XPBS/1% skim milk. Photobiotinylated his-tagged-HER-3 ECD @ 500 ng/ml in 1XPBS/1% skim milk was bound to the neutravidin

plates by incubating for 1 hour at room temperature. Hybridoma supernatant, serially diluted 1:2.5 from a starting dilution of 1:31 to a final dilution of 1:7568 in 1XPBS/1% skim milk/0.05% azide, was added at 50 μ l/well, and then incubated for 20 hours at room temperature. Serially dilutions were used to ensure obtaining OD readings for each unknown in the linear range of the assay. Next, a secondary detection antibody, goat anti human IgG Fc HRP at 400 ng/ml in 1XPBS/1%skim milk was added at 50 μ l/well. After 1 hour at room temperature, the plates were again washed 5 times with water and 50 μ L of one-component TMB substrate were added to each well. The reaction was stopped after 30 minutes by the addition of 50 μ l of 1M hydrochloric acid to each well and the plates were read at wavelength 450nm. A standard curve was generated from the two IgG1 HER-3 mAbs from cohort 1, serially diluted at 1:2 from 1000 ng/ml to 0.06 ng/ml and assessed in ELISA using the above protocol. For each unknown, OD readings in the linear range of the assay were used to estimate the concentration of human HER-3 IgG in each sample.

The limited antigen analysis is a method that affinity ranks the antigen-specific antibodies prepared in B-cell culture supernatants relative to all other antigen-specific antibodies. In the presence of a very low coating of antigen, only the highest affinity antibodies should be able to bind to any detectable level at equilibrium. (See, e.g., PCT Publication WO/03048730A2 entitled "IDENTIFICATION OF HIGH AFFINITY MOLECULES BY LIMITED DILUTION SCREENING" published on June 12, 2003). In this instance, two mAbs from cohort 1, both of known concentration and known KD, were used as benchmarks in the assay.

Neutravidin plates were made by coating neutravidin at 8 μ g/ml in 1XPBS/0.05% sodium azide on Costar 3368 medium binding plates at 50 μ l/well with overnight incubation at 4° C. The next day the plates were blocked with 1XPBS/1% skim milk. Biotinylated his-tagged-HER-3 ECD (50 μ l/well) was bound to 96-well neutravidin plates at five concentrations: 125, 62.5, 31.2, 15.6, and 7.8 ng/ml in 1XPBS/1% skim milk for 1 hour at room

temperature. Each plate was washed 5 times with water. Hybridoma supernatants diluted 1:31 in 1XPBS/1%skim milk/0.05% azide were added at 50 μ l/well. After 20 hours incubation at room temperature on a shaker, the plates were again washed 5 times with dH₂O. Next, a secondary detection antibody, goat anti human IgG Fc HRP (Horsh Radish Peroxidase) at 400 ng/ml in 1XPBS/1%skim milk was added at 50 μ l/well. After 1 hour at room temperature, the plates were again washed 5 times with dH₂O and 50 μ L of one-component TMB substrate were added to each well. The reaction was stopped after 30 minutes by the addition of 50 μ L of 1M hydrochloric acid to each well and the plates were read at wavelength 450nm. OD readings from an antigen concentration that yielded OD values in the linear range were used in for data analysis.

Plotting the high antigen data, which comparatively estimates specific antibody concentration (see above for details), versus the limited antigen OD illustrated the relatively higher affinity antibodies, e.g., those that bound had higher OD in the limited antigen assay while having lower amounts of IgG HER-3 antibody in the supernatant.

Hybridomas from cohorts 3 and 4 for the 33 best performing antibodies in these sets of assays were advanced to cloning by limiting dilution hybridoma plating.

Alternatively, FACS analysis of HER-3 expression of Rat1/pLXSN and Rat1/HER-3 cells showed similar results (no crossreactivity with endogenous rat epitopes) (Fig. 2) .

In detail 1×10^5 cells were harvested with 10 mM EDTA in PBS, washed once with FACS buffer (PBS, 3 % FCS, 0.4 % azide) and seeded on a 96-well round bottom plate. The cells were spun for 3 min at 1000 rpm to remove supernatant and then resuspended with the specific HER-family antibodies (3 μ g/ml). Cell suspensions were incubated on ice for 45 min, washed twice with FACS buffer and resuspended with secondary antibody (100 μ l/well)

donkey-anti-human-PE (Jackson ImmunoResearch, PA) diluted 1:50 in FACS buffer. The cell suspensions were incubated on ice and in the dark for 30 min, washed twice with FACS buffer and analyzed (FACS, Beckman Coulter).

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EXAMPLE 8: Structural analysis of anti-HER-3 antibodies of the invention

In the following discussion, structural information related to antibodies prepared in accordance with the invention is provided. In order to analyze structures of antibodies produced in accordance with the present invention, genes encoding the heavy and light chain fragments were amplified out of the particular hybridoma. Sequencing was accomplished as follows:

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The VH and VL transcripts were amplified from individual hybridoma clones in 96 well plate using reverse transcriptase polymerase chain reaction (RT-PCR). Poly(A)+-mRNA was isolated from approximately 2×10^5 hybridoma cells using a Fast-Track kit (Invitrogen). Four PCR reactions were run for each Hybridoma: two for light chain (kappa (κ), and two for gamma heavy chain (γ). The QIAGEN OneStep room temperature-PCR kit was used for amplification (Qiagen, Catalog No.210212). In the coupled room temperature-PCR reactions, cDNAs were synthesized with blend of room temperature enzymes (Omniscript and Sensiscript) using antisense sequence specific primer corresponded to C- κ , or to a consensus of the CH1 regions of Cy genes. Reverse transcription was performed at 50 °C for 1 hr followed by PCR amplification of the cDNA by HotStarTaq DNA Polymerase for high specificity and sensitivity. Each PCR reaction used a mixture of 5'-sense primers; primer sequences were based on the leader sequences of VH and VK available at the Vbase website (<http://vbase.mrc-cpe.cam.ac.uk/>).

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PCR reactions were run at 94 °C for 15 min, initial hot start followed by 40 cycles of 94 °C for 30 sec (denaturation), 60 °C for 30 sec (annealing) and 72 °C for 1 min (elongation).

PCR products were purified and directly sequenced using forward and reverse PCR primers using the ABI PRISM BigDye terminator cycle sequencing ready reaction Kit (Perkin Elmer). Both strands were sequenced using Prism dye-terminator sequencing kits and an ABI 377 sequencing machine.

Sequence analysis

Analyses of human V heavy and V kappa cDNA sequences of the HER3 antibodies were accomplished by aligning the HER-3 sequences with human germline V heavy and V kappa sequences using Abgenix in-house software (5AS). The software identified the usage of the V gene, the D gene and the J gene as well as nucleotide insertions at the recombination junctions and somatic mutations. Amino acid sequences were also generated in silico to identify somatic mutations. Similar results could be obtained with commercially available sequence analysis software and publicly available information on the sequence of human V, D, and J genes, e.g., Vbase (<http://vbase.mrc-cpe.cam.ac.uk/>).

Molecular cloning of mAb U1-59

Total RNA was extracted from the tissue culture well containing multiple hybridomas lineages, including the hybridoma lineage secreting antibody U1-59. A heavy chain variable region was amplified using 5'-leader VH family specific primers, with 3'-C-gamma primer. A major band was amplified using a VH4 primer, no other bands were visible. The VH4-34 gamma fragment was cloned into pCDNA expression vector in frame with a human gamma 1 constant region gene.

An IgM heavy chain variable region was amplified using 5' VH family specific primers with 3' mu constant region primer. A major band was amplified using VH2 primer, no other bands were visible. The VH2-5 mu fragment was cloned into pCDNA expression vector in frame with a human mu constant

region gene. V kappa chains were amplified and sequenced. Four kappa chain RT-PCR products were identified. The products were sequenced and after sequence analysis via in silico translation, only three of them had open-reading frames. These three functional kappa chains were cloned out of the oligoclonal U1-59 hybridoma well identified based on V kappa gene usage as (1) VK1 A3-JK2, (2) VK1 A20-JK3 and (3) B3-JK1. All V-kappa were cloned into pCDNA expression vector in frame with a human kappa light chain constant region gene.

Transfections:

Each heavy chain was transfected with each of the kappa chains in transient transfections for a total of 6 heavy chain/kappa light chain pairs. The transfection of the gamma chain with the A20 kappa chain gave poor antibody expression, while no antibody was secreted or detected when the A20 kappa chain was co-transfected with the mu chain. A total of three IgG sups and two IgM sups were available for HER-3 binding assay.

Chain	VH	D	J	Constant	ORF
Heavy	VH4-34	D1-20	JH2	Gamma	yes
Heavy	VH2-5	D6-6	JH4b	Mu	yes
Light	A3		JK2	Kappa	yes
Light	A20		JK3	Kappa	yes
Light	B3		JK1	Kappa	yes
Light	A27		JK3	Kappa	NO

Binding activity to HER-3+ cell lines was detected in FACS with the IgG1 mAb consisting of the VH4-34 and the B3 kappa chain. No other VH/Vk combinations gave fluorescence signal above background in FACS using HER-3+ cell lines.

Binding competition of the anti-HER-3 antibodies

Multiplexed competitive antibody binning was performed as published in Jia et al. *J Immunol Methods*. 288, 91-98 (2004) to assess clusters of HER-3 antibodies that competed for binding to HER-3. Tested HER-3 antibodies

from cohort 1 clustered into 5 bins based on competition for binding.

Bin#1	Bin#2	Bin#3	Bin#4	Bin#5
U1-42	U1-48	U1-52	U1-38	U1-45
U1-44	U1-50		U1-39	U1-40
U1-62	U1-51			U1-41
U1-46				U1-43
U1-47	U1-49			U1-61
U1-58				U1-53
				U1-55

Epitope characterization of anti-HER-3 antibodies

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The epitopes of human anti-HER-3 antibodies of the invention were characterized. First a dot blot analysis of the reduced, denatured HER-3-His tagged purified ECD protein showed absence of binding by the anti-HER-3 antibodies tested (U1-59, U1-61, U1-41, U1-46, U1-53, U1-43, U1-44, U1-47, U1-52, U1-40, U1-49)) demonstrating that all had epitopes sensitive to reduction of disulfide bonds, suggesting that all had discontinuous epitopes. Next, the antibodies were mapped to defined domains in the HER-3 molecule by engineering various human-rat HER-3 chimeric molecules, based on the division of the HER-3 extra-cellular domain into four domains:

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- 1) L1 (D1): the minor ligand-binding domain,
- 2) S1 (D2): the first cysteine-rich domain,
- 3) L2 (D3): the major ligand-binding domain, and
- 4) S2 (D4): the sec cysteine-rich domain.

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The extra-cellular domain (ECD) of Human HER-3 cDNA was amplified from RAT1-HER-3 cells. The rat HER-3 cDNAs was amplified by RT-PCR from rat liver RNA and confirmed by sequencing. The cDNAs expressing the ECD of human and rat Her3 were cloned into mammalian expression vectors as V5-His fusion proteins. Domains from the human HER-3 ECD were swapped into the scaffold provided by the rat HER-3 ECD by using the MfeI, BstXI and DraIII internal restriction sites. By this means, various chimeric

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rat/human HER-3 ECD HIS fusion proteins (amino acids 1-160, 161-358, 359-575, 1-358, 359-604) were constructed and expressed via transient transfection of HEK 293T cells. Expression of the constructs was confirmed using a rat polyclonal antibody against human HER-3. The human monoclonal antibodies were tested in ELISA for binding to the secreted chimeric ECDs.

Two of the human antibodies, including antibody U1-59, cross-reacted with rat HER-3. To assign binding domains, these mAbs were tested against a truncated form of HER-3 consisting of L1-S1-V5his tagged protein purified from the supernatant of HEK 293T cells transfected with a plasmid DNA encoding the expression of the L1-S1 extra-cellular domains of HER3. mAb U1-59 bound to the L1-S1 protein in ELISA, implying that its epitope is in L1-S1. mAb 2.5.1 did not bind to the L1-S1 protein, implying that its epitope is in L2-S2. Further mapping of antibody U1-59 was accomplished using SELDI time of flight mass spectroscopy with on-chip proteolytic digests of mAb-HER-3 ECD complexes.

Mapping U1-59 epitopes using SELDI

Further mapping of antibody U1-59 was accomplished using a SELDI time of flight mass spectroscopy with on-chip proteolytic digests of mAb-HER-3 ECD complexes. Protein A was covalently bound to a PS20 protein chip array and used to capture mAb U1-59. Then the complex of the PS20 protein chip and the monoclonal antibody was incubated with HER-3-His purified antigen. Next the antibody-antigen complex was digested with high concentration of Asp-N. The chip was washed, resulting in retention of only the HER-3 peptide bound to the antibody on the chip. The epitope was determined by SELDI and identified by mass of the fragment. The identified 6814 D fragment corresponds to two possible expected peptides generated from a partial digest of the HER-3-his ECD. Both overlapping peptides map to the domain S1. By coupling SELDI results with binding to a HER-3 deletion construct, the epitope was mapped to residues 251 to 325.

The location of the binding domains in the extracellular part of HER-3 that are recognized by the human anti-HER-3 mAbs of the invention are summarized in Table 4. The epitope domain mapping results were consistent with results from antibody competition binding competition bins, with antibodies that cross-competed each other for binding to HER-3 also mapping to the same domains on HER-3 (Fig. 3).

TABLE 4

A summary of mAb's binding domain based on ELISA assay results

mAb	Rat XR	Binding domain	mAb	Rat XR	Binding domain
✓ U1-59	Yes	S1	U1-2	No	L2
U1-61	No	L2	U1-7	No	L2
U1-41	No	L2	U1-9	No	L2
U1-46	No	S1	U1-10	No	L2
✓ U1-53	No	L2	U1-12	No	L2
U1-43	No	L2	U1-13	No	L2
U1-44	No	S1	U1-14	No	L2
U1-47	No	S1	U1-15	No	L2
U1-52	Yes	L2S2	U1-19	No	L2
U1-40	No	L2	U1-20	No	L2
✓ U1-49	No	L1	U1-21	No	L2
U1-21	No	L2	U1-28	No	L2
U1-22	No	L2	(U1-31)	No	L2
U1-23	No	L2	U1-32	No	L2
U1-24	No	L2	(U1-35)	No	L2
U1-25	No	L2	U1-36	No	L2
U1-26	No	L2	(U1-37)	No	L2
U1-27	No	L2			

XR = cross-reactive

EXAMPLE 9: Determination of canonical classes of antibodies

Chothia, *et al.* have described antibody structure in terms of "canonical

classes" for the hypervariable regions of each immunoglobulin chain (*J. Mol. Biol.*, 1987 Aug 20, 196(4):901-17). The atomic structures of the Fab and VL fragments of a variety of immunoglobulins were analyzed to determine the relationship between their amino acid sequences and the three-dimensional structures of their antigen binding sites. Chothia, *et al.* found that there were relatively few residues that, through their packing, hydrogen bonding or the ability to assume unusual phi, psi or omega conformations, were primarily responsible for the main-chain conformations of the hypervariable regions. These residues were found to occur at sites within the hypervariable regions and in the conserved β -sheet framework. By examining sequences of immunoglobulins having unknown structure, Chothia, *et al.* show that many immunoglobulins have hypervariable regions that are similar in size to one of the known structures and additionally contained identical residues at the sites responsible for the observed conformation.

Their discovery implied that these hypervariable regions have conformations close to those in the known structures. For five of the hypervariable regions, the repertoire of conformations appeared to be limited to a relatively small number of discrete structural classes. These commonly occurring main-chain conformations of the hypervariable regions were termed "canonical structures." Further work by Chothia, *et al.* (*Nature*, 1989 Dec 21-28, 342 (6252):877-83) and others (Martin, *et al. J. Mol. Biol.*, 1996 Nov 15, 263(5): 800-15) confirmed that there is a small repertoire of main-chain conformations for at least five of the six hypervariable regions of antibodies.

The CDRs of each antibody described above were analyzed to determine their canonical class. As is known, canonical classes have only been assigned for CDR1 and CDR2 of the antibody heavy chain, along with CDR1, CDR2 and CDR3 of the antibody light chain. The tables below summarize the results of the analysis. The canonical class data is in the form of HCDR1-HCDR2-LCDR1-LCDR2-LCDR3, wherein "HCDR" refers to the heavy chain CDR and "LCDR" refers to the light chain CDR. Thus, for example, a canonical class of 1-3-2-1-5 refers to an antibody that has a

HCDR1 that falls into canonical class 1, a HCDR2 that falls into canonical class 3, a LCDR1 that falls into canonical class 2, a LCDR2 that falls into canonical class 1, and a LCDR3 that falls into canonical class 5.

5 Assignments were made to a particular canonical class where there was 70 % or greater identity of the amino acids in the antibody with the amino acids defined for each canonical class. The amino acids defined for each antibody can be found, for example, in the articles by Chothia, *et al.* referred to above. Table 5 and Table 6 report the canonical class data for each of the HER-3
10 antibodies. Where there was less than 70 % identity, the canonical class assignment is marked with an asterisk ("*") to indicate that the best estimate of the proper canonical class was made, based on the length of each CDR and the totality of the data. Where there was no matching canonical class with the same CDR length, the canonical class assignment is marked with a
15 letter s and a number, such as "s18", meaning the CDR is of size 18. Where there was no sequence data available for one of the heavy or light chains, the canonical class is marked with "Z".

TABLE 5

Antibody (sorted)	H1-H2-L1-L2-L3	H3length	Antibody (sorted)	H1-H2-L1-L2-L3	H3length
U1-38	3-1-4-1-1	9	U1-7	3-1-2-1-1	12
U1-39	1-1-4-1*-1	6	U1-9	3-1-2-1-1	12
U1-40	3-1-4-1-1	15	U1-10	3-1-2-1-1	12
U1-41	3-1-2-1-1	15	U1-12	3-1-2-1-1	12
U1-42	1-2-2-1-1	9	U1-13	3-1-4-1-1	7
U1-43	3-1-2-1-1	17	U1-14	3-1-2-1-1	12
U1-44	1-2-2-1-1	9	U1-15	3-1-8-1-1	14
U1-45	1-2*-2-1-1	16	U1-19	3-1-Z-Z-Z	12
U1-46	3-s18-Z-Z-Z	17	U1-20	3-1-2-1-1	19
U1-47	3-s18-2-1-1	16	U1-21	3-1-2-1-1	12
U1-48	1-1-Z-Z-Z	16	U1-22	3-1-2-1-1	12
U1-49	1-3-4-1-1	17	U1-23	3-1-2-1-1	12
U1-50	3-1-2-1-1	17	U1-24	3-1-2-1-1	12
U1-51	1-1-3-1-1	19	U1-25	3-1-2-1-1	12
U1-52	3-1-8-1-1	15	U1-26	3-1-2-1-1	12
U1-53	1-3-2-1-1	10	U1-27	3-1-2-1-1	12
U1-55	3-1-4-1-1	15	U1-28	3-1-2-1-1	12
U1-57	3-1-4-1-1	15	U1-31	1-2-2-1-1	13
U1-58	1-3-2-1-1	12	U1-32	3-1-2-1-1	12
U1-59	1-1-3-1-1	9	U1-35	1-3-2-1-1	14
U1-61.1	3-1*-2-1-1	16	U1-36	3-1-2-1-1	12
U1-62	1-2-8-1-1	12	U1-37	1-2-Z-Z-Z	13
U1-2	3-1-2-1-1	12			

Table 7 is an analysis of the number of antibodies per class. The number of antibodies having the particular canonical class designated in the left column is shown in the right column. The four mAbs lacking one chain sequence data and thus having "Z" in the canonical assignment are not included in this counting.

The most commonly seen structure is 3-1-2-1-1: Twenty-one out of forty-one mAbs having both heavy and light chain sequences had this combination.

TABLE 6

H1-H2-L1-L2-L3	Count
1-1-3-1-1	2
1-1-4-1*-1	1
1-2-2-1-1	4
1-2-8-1-1	1
1-3-2-1-1	3
1-3-4-1-1	1
3-1-2-1-1	21
3-1-4-1-1	5
3-1-8-1-1	2
3-s18-2-1-1	1

EXAMPLE 10: Determination of antibody affinity

5 Affinity measurements of anti-HER-3 antibodies of the invention were performed by indirect FACS Scatchard analysis. Therefore, 10^5 cells of interest or SK-Br 3 cells were harvested with 10 mM EDTA in PBS, washed once with FACS buffer (PBS, 3 % FCS, 0.4 % azide) and seeded on a 96-well round bottom plate. The cells were spun for 3 min at 1000 rpm to
10 remove supernatant and then resuspended with α -HER-3 antibody (3 μ g/ml) or with antibody dilutions (100 μ l/well) starting with 20 μ g/ml human monoclonal antibody in FACS buffer, diluted in 1:2 dilution steps. Cell suspensions were incubated on ice for 1 hr, washed twice with FACS buffer and resuspended with secondary antibody (100 μ l/well) donkey-anti-human-
15 PE (Jackson) diluted 1:50 in FACS buffer. The cell suspensions were incubated on ice and in the dark for 30 min, washed twice with FACS buffer and analyzed (FACS, Beckman Coulter). According to the FACS Scatchard analysis, the fluorescence mean was calculated for each measurement. Background staining (= without 1st antibody) was subtracted from each
20 fluorescence mean. Scatchard plot with x-value = fluorescence mean and y-value = fluorescence mean/concentration of mAb (nM) was generated. The KD was taken as the absolute value of 1/m of linear equation. Fig. 4 shows a kinetic analysis using the U1-59 antibody of the invention. In the following table 8 affinity measurements for certain antibodies of the invention selected
25 in this manner are provided.

TABLE 7

clone	KD (nM)
U1-38	n.d.
U1-39	102
U1-40	6,7
U1-41	0,18
U1-42	n.d.
U1-43	0,57
U1-44	4
U1-52	16,8
U1-61	0,13
U1-62	20,4
U1-46	13,8
U1-47	9,38
U1-49	1
U1-50	39,3
U1-51	131,6
U1-53	0,082
U1-55.1	3,7
U1-58	6,4
U1-59	3,69
U1-24	0,06
U1-7	0,02

EXAMPLE 11: Anti-HER-3 antibodies of the invention induce HER-3 receptor endocytosis

HER-3 has been identified as a factor that can influence initiation and progression of hyperproliferative diseases through serving as an important gatekeeper of HER family mediated cell signaling. Thus, if HER-3 is effectively cleared from the cell surface/membrane by receptor internalization, cell signaling and therefore transformation and/or maintenance of cells in malignancy can be ultimately diminished or suppressed.

In order to investigate whether anti-HER-3 antibodies of the invention are

capable of inducing accelerated endocytosis of HER-3, the relative amount of HER-3 molecules on the cell surface after 0.5 and 4 hr incubation of the cells with anti-HER-3 antibodies of the invention were compared. 3×10^5 cells were seeded in normal growth medium in 24-well dish and left to grow overnight. Cells were preincubated with 10 $\mu\text{g/ml}$ anti-HER-3 mAbs in normal growth medium for the indicated times at 37 °C. Cells were detached with 10 mM EDTA and incubated with 10 $\mu\text{g/ml}$ anti-HER-3 mAbs in wash buffer (PBS, 3 % FCS, 0.04 % azide) for 45 min at 4 °C. Cells were washed twice with wash buffer, incubated with donkey-anti-human-PE secondary antibody (Jackson) diluted 1:100 for 45 min at 4 °C, washed twice with wash buffer and analyzed by FACS (BeckmanCoulter, EXPO).

Data shown in Fig. 5 demonstrate that treatment of cells with anti-HER-3 antibodies leads to internalization of the receptor. Data are shown as % internalization and refer to the reduction of the mean fluorescence intensity of anti-HER3 treated samples relative to control-treated samples.

EXAMPLE 12: Inhibition of ligand binding to human cancer cells SKBr3 by human anti-HER-3 antibodies of the invention

Radioligand competition experiments were performed in order to quantitate the ability of the anti-HER-3 antibodies of the invention to inhibit ligand binding to HER-3 in a cell based assay. Therefore, the HER-3 receptor binding assay was performed with 4×10^5 SK-BR-3 cells which were incubated with varying concentrations of antibodies for 30 min on ice. 1.25 nM [^{125}I]- α -HRG/[^{125}I]- β -HRG were added to each well and the incubation was continued for 2 hr on ice. The plates were washed five times, air-dried and counted in a scintillation counter. Figs. 6a-e show the results of these experiments performed with representative anti-HER-3 antibodies of the invention and demonstrate that the antibodies of the invention are capable of specifically reducing the binding of [^{125}I]- α -HRG/[^{125}I]- β -HRG to cells expressing endogenous HER-3.

EXAMPLE 13: Inhibition of ligand-induced HER-3 phosphorylation by human anti-HER-3 antibodies of the invention

ELISA experiments were performed in order to investigate whether the antibodies of the invention are able to block ligand β -HRG-mediated activation of HER-3. Ligand-mediated HER-3 activation was detected by increased receptor tyrosine phosphorylation.

Day 1: 1 x 96 well dish was coated with 20 μ g/ml Collagen I in 0,1 M acetic acid for 4 hr at 37 °C. 2.5×10^5 cells were seeded in normal growth medium

Day 2: Cells were starved in 100 μ l serum free medium for 24 hr.

Day 3: Cells were preincubated with 10 μ g/ml anti-HER-3 mAbs for 1 hr at 37 °C and then treated with 30 ng/ml β -HRG-EGF domain (R&D Systems) for 10 min. Medium was flicked out and cells were fixed with 4 % formaldehyde solution in PBS for 1 hr at room temperature. Formaldehyde solution was removed and cells were washed with wash buffer (PBS/0.1 % Tween 20). Cells were quenched with 1 % H_2O_2 , 0.1 % NaN_3 in wash buffer and incubated for 20 min at room temperature, then blocked with NET-Gelantine for 5 hr at 4 °C. Primary antibody phospho-HER-3 (Tyr1289) (polyclonal rabbit; Cell signaling #4791; 1:300) was added overnight at 4 °C.

Day 4: The plate was washed 3x with wash buffer, then incubated with anti-rabbit-POD diluted 1:3000 in PBS - 0.5 % BSA was added to each well and incubated for 1.5 hr at room temperature. The plate was washed 3x with wash buffer and once with PBS. Tetramethylbenzidine (TMB, Calbiochem) was added and monitored at 650 nm. The reaction was stopped by addition of 100 μ l 250 nM HCl and the absorbance was read at 450 nm with a reference wavelength of 650 nm using a Vmax plate reader (Thermo Lab Systems).

Fig. 7a shows representative results of this experiment, demonstrating that

anti-HER-3 antibodies of the invention were able to reduce ligand-mediated HER-3 activation as indicated by decreased receptor tyrosine phosphorylation. Data are shown as percent reduction by therapeutic antibodies relative to a control antibody.

5

To test potency of mAb U1-53 to inhibit ligand induced HER-3 activation, MCF-7 cells were starved for 24 hr, incubated with mAb U1-53 for 1 hr at 37 °C and stimulated with 10 nM HRG- β for 10 min. Lysates were transferred to 1B4 (mouse anti-HER-3 mAb) ELISA plates and phosphorylation of HER-3 was analysed with antibody 4G10. As shown in Fig. 7b phosphorylation of HER-3 was almost completely inhibited in a dose dependent manner with an IC50 of 0.14 nM.

10

EXAMPLE 14: Inhibition of ligand-induced p42/p44 MAP-Kinase phosphorylation by human anti-HER-3 antibodies of the invention

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Next ELISA experiments were performed in order to investigate whether the antibodies of the invention are able to block ligand β -HRG-mediated activation of p42/p44 MAP-Kinase. Ligand-mediated HER-3 activation was detected by increased protein (Thr202/Tyr204) phosphorylation.

20

Day 1: 1 x 96 well dish was coated with 20 μ g/ml Collagen I in 0,1 M acetic acid for 4 hr at 37 °C. 3×10^5 cells were seeded in normal growth medium

25

Day 2: Cells were starved in 100 μ l serum free medium for 24 hr.

30

Day 3: Cells were preincubated with 5 μ g/ml anti-HER-3 mAbs for 1 hr at 37 °C and then treated with 20 ng/ml β -HRG-EGF domain (R&D Systems) for 10 min. Medium was flicked out and cells were fixed with 4 % formaldehyde solution in PBS for 1 hr at room temperature. Formaldehyde solution was removed and cells were washed with wash buffer (PBS/0.1 % Tween 20). Cells were quenched with 1 % H_2O_2 , 0.1 % NaN_3 in wash buffer and incubated for 20 min at room temperature, then blocked with PBS/0.5 %

BSA for 5 hr at 4 °C. Primary antibody phospho-p44/p42 MAP Kinase (Thr202/Tyr204) (polyclonal rabbit; Cell signaling #9101; 1:3000) was added overnight at 4 °C.

5 Day 4: The plate was washed 3x with wash buffer, then incubated with anti-rabbit-HRP diluted 1:5000 in PBS - 0.5 % BSA was added to each well and incubated for 1.5 hr at room temperature. The plate was washed 3x with wash buffer and once with PBS. Tetramethylbenzidine (TMB, Calbiochem) was added and monitored at 650 nm. The reaction was stopped by addition
10 of 100 µl 250 nM HCl and The absorbance was read at 450 nm with a reference wavelength of 650 nm using a Vmax plate reader (Thermo Lab Systems).

Fig. 8 shows representative results of this experiment. The antibodies of the
15 invention were able to reduce ligand-mediated p42/p44 MAP-Kinase activation as indicated by decreased phosphorylation. Data are shown as percent reduction by therapeutic antibodies relative to a control antibody.

EXAMPLE 15: Inhibition of β-HRG-induced phospho-AKT phosphorylation
20 by human anti-HER-3 antibodies of the invention.

In the following ELISA experiment we investigated whether the anti-HER-3
antibodies of the invention are able to block ligand β-HRG-mediated
activation of AKT-Kinase. Ligand-mediated AKT activation was detected by
25 increased protein (Ser473) phosphorylation.

Day 1: 1 x 96 well dish was coated with 20 µg/ml Collagen I in 0,1 M acetic acid for 4 hr at 37 °C. 3×10^5 cells were seeded in normal growth medium

30 Day 2: Cells were starved in 100 µl serum free medium for 24 hr.

Day 3: Cells were preincubated with 5 µg/ml anti-HER-3 mAbs for 1 hr at 37 °C and then treated with 20 ng/ml β-HRG-EGF domain (R&D Systems)

for 10 min. Medium was flicked out and cells were fixed with 4 % formaldehyde solution in PBS for 1 hr at room temperature. Formaldehyde solution was removed and cells were washed with wash buffer (PBS/0.1 % Tween 20). Cells were quenched with 1 % H_2O_2 , 0.1 % NaN_3 in wash buffer and incubated for 20 min at room temperature, then blocked with PBS/0.5 % BSA for 5 hr at 4 °C. Primary antibody phospho-Akt (Ser473) (polyclonal rabbit; Cell signaling #9217; 1:1000) was added overnight at 4 °C.

Day 4: The plate was washed 3x with wash buffer, then incubated with anti-rabbit-HRP diluted 1:5000 in PBS-0.5 % BSA was added to each well and incubated for 1.5 hr at room temperature. The plate was washed 3x with wash buffer and once with PBS. Tetramethylbenzidine (TMB, Calbiochem) was added and monitored at 650 nm. The reaction was stopped by addition of 100 μ l 250 nM HCl and The absorbance was read at 450 nm with a reference wavelength of 650 nm using a Vmax plate reader (Thermo Lab Systems).

Fig. 9 shows representative results of this experiment. The anti-HER-3 antibodies of the invention were able to reduce β -HRG-mediated AKT as indicated by decreased phosphorylation. Data are shown as percent reduction by therapeutic antibodies relative to a control antibody.

EXAMPLE 16: Inhibition of α -HRG/ β -HRG-mediated MCF7 cell proliferation by human anti-HER-3 antibodies of the invention

In vitro experiments were conducted in order to determine the ability of the antibodies of the invention to inhibit HRG-stimulated cell proliferation. 2000 MCF7 cells were seeded in FCS-containing medium on 96-well plates overnight. Cells were preincubated in quadruplicates with antibody diluted in medium with 0.5 % FCS for 1 hr at 37 °C. Cells were stimulated with 30 ng/ml α - or 20 ng/ml β -HRG (R&D Systems) by adding ligand directly to antibody solution and were then left to grow for 72 hr. AlamarBlue™ (BIOSOURCE) was added and incubated at 37 °C in the dark. Absorbance

was measured at 590 nm every 30 min. The data were taken 90 min after addition of alamar blue. The results as indicated in Fig. 10 show that representative antibodies of the invention inhibit HRG-induced cell growth in human cancer cells. Data are shown as percent reduction by therapeutic antibodies relative to a control antibody.

EXAMPLE 17: Inhibition of β -HRG-induced MCF7 cell migration by human anti-HER-3 antibodies of the invention

Transmigration experiments were performed in order to investigate whether the antibodies of the invention block cell migration. Serum-starved MCF7 cells were preincubated by adding the indicated amount of antibody to the cell suspension and incubating both for 45 min at 37 °C. 500 μ l cell suspension (50,000 cells) was then placed in the top chamber of collagen I-coated transwells (BD Falcon, 8 μ m pores). 750 μ l medium (MEM, amino acids, Na-pyruvate, Pen.-Strept., 0,1 % BSA, without fetal calf serum) alone or containing the ligands β -HRG-EGF domain (R&D Systems) were used in the bottom chamber. Cells were left to migrate for 8 hr at 37 °C and were stained with DAPI.

Stained nuclei were counted manually; percent inhibition was expressed as inhibition relative to a control antibody.

Fig. 11 shows the result of the experiment demonstrating that representative anti-HER-3 antibodies of the invention reduce HRG-induced cell migration.

EXAMPLE 18: Colony formation assay (soft agar assay)

Soft agar assays were conducted in order to investigate the ability of the anti-HER-3 antibodies of the invention to inhibit anchorage independent cell growth. The soft agar colony formation assay is a standard *in vitro* assay to test for transformed cells, as only such transformed cells can grow in soft agar.

750 to 2000 cells (depending on the cell line) were preincubated with indicated antibodies at 10 µg/ml in IMDM medium (Gibco) for 30 min and resuspended in 0.4 % Difco noble agar. The cell suspension was plated on 0.75 % agarose underlayer containing 20 % FCS in quadruplicate in a 96-well plate. Colonies were allowed to form for 14 days and were then stained with 50 µl MTT (0.5 mg/ml in PBS) overnight. Figs. 12 a-i show the results of these experiments performed with three representative antibodies of the invention. These results demonstrate that anti-HER-3 antibodies of the invention reduce anchorage independent cell growth of MDA-MB361 and NCI-ADR breast cancer cells (Fig. 12a,b), MKN-28 gastric cancer (Fig. 12c), HT144 melanoma cells (Fig. 12d), Skov3 ovary carcinoma cells (Fig. 12e), PPC-1 prostate cancer cells (Fig. 12f), BX-PC3 pancreas cancer cells (Fig. 12g), A431 epidermoid carcinoma cells (Fig. 12h) and lung carcinoma cells (Fig. 12i). Colonies were counted with a Scanalyzer HTS camera system (Lemnatec, Wuersele).

EXAMPLE 19: Human anti-HER-3 antibodies inhibit human breast carcinoma growth in nude mice

The anti-tumor efficacy of therapeutic antibodies is often evaluated in human xenograft tumor studies. In these studies, human tumors grow as xenografts in immunocompromised mice and therapeutic efficacy is measured by the degree of tumor growth inhibition. In order to determine, if the anti-HER-3 antibodies of the invention interfere with tumor growth of human breast cancer cells in nude mice, 5×10^6 T47D cells were implanted in female NMRI nude/nude mice. Tumors were subcutaneous, grown on the back of the animal. Treatments began when tumors reached a mean volume of 20 mm³; eight days post implantation. Prior to first treatment, mice were randomized and statistical tests performed to assure uniformity in starting tumor volumes (mean, median and standard deviation) across treatment groups. Treatment started with a loading dose of 50 mg/kg followed by 25 mg/kg injections once a week by intraperitoneal injection. A control arm received doxorubicin (pharmaceutical grade). All animals were supplemented with 0.5

mg/kg/week oestrogen injected i.p.

Details of the treatment groups are given below.

Gr	N	1 st Compound	Loading (mg/kg)	Weekly dose (mg/kg)	Route	Schedule
1.	10	PBS		-	i.p.	once/week
2.	10	doxorubicin		8mg/kg	i.v.	once/week*
3.	10	U1-53	50mg/kg 20ml/kg	25mg/kg 10ml/kg	i.p.	once/week

5 * doxorubin treatment as described by Boven *et al.*, Cancer Research, 1992.

Data for median tumor volume (Fig. 13) demonstrated that administration of an anti-HER-3 antibody of the invention resulted in reduction of tumor growth.

10 EXAMPLE 20: Human anti-HER-3 antibodies inhibit human pancreatic tumor growth in SCiD mice

To test the therapeutic potential of anti-HER3 antibodies in other solid tumor types the anti-HER-3 antibodies, U1-53 and U1-59, were tested in mice with established tumors derived from the human pancreatic tumor cell line BxPC3. As controls sets of mice treated with either the vehicle control, PBS, or the established therapeutic antibody, Erbitux, were included. 5×10^6 BxPC3 cells were inoculated subcutaneously without Matrigel into CB17 SCiD mice. Mice bearing established tumors with a mean volume of 140mm^2 received 50mg/kg of U1-53, U1-59, Erbitux or the equivalent volume of PBS via intraperitoneal injection. Thereafter the mice received once weekly 25mg/kg injections for the duration of the study.

25 The results for this experiment are shown in Fig. 14. U1-53 and U1-59 reduced the growth of the human pancreatic tumors in a cytostatic fashion. Notably, in this experiment, U1-53 and U1-59 were more effective than the EGFR-targeting antibody Erbitux at delaying tumor growth. These data demonstrated the therapeutic efficacy of anti-HER-3 antibodies of the

invention in comparison to a benchmark therapeutic agent.

EXAMPLE 21: Combining the human anti-HER-3 antibodies with anti-EGFR antibodies increases anti-tumor activity

5

The monotherapy of hyperproliferative diseases with targeted antibodies is often hampered by problems such as, on the one hand, the development of resistance to drugs, and on the other hand, a change in the antigenicity. For example; loss of antigenicity after prolonged treatment may render tumor
10 cells insensitive to therapeutic antibodies, since those tumor cells that do not express or have lost the targeted antigen have a selective growth advantage. These problems might be evaded by using the antibodies of the invention in combination with a therapeutic antibody that targets a different receptor on the tumor cells, or another antineoplastic agent. Intervening in
15 multiple signaling pathways or even related pathways but at multiple intervention steps might also provide therapeutic benefit. These combined treatment modalities are likely to be more efficacious, because they combine two anti-cancer agents, each operating via a different mechanism of action.

20 In order to demonstrate the feasibility of the anti-HER-3 antibodies of the invention, U1-53 and U1-59, as suitable combination agents, we compared monotherapeutic administrations of U1-53 or U1-59 with those in which either U1-53 or U1-59 was combined with the anti-EGFR specific antibody, Erbitux. 5×10^5 BxPC3 cells were inoculated subcutaneously with Matrigel
25 into CB17 SCID mice. After tumor volumes had reached 200 mm³, mice were randomized into individual treatment groups. Weekly intraperitoneal administrations of U1-53, U1-59 and Erbitux as single agents or combinations of either anti-HER3 antibodies with Erbitux or as a cocktail of two anti HER-3 antibodies were performed. All antibodies were dosed at a
30 single loading doses of 50 mg/kg/week, followed by weekly injections of 25 mg/kg for six weeks. Control arms received bi-weekly administrations of Gemcitabine (120 mg/kg), weekly pooled human IgG or weekly vehicle (PBS) injections. The regimens are detailed below.

Gr	N	Compound	Loading dose (mg/kg)	Weekly dose (mg/kg)	Route	Schedule
4.	12	PBS	20ml/kg	10ml/kg	q7d	i.p.
5.	12	Pooled human IgG	50mg/kg	25mg/kg	q7d	i.p.
6.	12	U1-53	50mg/kg	25mg/kg	q7d	i.p.
7.	12	U1-59	50mg/kg	25mg/kg	q7d	i.p.
8.	12	Erbtux	50mg/kg	25mg/kg	q7d	i.p.
9.	12	U1-53 + Erbitux	25mg/kg each	12.5mg/kg each	q7d	i.p.
10	12	U1-59 + Erbitux	25mg/kg each	12.5mg/kg each	q7d	i.p.
11	12	U1-53 + U1-59	25mg/kg each	12.5mg/kg each	q7d	i.p.
12	12	Gemcitabine	none	120 mg/kg	2x weekly	ip

The results for this experiment are shown in Fig. 15. Antibodies U1-53 and U1-59, when administered as single agents, delayed the growth of the human pancreatic tumors to the same degree as Gemcitabine, which is often used as a standard anti-pancreatic cancer chemotherapy. Co-administration of Erbitux with U1-53 or U1-59 resulted in a significantly greater reduction of tumor growth than observed with either single agent administration of U1-53, U1-59 or Erbitux. Thus, a beneficial therapeutic response can be achieved by combining the anti-HER-3 antibodies of the invention with suitable antibodies that target separate tumor antigens.

In summary, the anti-HER-3 antibodies of the invention have potent therapeutic efficacy against human tumors in vivo. They can be effectively combined with other anti-neoplastic therapeutics for increased anti-tumor activity.

EXAMPLE 22: Human anti-HER-3 antibodies inhibit human melanoma tumor growth in nu/nu mice

Members of the erbB family of receptors, including Her3, are abnormally
5 expressed in a large variety of epithelial cancers and they are known to play
important roles in the growth and survival of many these solid tumors.
These tumors include melanomas, head and neck squamous cell cancers,
non-small cell lung cancers and prostate, glioma, gastric, breast, colorectal,
pancreatic, ovarian cancers. In order to verify, that the anti-Her3 antibodies
10 of the invention are not restricted in their anti-cancer activity to individual
tumor types, e.g. pancreatic cancers (see Example 21), but can be used as
therapeutics against many HER-3-dependent tumors, we tested U1-53 and
U1-59 in additional xenograft studies. One example is shown in Fig. 16. 5×10^5
human melanoma cells, HT144, were injected subcutaneously into CB17
15 SCID mice, followed by immediate subsequent intraperitoneal injection of
50mg/kg of U1-53 and U1-59, the equivalent volume of PBS or Dacarbacin
(DITC) at 200mg/kg. Thereafter, mice received 25mg/kg of U1-53 or U1-59
once weekly, whereas DITC was given once every two weeks at 200mg/kg.

20 The median tumor volumes from each treatment group are shown in Figure
16. Administration of the antibodies of the invention resulted in growth
reduction of the human melanomas when compared to tumors that had been
treated with the vehicle control. These results demonstrate that the
antibodies of the invention are not restricted in their therapeutic potential
25 and target a wide variety of HER-3 expressing cancers.

EXAMPLE 23: Human anti-HER-3 antibodies inhibit growth of colon carcinoma xenografts in mice

30 HT-29 human colon carcinoma cells were suspended in medium with 2:1
ratio of Matrigel to a final concentration of 10×10^6 cells/ml. 0.2 ml of cell
suspension were injected s.c. into the right flank of 4-5-week-old CD1 nu/nu
mice. A total of 95 mice were used.

The mice were randomly assigned to control and treatment groups. The treatment started on the same day. Duration of treatment was 29 days. Upon completion of the study, three tumours per group were collected 3 hours after administration of treatment. The tumours were fast-frozen and kept at -80 °C.

The following treatment protocol was carried out:

Control group: non-specific human IgG 25 mg/kg, twice weekly, intraperitoneal

Treatment group: antibody U1-53, 25 mg/kg, twice weekly, intraperitoneal

Treatment group: antibody U1-7, 25 mg/kg, twice weekly, intraperitoneal

Treatment group: antibody U1-59, 25 mg/kg, twice weekly, intraperitoneal

Treatment group 5-FU: 5-fluorouracil, 50 mg/kg, 9d x 5, intraperitoneal

The median tumor volumes from each group are shown in Fig. 17. Administration of the antibodies of the invention resulted in growth reduction of the HT-29 colon carcinoma tumors when compared to tumors that had been treated with non-specific human IgG1.

EXAMPLE 24: Human anti-HER-3 antibodies inhibit lung cancer growth in mice

Calu-3 human non-small cell lung cancer cells were suspended in medium with 1:1 ratio of Matrigel to a final concentration of 5×10^6 cells/ml. 0.05 ml of cell suspension were injected s.c. into the right flank of 9-week-old female CB17 scid mice. A total of 60 mice were used.

The mice were randomly selected to control and treatment groups. Treatment started on the same day. The duration of treatment was 32 days.

The following treatment protocol was carried out:

PBS vehicle group

hG control group: non-specific human IgG: 25 mg/kg, twice weekly, intraperitoneal

Treatment group antibody U1-53, 25 mg/kg, twice weekly, intraperitoneal

Treatment group antibody U1-7, 25 mg/kg, twice weekly, intraperitoneal

Treatment group antibody U1-59, 25 mg/kg, twice weekly, intraperitoneal

The median tumor volumes from each control and treatment group are shown in Fig. 18. Administration of the antibodies of the invention resulted in growth reduction of the human non-small lung cancer xenografts when compared to tumors that had been treated with the PBS vehicle control or non-specific human IgG.

EXAMPLE 25: Human anti-HER-3 antibodies inhibit human pancreatic tumor growth in Balb/C-mice

Human pancreatic BxPC3 tumor cells were suspended in medium with a 2:1 ratio of Matrigel to a final concentration of 5×10^6 cells per ml. 0.2 ml of cell suspension were injected s.c. into the right flank of 5-7- week-old female BalbC nu/nu mice. A total of 100 mice were used.

The mice were randomly distributed into control and treatment groups. The treatment started on the same day. The treatment duration was 27 days.

The following treatment protocol was carried out:

hlgG control group: non-specific human IgG2, 25 mg/kg, twice weekly, intraperitoneal

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Treatment group antibody U1-53, 25 mg/kg, twice weekly, intraperitoneal

Treatment group antibody U1-7, 25 mg/kg, twice weekly, intraperitoneal

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Treatment group antibody U1-59, 25 mg/kg, weekly, intraperitoneal

Gemzar treatment group, gemcitabine, 80 mg/kg, weekly, intraperitoneal

15

The median tumor volumes from each control and treatment group are shown in Fig. 19. Administration of the antibodies of the invention resulted in growth reduction of the human pancreatic tumors when compared to tumors that had been treated with non-specific human IgG or with Gemzar.

20

The inhibition of HER-3 in the human pancreatic tumors could also be shown in a pharmacodynamic experiment. The BxPC3 tumor xenografts were grown as described above. 3 mice were treated with 500 µg of an IgG1 control antibody and 3 mice were treated with 500 µg of the anti-HER-3 antibody U1-59. The mice were treated on day 1 and day 4 and then sacrificed on day 5 to measure the antibody-dependent inhibition of HER-3 phosphorylation (pHER-3).

25

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The tumors were homogenized in a standard RIPA buffer with protease inhibitors. 50 µg clear lysate was separated on a 4-20 % Tris-glycine gel, transferred onto a nitrocellulose membrane and blocked in 3 % bovine serum albumin (BSA). Immunoblotting was performed using an anti-pHER-3 antibody (antibody 21D3, Cell Signaling technology). An anti-actin antibody (AB a-2066, Sigma) was used as a control.

The expression was detected by enhanced chemiluminescence (Amersham Biosciences, Piscataway, NJ). The images were captured with the Versadoc 5000 Imaging System (BioRad, Hercules, CA).

5 The results are shown in Fig. 20. After administration of the human anti-HER-3-antibody U1-59 phosphorylation of HER-3 was no longer detectable. Thus, the antibodies of the invention are capable of significantly reducing HER-3 activation in human pancreatic tumor cells.

10 EXAMPLE 26: Use of anti-HER-3 antibodies of the invention as a diagnostic agent

Anti-HER-3 mAb can be used in the diagnostic of malignant diseases. HER-3 is expressed on tumor cells in a very distinct way compared to normal
15 tissue and, therefore, an expression analysis of HER-3 would assist in the primary diagnosis of solid tumors, staging and grading of solid tumors, assessment of prognostic criteria for proliferative diseases and neoplasias and risk management in patients with HER-3 positive tumors.

20 A. Detection of HER-3 antigen in a sample

An Enzyme-Linked Immunosorbent Assay (ELISA) for the detection of HER-3 antigen in a sample is developed. In the assay, wells of a microtiter plate, such as a 96-well microtiter plate or a 384-well microtiter plate, are adsorbed
25 for several hr with a first fully human monoclonal antibody directed against the HER-3 antigen. The immobilized antibody serves as a capture antibody for any of the HER-3 antigen that may be present in a test sample. The wells are rinsed and treated with a blocking agent such as milk protein or albumin to prevent nonspecific adsorption of the analyte.

30 Subsequently the wells are treated with a test sample suspected of containing the HER-3 antigen, or with a solution containing a standard amount of the HER-3 antigen. Such a sample is, for example, a serum

sample from a subject suspected of having levels of circulating HER-3 antigen considered to be diagnostic of a pathology. After rinsing away the test sample or standard, the wells are treated with a second fully human monoclonal anti-HER-3 antibody of the invention that is labelled by conjugation with biotin. The labeled anti-HER-3 antibody serves as a detecting antibody. After rinsing away excess secondary antibody, the wells are treated with avidin-conjugated horseradish peroxidase (HRP) and a suitable chromogenic substrate. The concentration of the HER-3 antigen in the test samples is determined by comparison with a standard curve developed from the standard samples.

B. Detection of HER3-antigen in Immunohistochemistry (IHC)

In order to determine HER3-antigen in tissue sections by IHC, Paraffin-embedded tissues are first deparaffinized in xylene for 2 x 5 min and then hydrated with 100% Ethanol 2 x 3 min, 95% Ethanol 1 min and rinsed in distilled water. Antigenic epitopes masked by formalin-fixation and paraffin-embedding are exposed by epitope unmasking, enzymatic digestion or saponin. For epitope unmasking paraffin sections are heated in a steamer, water bath or microwave oven for 20-40 min in a epitope retrieval solution as for example 2N HCl solution (pH 1.0). In the case of an enzyme digestion, tissue sections are incubated at 37°C for 10-30 minutes in different enzyme solutions such as proteinase K, trypsin, pronase, pepsin etc.

After rinsing away the epitope retrieval solution or excess enzyme, tissue sections are treated with a blocking buffer to prevent unspecific interactions. The primary antibody is incubated at appropriate dilutions in dilution buffer for 1 hour at room temperature or overnight. Excess primary antibody is rinsed away and sections are incubated in peroxidase blocking solution for 10 min at room temperature. After another washing step, tissue sections are incubated with a secondary antibody labelled with a group that might serve as an anchor for an enzyme. Examples therefore are biotin labelled secondary antibodies that are recognized by streptavidin coupled

horseradish peroxidase. Detection of said antibody/enzyme complex is achieved by incubating with a suitable chromogenic substrate.

C. Determination of HER-3 antigen concentration in serum of patients

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A sandwich ELISA is developed to quantify HER-3 levels in human serum. The two fully human monoclonal anti-HER-3 antibodies used in the sandwich ELISA, recognized different domains on the HER-3 molecule and do not compete for binding, for example, see Example 8. The ELISA is performed as follows: 50 μ l of capture anti-HER-3 antibody in coating buffer (0.1 M NaHCO₃, pH 9.6) at a concentration of 2 μ g/ml were coated on ELISA plates (Fisher). After incubation at 4 °C overnight, the plates are treated with 200 μ l of blocking buffer (0.5 % BSA, 0.1 % Tween 20, 0.01 % Thimerosal in PBS) for 1 hr at 25 °C. The plates were washed (3x) using 0.05 % Tween 20 in PBS (washing buffer, WB). Normal or patient sera (Clinomics, Bioreclamation) are diluted in blocking buffer containing 50 % human serum. The plates are incubated with serum samples overnight at 4 °C, washed with WB, and then incubated with 100 μ l/well of biotinylated detection anti-HER-3 antibody for 1 hr at 25 °C. After washing, the plates are incubated with HRP-Streptavidin for 15 min, washed as before, and then treated with 100 μ l/well of o-phenylenediamine in H₂O₂ (Sigma developing solution) for color generation. The reaction is stopped with 50 μ l/well of H₂SO₄ (2 M) and analyzed using an ELISA plate reader at 492 nm. The concentration of HER-3 antigen in serum samples is calculated by comparison to dilutions of purified HER-3 antigen using a four parameter curve fitting program.

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Staging of cancer in a patient

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Based on the results set forth and discussed under items A, B and C., through use of the present invention, it is possible to stage a cancer in a subject based on expression levels of the HER-3 antigen. For a given type of cancer, samples of blood are taken from subjects diagnosed as being at

various stages in the progression of the disease, and/or at various points in the therapeutic treatment of the cancer. The concentration of the HER-3 antigen present in the blood samples is determined using a method that specifically determines the amount of the antigen that is present. Such a method includes an ELISA method, such as the method described under items A. and B. Using a population of samples that provides statistically significant results for each stage of progression or therapy, a range of concentrations of the HER-3 antigen that may be considered characteristic of each stage is designated.

In order to stage the progression of the cancer in a subject under study, or to characterize the response of the subject to a course of therapy, a sample of blood is taken from the subject and the concentration of the HER-3 antigen present in the sample is determined. The concentration so obtained is used to identify in which range of concentrations the value falls. The range so identified correlates with a stage of progression or a stage of therapy identified in the various populations of diagnosed subjects, thereby providing a stage in the subject under study.

EXAMPLE 27: Uses of anti-HER-3 antibodies and antibody conjugates of the invention for treatment or prevention of hyperproliferative diseases

Many solid tumors are driven by HER family mediated signalling and it has been demonstrated that HER-3 is a crucial partner through complex formation between HER-1, HER-2 and HER-4. Therefore, a reduction or elimination of HER-3 mediated signaling would impact all other HER family members and impair cell signaling leading to a wide window of therapeutic interventions and potential in combination therapy with other targeted agents, biologics and cytotoxic agents. Thus, anti-HER-3 antibodies of the invention can be used for treatment of certain hyperproliferative or HER-3 associated disorders, that are based on a number of factors as for example HER-3 expression. Tumor types as breast cancer, gastrointestinal cancer, pancreas cancer, prostate cancer, ovarian cancer, stomach cancer,

endometrial cancer, salivary gland cancer, lung cancer, kidney cancer, colon cancer, colorectal cancer, thyroid cancer, bladder cancer, glioma, melanoma, other HER-3 expressing or overexpressing cancers, appear to present preferred indications, but indications are not limited to those on the preceding list. In addition the following groups of patients will benefit from anti-HER-3 directed mAb treatment:

- Patients with resistance to anti-HER-2 mAb treatment
- Patients not eligible for the treatment with anti-HER-2 mAb
- Patients with resistance to anti-HER-1 mAb or small molecule anti-EGFR inhibitor
- Patients with non-small cell lung cancer resistant to erlotinib or gefitinib.

Anti-HER-3 antibodies of the invention would be used either as a monotherapy or in combination with one or more agent in a so called "combination therapy". Said combination therapy may include, but is not limited to, agents that were specified previously in the invention. Combination therapy with anti-HER3 antibodies and other agents may extend patient survival, time to tumor progression or quality of patient life. Protocol and administration design will address therapeutic efficacy as well as the ability to reduce the usual doses of standard therapies, as for example chemo- or radiation therapy.

Treatment of humans with anti-HER-3 antibodies of the invention

To determine the *in vivo* effects of anti-HER-3 antibody treatment in human patients with tumors, such human patients are injected over a certain amount of time with an effective amount of anti-HER-3 antibody of the invention. At periodic times during the treatment, the human patients are monitored to determine whether their tumors progress, in particular, whether the tumors grow and metastasize.

A tumor patient treated with the anti-HER-3 antibodies of the invention has a lower level of tumor growth and/or metastasis compared to the level of tumor growth and metastasis in tumor patients treated with the current standard of

care therapeutics.

Treatment with anti-HER-3 antibody conjugates of the invention

5 To determine the *in vivo* effects of anti-HER-3 antibody conjugates of the invention, human patients or animals exhibiting tumors are injected over a certain amount of time with an effective amount of anti-HER-3 antibody conjugate of the invention. For example, the anti-HER-3 antibody conjugate administered is DM1-anti-HER-3 antibody conjugate, an auristatin-anti-HER-
10 3 antibody conjugate or radioisotope-anti-HER-3 antibody conjugate. At periodic times during the treatment, the human patients or animals are monitored to determine whether their tumors progress, in particular, whether the tumors grow and metastasize.

15 A human patient or animal exhibiting tumors and undergoing treatment with, for example, DM1-anti-HER-3 antibody or radioisotope-anti-HER-3 antibody conjugates has a lower level of tumor growth and metastasis when compared to a control patient or animal exhibiting tumors and undergoing treatment with an alternate therapy. Control DM1-antibodies that may be
20 used in animals include conjugates comprising DM1 linked to antibodies of the same isotype of the anti-HER-3 antibodies of the invention, but more specifically, not having the ability to bind to HER-3 tumor antigen. Control radioisotope-antibodies that may be used in animal tests include conjugates comprising radioisotope linked to antibodies of the same isotype of the anti-
25 HER-3 antibodies of the invention, but more specifically, not having the ability to bind to HER-3 tumor antigen. Note: the control conjugates would not be administered to humans.

GENERAL REMARKS

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The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the deposited

embodiment is intended as a single illustration of certain objects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any object of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustrations that it represents.

The foregoing description and Examples detail certain preferred embodiments of the invention and describes the best mode contemplated by the inventors. It will be appreciated, however, that no matter how detailed the foregoing may appear in text, the invention may be practiced in many ways and the invention should be construed in accordance with the appended claims and any equivalents thereof.

Furthermore, unless otherwise defined, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Moreover, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures utilized in connection with, and techniques of, cell and tissue culture, molecular biology, and protein and oligo- or polynucleotide chemistry and hybridization described herein are those well known and commonly used in the art. Standard techniques are used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g. electroporation, lipofection). Enzymatic reactions and purification techniques are performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. See e.g. Sambrook *et al.* *Molecular Cloning: A Laboratory Manual* (3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2001)), which is

incorporated herein by reference. The nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art.

5 Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

INCORPORATION BY REFERENCE

10

All references cited herein, including patents, patent applications, papers, text books, and the like, including the references cited therein, are hereby incorporated herein by reference in their entirety.

15

SEQUENCE LISTING

- Antibody U1-39
- 1 Heavy Chain DNA:
GAGGTGCAGCTGGTGGAGTCTGGAGGAGGCTTGATCCAGCCTGGGGGGTCCCTGAGACTC
TCCTGTGCAGCCTCTGGGTTTACCGTCAGTAGCAACTACATGAGCTGGGTCCGCCAGGCT
CCAGGGAAGGGGCTGGATTGGGTCTCAGTTATTTATAGCGGTGGTAGCACATACTACGCA
GACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTT
CAAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGGGCAGTGG
CTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA
 - 2 Heavy Chain Protein:
EVQLVESGGGLIQPGSLRLSCAASGFTVSSNYMSWVRQAPGKGLDWVSVIYSGGSTYYA
DSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGQWLDVWGQTTVTVSS
 - 3 Light Chain DNA:
GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCC
ATCTCCTGCAGGTCAAGTCAGAGCCTCCTGCATAGTAATGGATACAACCTATTTGGATTGG
TACCTGCAGAGGCCAGGGCAGTCTCCACAACCTCCTGTTCTATTTGGGTTTTTCATCGGGCC
TCCGGGGTCCCTGACAGGTTTCACTGGCAGTGGATCAGGCACAGATTTTACACTGAAAATC
AGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCAGGCAAGCTCTACAAACTCCG
CTCACTTTCCGGCGGAGGGACCAAGGTGGAGATCAAA
 - 4 Light Chain Protein:
DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQRPQSPQLLFYLGPHRA
SGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCRQALQTPLEGGGTVKVEIK
- Antibody U1-40
- 5 Heavy Chain DNA:
CAGGTGCAGCTGCAGGAGTCGGGGCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTC
ACCTGTACTGTCTCTGGTGGCTCCATCAGCAGTGGTGGTTACTACTGGAGCTGGATCCGC
CAGCACCCAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTCCAGTGGGAGCACCTAC
TACAACCCGTCCCTCAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
TCCCTGAAGCTGAGCTCTGTGACTGCCCGGACACGGCCGTGTATTACTGTGCGAGAGAT
AGGGAACCTGGAACCTTTACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCAG
GTCACCGTCTCCTC
 - 6 Heavy Chain Protein:
QVQLQESGPGLVKPSQTLSTCTVSGGSISSGGYYWSWIRQHPGKLEWIGYIYSSGSTY
YNPSLKSRTVISVDTSKNQFSLKLSVTAADTAVYYCARDRELELYYYYYGMDVWGQGT
TVTS
 - 7 Light Chain DNA:
GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCC
ATCTCCTGCAGGTCTAGTCAGAGCCTCCTGTATAGTAATGGATACAACCTATTTGGATTGG
TACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCTGATCTATTTGGGTTCTAATCGGGCC
TCCGGGGTCCCTGACAGGTTTCACTGGCAGTGGATCAGGCACAGATTTTACACTGAAAATC
AGCAGAGTGGAGGCTGAGGATGTTGGGATTTATTACTGCATGCAAGCTCTACAAACTCCG
CTCACTTTCCGGCGGAGGGACCAAGGTGGAGATCAAA
 - 8 Light Chain Protein:
DIVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGQSPQLLIYLGSNRA
SGVPDRFSGSGSGTDFTLKI SRVEAEDVGIYYCMQALQTPLEGGGTVKVEIK
- Antibody U1-38
- 9 Heavy Chain DNA:
CAGATCACCTTGAAGGAGTCTGGTCCTACGCTGGTGAACCCACACAGACCCTCAGCTG
ACCTGCACCTTCTCTGGGTTCTCACTCAGCACTAGTGGAGTGGGTGTGGGCTGGATCCGT
CAGCCCCAGGAAAGGCCCTGGACTGGCTTGCACTCATTTATTGGAATGATGATAAGCGC

- TACAGCCCATCTCTGAAGAGCAGGCTCACCATCACCAGGACACCTCCAAAAACCAGGTG
GTCCTTACAATGACCAACATGGATCTTGTGGACACAGCCACATATTACTGTGTACACAGA
GACGAAGTTCGAGGGTTTGACTACTGGGGCCAGGGAACCTGGTCACCGTCTCCTCA
- 10 Heavy Chain Protein:
QITLKESGPTLVKPTQTLTLCTFSGFSLSTSGVGVGWIRQPPGKALDWLALIYWNDDKR
YSPSLKSRITITKDTSKNQVLTMTNMDLVDATYYCVHRDEVRFDYWGQGLVTVSS
- 11 Light Chain DNA:
GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCTTGGACAGCCGGCCTCC
ATCTCCTGCAGGTCTAGTCAAAGCCTCGTATACAGTGATGGATACACCTACTTGCATTGG
TTTCAGCAGAGGCCAGGCCAATCTCCAAGGCGCCTTATTATAAGGTTTCTAACTGGGAC
TCTGGGGTCCCAGACAGATTCAAGCGGAGTGGGTCAGGCACTGATTTCACTGAAAATC
AGCAGGGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCAAGGTGCACACTGGCCG
ATCACCTTCGGCCAAGGGACAGACTGGAGATTAAA
- 12 Light Chain Protein:
DVVMTQSPSLPVTLGQPASISCRSSQSLVYS DGYTYLHWFOQRPGQSPRRLIYKVS NWD
SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGAHWPIITFGQGRLEIK
- Antibody U1-41
- 13 Heavy Chain DNA:
CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGACCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGGGTACTACTGGAGCTGGATCCGC
CAGCACCAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCCTCAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
TCCCTGAAGCTGAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTCTGTGCGAGAGAT
CGGGAACCTTGAGGCTTACTCCAATACTACGGTGTGGACGTCTGGGGCCAAGGGACACG
GTCACCGTCTCCTC
- 14 Heavy Chain Protein:
QVQLQESGPGLVKPSQTLSTCTVSGGSISSGGYYWSWIRQHPGKLEWIGYIYSGSTY
YNPSLKSRVTLISVDTSKNQPSLKLSSVTAADTAVYFCARDRELEGYSNYGVDVWGQGT
TVTS
- 15 Light Chain DNA:
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGGCCATTAGCAACTATTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTCACTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCT
GAAGATTTTGCAACTTATTACTGTCAACAGAATAATAGTCTCCCGATCACCTTCGGCCAA
GGGACACGACTGGAGATTAAA
- 16 Light Chain Protein:
DIQMTQSPSSLSASVGRVTITCRASQAISNYLWYQQKPGKAPKLLIYAASSLSQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQQMNSLPITFGQGRLEIK
- Antibody U1-42
- 17 Heavy Chain DNA:
GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAGCCCGGGGAGTCTCTGAAGATC
TCCTGTAAAGGTTCTGGATACAGCTTTACCAGCTACTGGATCGGCTGGGTGCGCCAGATG
CCCCGGAAAGGCCTGGAGTGGATGGGGATCATCTATCCTGGTGACTCTGATACCAGATA
AGCCCGTCCCTTCCAAGGCCAGGTCAACATCTCAGCCGACAACTCCATCAGCAGCCCTAC
CTGCAGTGGAGCAGCCTGAAGGCCCTCGGACACCGCCATGTATTACTGTGCGAGACATGAA
AACTACGGTGACTACAATACTGGGGCCAGGGAACCTGGTCACCGTCTCCTCA
- 18 Heavy Chain Protein:
EVQLVQSGAEVKKPGESLTKISCKSGSYSTSYNIGWVRQMPGKLEWIMGIIYPGDS DTRY
SPSFQGGVITISADKSI STAYLQWSSLKASDTAMYYCARHENYGDYNYWGQGLVTVSS
- 19 Light Chain DNA:

- GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTGCGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGAGCATTGCGAGCTATTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGCTGCTTCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCACTTTACTGCTGTCAACAGAGTAACGGTCCCCGCTCACTTTGGGCGGA
GGGACCAAGGTGGAGATCAAA
- 20 Light Chain Protein:
DIQMTQSPSSLSASVGDRTITCRASQSIRSYLNWYQOKPGKAPKLLIYAASSLQSGVPS
RFSGSGSGTDFTLTISLQPEDFALYCCQQSNGSPLTFGGGKVEIK
- Antibody U1-43
- 21 Heavy Chain DNA:
CAGGTGCAGCTGCAGGAGTCCGGGCCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGGTTFCTACTGGAGCTGGATCCGC
CAGCACCAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCTCAGGAGTCCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
TCCCTGAAGCTGAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGAT
AGAGAGAGAGAGTGGGATGATTACGGTGACCCCCAAGGTATGGACGTCTGGGGCCAAGGG
ACCACGGTCACCGTCTCCTC
- 22 Heavy Chain Protein:
QVQLQESGPGLVKPSQTLSTCTVSGGSISSGGYWSWIRQHPGKGLEWIGYIYSGSTY
YNPSLSRVRTISVDTSKNQFSLKLSVTAADTAVVYCARDREREWDDYGD PQGMDVWGQG
TIVTVS
- 23 Light Chain DNA:
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTACATTTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCCATGCTGCATCCAGTTTACAAAGTGGGGTCCCATCA
AGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGTAGTCTGCAACCT
GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTAACCCGCTCACTTTTCGGGCGGA
GGGACCAAGGTGGAGATCCAA
- 24 Light Chain Protein:
DIQMTQSPSSLSASVGDRTITCRASQSISSYLHWYQOKPGKAPKLLIHAASSLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQSYSNPLTFGGGKVEIQ
- Antibody U1-44
- 25 Heavy Chain DNA:
GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGAGTCTCTGAAGATC
TCCTGTAAGGGTTCTGGATACAGCTTTACCAGCTACTGSATCGGCTGGGTGCGCCAGATG
CCCGGGAAGGGCCTGGAGTGGATGGGGATCATCTGGCCTGGTACTCTGATACCATATAC
AGCCCGTCCTTCCAAGGCCAGGTCAACATCTCAGCCGACAAGTCCATCAGCACCGCCTAC
CTGCAGTGGAGCAGCCTGAAGGCCCTCGGACACCGCCATGTATTACTGTGCGAGACATGAA
AACTACGGTGACTACAACACTACTGGGGCCAGGGAACCCCTGGTCACCGTCTCCTCA
- 26 Heavy Chain Protein:
EVQLVQSGAEVKKPGESLKISCKSGSYFTSYWIGWVRQMPGKGLEWMGIWPGDSDTIY
SPSFQGVFTISADKSI STAYLQWSS LKASDTAMYYCARHENYGDYNYWGQGLVTVSS
- 27 Light Chain DNA:
GACATCCAGATGAGCCAGTCTCCATCCTCCCTGTCTGCATCTGTGGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGAGCATTGGAAGTTATTTAAATTGGTATCAGCAGAAACCG
GGGAATGCCCCCTAAACTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCACTTTACTACTGTCAACAGAGTATCAGTTCCCCGCTCACTTTTCGGGCGGA
GGGACCAAGGTGGAGATCAAA

28 Light Chain Protein:
DIQMTQSPSSLSASVGDRVTITCRASQSIRSYLNWYQQKPGNAPKLLIYAASSLQSGVPS
RFSGSGSGTDFTLTISLQPEDFALYYCQQSISPLTFGGGTKVEIK

Antibody (U1-45)

29 Heavy Chain DNA:
CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTC
TCCTGCAAGGCTTCTGGATACACCTTCACCAGTTATGATATCAACTGGGTCCGACAGGCC
ACTGGACAAGGGCTTGAGTGGATGGGATGGATGAACCCTAACAGTGGTGACACTGGCTAT
GCACAGGTGTTCCAGGGCAGAGTCACCATGACCTGGAACACCTCCATAAGCACAGCCTAC
ATGGAAGTGAAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGATTGGG
GATCTCCCGTATGACTACAGTTACTACGAATGGTTCGACCCCTGGGGCCAGGGAACCTG
GTCACCGTCTCCTC

30 Heavy Chain Protein:
QVQLVQSGAEVKKPGASVKVSCASGYTFTSYDINWVRQATGQGLEWMGWMNPNSGDTGY
AQVYFQGRVTMTWNTSISTAYMELSSLRSEDVAVYYCARFGDLFYDYSYEWFDPWGQGT
LVTVS

31 Light Chain DNA:
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCCGGGCAAGCCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAGACCA
GGGAAAGCCCCCTAAGCTCCTGATCTATGCAGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCGCTCACTTTCGGCGGA
GGGACCAAGGTGGAGATCAAA

32 Light Chain Protein:
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQRPGKAPKLLIYAASSLQSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCQSYSTPLTFGGGTKVEIK

Antibody (U1-46)

33 Heavy Chain DNA:
CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAAGCCCTCGCAGACCCCTCTCACTC
ACCTGTGCCATCTCCGGGGACAGTGTCTCTAGCAACAGTGCTGCTTGGAAGTGGATCAGG
CAGTCCCCATCGAGAGGCCTTGAGTGGCTGGGAAGGACATACTACAGGTCCAAGTGGTAT
AATGATTATGCAGTATCTGTGAAAAGTGAATAACCATCAACCCAGACACATCCAAGAAC
CAGTTCTCCCTGCAGCTGAAGTCTGTGACTCCCGAGGACACGGCTGTGTATTACTGTGCA
AGAGATCTCTACGATTTTGGAGTGGTTATCCCTACTACTACGGTATGGACGTCTGGGGC
CAAGGGACACGGTCACCGTCTCCTC

34 Heavy Chain Protein:
QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSAANNWIRQSPSRGLEWLGRTYYRSKWY
MDYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARDLYDFWSGYPYYGMDVWG
QGTTVTVS

Antibody U1-47

35 Heavy Chain DNA:
CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAAGCCCTCGCAGACCCCTCTCACTC
ACCTGTGCCATCTCCGGGGACAGTGTCTCTAGCAACAGTGCTGCTTGGAAGTGGATCAGG
CAGTCCCCATCGAGAGGCCTTGAGTGGCTGGGAAGGACATACTACAGGTCCAAGTGGTAT
AATGATTATGCAGTATCTGTGAAAAGTGAATAACCATCAACCCAGACACATCCAAGAAC
CAGTTCTCCCTGCAGCTGAAGTCTGTGACTCCCGAGGACACGGCTGTGTATTACTGTGCA
AGAGATTACTATGGTTCGGGGAGTTTCTACTACTACTACGGTATGGACGTCTGGGGCCAA
GGGACCACGGTCACCGTCTCCTC

36 Heavy Chain Protein:
QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSAANNWIRQSPSRGLEWLGRTYYRSKWY

NDYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARDYYGSGSFYTYTGMDVWGQ
GTTVTVS

37 Light Chain DNA:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGGTCCTGATCTATGCTGCATCCAATTTGCAAAGTGGGGTCCCATCA
AGGTTAGTGGCAGTGGATCTGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTCGGACGTTGCGCCAA
GGGACCAAGGTGGAAATCAAA

38 Light Chain Protein:

DIQMTQSPSSLSASVGDRTTTCRASQSISSYLWYQOKPGKAPKVLIIYAASNLQSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQQSYSTPRTFGQGTKVEIK

Antibody U1-48

39 Heavy Chain DNA:

CAGGTGCAGCTGCAGGAGTCGGGGCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTTACTACTGGAGCTGGATCCGGCAGCCC
GCCCCGAAGGGACTGGAGTGGATTGGGCATATCTATACCACTGGGAGCACCACACTACAAC
CCCTCCCTCAAGAGTCGAGTCACCATGTCTAGTAGACACGTCCTCAAGAACCAGTTCTCCCTG
AAGCTGAGCTCTGTGACCGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGAAGCGATT
TTTGGAGTGGGCCCCCTACTACTACTACGGTATGGACGTCCTGGGGCCCAAGGGACCACGGTC
ACCGTCTCCTC

40 Heavy Chain Protein:

QVQLQESGPGLVKPSSETLSLTCTVSGGSISSYYWSWIRQAGKLEWIGHIYTSGSTNYN
PSLKSRTMSVDTSKNQFSLKLSSVTAADTAVYYCAREAIPEGVGPYYTYGMDVWGQTTV
TVS

Antibody U1-49

41 Heavy Chain DNA:

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTC
TCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATATGCACTGGGTGCGACAGGCC
CCTGGACAAAGGCTTGAGTGGATGGGATGGATCAACCCTAATATTGGTGGCACAACTGT
GCACAGAAGTTTCAGGGCAGGGTCAACATGACCAGGGACACGTCCATCAGCACAGCCTAC
ATGGAGCTGAGCAGGCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAGGGGGA
CGGTATAGCAGCAGCTGGTCTACTACTACTACGGTATGGACGTCCTGGGGCCCAAGGGACC
ACGGTCACCGTCTCCTC

42 Heavy Chain Protein:

QVQLVQSGAEVKKPGASVKVSKASGYTFTGYYMHWVRQAPGQGLEWMGWINPNIGGTNC
AQKFQGRVTMTDRDTSISTAYMELSRRLSDDTAVYYCARGGRYSSWSYTYTYGMDVWGQGT
TVTVS

43 Light Chain DNA:

GATATTCTGATGACCCAGACTCCACTCTCTCTGTCCGTACCCCTGGACAGCCGGCCTCC
ATCTCCTGCAAGTCTAGTCAGAGCCTCCTGCTTAGTGATGGAGGGACCTATTTGTATTGG
TACCTGCAGAAGCCAGGCCAGCCTCCACAGCTCCTGATCTATGAAGTTTCCAACCGGTTT
TCTGGAGTGGCAGATAGGTTTCACTGGCAGCGGGTCAAGGACAGATTTCACTGAAAATC
AGCCGGGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCAAAGTATGCAGCTTCCG
ATCACCTTCGGCCCAAGGGACACGACTGGAAATTAAT

44 Light Chain Protein:

DILMTQTPLSLSVTPGQPASISCKSSQSLLLSDDGGTYLYWYLQKPGQPPQLLIYEVSNRF
SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQSMQLPITFGQTRLEIK

Antibody U1-50

45 Heavy Chain DNA:

- CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCGTCAGCAGTGGTGGTTACTACTGGAGCTGGATCCGG
CAGCCCCCAGGGAAGGGACTGGAGTGGATTGGGTATATCTATTACAGTGGGAGCACCAAC
TACAACCCCTCCCTCAAGAGTCGAGTCACCATATCAGTAGACACGTCCAAGAACCAGTTC
TCCCTGAAGCTGAGCTCTGTGACCGCTGCGGACACGGCCGTGTATTACTGTGCGAGAGGG
GGGGACAGTAACACGAGGATTACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGG
ACCACGGTCACCGTCTCCTC
- 46 Heavy Chain Protein:
QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGGYYSWIRQPPGKGLEWIGYIYYSGSTN
YNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARGGDSNYEDYIYYGMDVWGQG
TTFVTVS
- 47 Light Chain DNA:
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTCCCGGCAAGTCAGAGCATTAGCATCTATTTACATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCTTGATCTCTGCTGCATCCAGTTTGCAAAGTGGGGTCCCGTCA
AGGTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGAAGTCTGCAACCT
GAAGATTTGCAACTTACTACTGTCAACAGAGTTACACTTCCCCGATCACCTTCGGCCAA
GGGACACGACTGGAGATTAA
- 48 Light Chain Protein:
DIQMTQSPSSLSASVGDRTITCRASQSSISYLEHWYQQKPKAPKLLISAASSLQSGVPS
RFGSGSGTDFTLTIRSLQPEDFATYYCQQSYTSPITFGQGRLEIK
- 49 Antibody U1-51
Heavy Chain DNA:
CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTTACTACTGGAGCTGGATCCGGCAGCCC
CCAGGGAAGGGACTGGAGTGGATTGGGTATATCTATTACAGTGGGAGCACCAACTACAAC
CCCTCCCTCAAGAGTCGAGTCACCATATCAGTAGACACGTCCAAGCACCAGTTCTCCCTG
AAGCTGAGCTCTGTGACCGCTGCGGACACGGCCGTGTATTACTGTGCGAGAGATTGAGT
TACTATGATAGTAGTGGTTATTACTTATACTACTACGCTATGCACGTCTGGGGCCAAGGG
ACCACGGTCACCGTCTCCTC
- 50 Heavy Chain Protein:
QVQLQESGPGLVKPSSETLSLTCTVSGGSISYYWSWIRQPPGKGLEWIGYIYYSGSTNYN
PSLKSRVTISVDTSKHQFSLKLSSVTAADTAVYYCARDSSYYDSSGYLYYYAMDVWGQG
TTFVTVS
- 51 Light Chain DNA:
GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACC
ATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGCTCCAACAATAAGAACTACTTAGCT
TGGTACCAGCAGAAACCAGGACAGCCTCCTAAGCTGCTCATTTCCCTGGGCATCTACCCGG
GAATCCGGGGTCCCTGACCGATTTCAGTGGCAGCGGTCTGGGACAGATTTCACTCTCACC
ATCAGCAGCCTGCAGGCTGAAGATGTGGCAGTTTATTACTGTGCAATATTATACTACT
CCTCTCACTTTCCGGCCCTGGGACCAAAGTGGATATCAAA
- 52 Light Chain Protein:
DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLISWASTR
ESGVPDRFSGSGSGTDFTLTISLQAEDVAVYYCQQYTTPLTFPGTKVDIK
- Antibody U1-53
- 53 Heavy Chain DNA:
GAGGTGCAACTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTC
TCCTGTGCAGCCTCTGGATTCACCTTCAGTATCTATAGCATGAAGTGGGTCCGCCAGGCT
CCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTAGTAGTAGTAGTACCATATACTAC
GCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAATGCCAAGAACTCACTGTAT
CTGCAAATGAACAGCCTGAGAGACGAGGACACGGCTGTGTATTACTGTGCGAGAGATAGG

- GGTGACTTCGATGCTTTTGATATCTGGGGCCAAGGCACAATGGTCAACGCTCTCTTCA
- 54 Heavy Chain Protein:
EVQLVESGGGLVQPGGSLRLSCAASGFTFSIYSMNWVRQAPGKLEWVSYISSSSTIYY
ADSVKGRFTISRDNKNSLYLQMNSLRDEDTAVYYCARDREGDFDAFDIWQGTHVTVSS
- 55 Light Chain DNA:
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCAGGCGAGTCAGGACATTACCAACTATTTGAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCAAGCTCCTGATCTACGATGCATCCAATTTGGAAACAGGGGTCCCATCA
AGGTTCACTGGAAGTGGATCTGGGACAGATTTTACTTTTACCATCAGCAGCCTGCAGCCT
GAAGATATTGCAACATATACTGTCAACAGTGTGAAAATTTCCCGATCACCTTCGGCCAA
GGGACACGACTGGAGATTAAA
- 56 Light Chain Protein:
DIQMTQSPSSLSASVGDRTTITCQASQDITNYLNWYQOKPGKAPKLLIYDASNLETGVPS
RFGSGSGSDFTFTTISLQPEDATYNCQQCENFPITFGQTRLEIK

Antibody U1-55

- 57 Light Chain DNA:
GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCC
ATCTCCTGCAGGTCTAGTCAGAGCCTCCTGTATAGTAATGGATACAAGTATTTGGATTGG
TACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCTGATCTATTTGGGTTCTAATCGGGCC
TCCGGGGTCCCTGACAGGTTCACTGGCAGTGGATCAGGCACAGATTTTACACTGAAAATC
AGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTATTGCATGCAGGCTCTACAACTCCG
ATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA
- 58 Light Chain Protein:
DIVMTQSPPLSLPVTPGEPASISCRSSQSLLYSNGYKYLDWYLQKPGQSPQLLIYLGSNRA
SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPITFGQTRLEIK

Antibody (U1-55.1)

- 59 Heavy Chain DNA:
CAGGTGCAGCTGCAGGAGTCGGGGCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCGTCAGCAGTGGTGGTTACTACTGGAAGTGGATCCGG
CAGCCCCCAGGGAAGGGACTGGAGTGGATTGGGTATATCAATTACAGTGGGAGCACCAAC
TACAACCCCTCCCTCAAGAGTCGAGTCACCATATCAGTAGACACGTCCAAGAACCAGTTC
TCCCTGAAGCTGAGCTCTGTGACCGCTGCGGACACGGCCGTGTATTACTGTGCGAGAGAT
CGAGAACTGGAACCTTACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACG
GTCACCGTCTCCTC
- 60 Heavy Chain Protein:
QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGGYYWNWIRQPPGKLEWIGYINYSGSTN
YNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDRELELYYYYYYGMVDVWGQGT
VTVS

Antibody (U1-57)

- 61 Heavy Chain DNA:
CAGGTGCAGCTGCAGGAGTCGGGGCCAGGACTGGTGAAGCCTTCTGAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCGTCAGCAGTGGTGGTTACTACTGGAAGTGGATCCGG
CAGCCCCCAGGGAAGGGACTGGAGTGGATTGGGTATATCAATTACAGTGGGAGCACCAAC
TACAACCCCTCCCTCAAGAGTCGAGTCACCATATCAGTAGACACGTCCAAGAACCAGTTC
TCCCTGAAGCTGAGCTCTGTGACCGCTGCGGACACGGCCGTGTATTACTGTGCGAGAGAT
CGAGAACTGGAACCTTACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACG
GTCACCGTCTCCTC
- 62 Heavy Chain Protein:
QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGGYYWNWIRQPPGKLEWIGYINYSGSTN
YNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDRELELYYYYYYGMVDVWGQGT

VTVS

Antibody U1-57.1

63 Light Chain DNA:

GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTACCCCTGGAGAGCCGGCCTCC
ATCTCCTGCAGGTCTAGTCAGAGCCTCCTGTATAGTAATGGATACAAGTATTTGGATTGG
TACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCATGATCTATTTGGGTTCTAATCGGGCC
TCCGGGGTCCCTGACAGGTTCACTGGCAGTGGATCAGGCACAGATTTTACACTGAAAATC
AGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTATTGTCATGCAGGCTCTACAACTCCG
ATCACCTTCGGCCAAGGGACAGACTGGAGATTAAA

64 Light Chain Protein:

DIVMTQSPLSLPVTGPGEPAISICRSSQSLLYSNGYKYLDWYLOKPGQSPQLMIYLGSNRA
SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPITFGQSTRLEIK

Antibody U1-58

65 Heavy Chain DNA:

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTC
TCCTGTGCAGCCTCTGGATTACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCT
CCAGGCAAGGGGCTGGAGTGGGTGGCAGTTTATATGGTATGATGGAAGTAATAAATACTAT
GCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCCAAGAACACGCTGTAT
CTGCAAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGCAGCT
CGCCTTGACTACTACTACGGTATGGACCTCTGGGGCCAAGGGACCACGGTCACCGTCTCC
TCA

66 Heavy Chain Protein:

QVQLVESGGGVVQPGRSLRLSCAASGFTTFSSYGMHWVRQAPGKGLEWVAVIWDGNSNKYY
ADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARAARLDYIYGMVWGQGTITVTVS
S

67 Light Chain DNA:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCTCC
ATCACTTGCCTGGGCAAGTCAGAGCATTAAACAGCTATTTAAATTGGTTTCAGCAGAAGCCA
GGGAAAGCCCCCTCAGCTCCTGATCTTTGGTGCATCCGGTTTGCAAAGTGGGGTCCCATCA
AGGTTCACTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAACAGTCTGCAACCT
GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTTCCCGCTCACCTTCGGCCAA
GGGACACGACTGGAGATTAAA

68 Light Chain Protein:

DIQMTQSPSSLSASVGRVSIICRASQISINYLWVWFQKPKAPQLLIIFGASGLQSGVPS
RFGSGSGSDFTLTINSLOPEDFATVYCCQSYSSPLTFGQSTRLEIK

Antibody U1-59

69 Heavy Chain DNA:

CAGGTGCAGCTACAGCAGTGGGGCGCAGGACTGTTGAAGCCTTCGGAGACCCTGTCCCTC
ACCTGCGCTGTCTATGGTGGGTCCCTTCAGTGGTTACTACTGGAGCTGGATCCGCCAGCCC
CCAGGGAAGGGGCTGGAGTGGATTGGGGAAATCAATCATAGTGGAGCACCACACTACAAC
CCGTCCCTCAAGAGTCGAGTCACCATATCAGTAGAAACGTCCAAGAACCAGTTCTCCCTG
AAGCTGAGCTCTGTGACCGCCGCGGACACGGCTGTGTATTACTGTGCGAGAGATAAGTGG
ACCTGGTACTTCGATCTCTGGGGCCGTGGCACCTGGTCACTGTCTCCTCA

70 Heavy Chain Protein:

QVQLQQWGAGLLKPSFSLTCAVYGGSFSGYYWSWIRQPPGKLEWIGEINHSGSTNYN
PSLKSRVTISVETSKNQFSLKLSVTAADTAVYYCARDKWTWYFDLWGRGTLTVSS

71 Light Chain DNA:

GACATCGAGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGGGAGAGGGCCACC
ATCAACTGCAGGTCCAGCCAGAGTGTTTTATACAGCTCCAGCAATAGGAACACTTAGCT
TGGTACCAGCAGAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCTTCTACCCGG

GAATCCGGGGTCCCTGACCGATTTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACC
ATCAGCAGCCTGCAGGCTGAAGATGTGGCAGTTTATTACTGTCAGCAATATTATAGTACT
CCTCGGACGTTCCGGCCAAGGGACCAAGGTGGAAATCAAA

72 Light Chain Protein:

DIEMTQSPDSLAVSLGERATINCRSSQSVLYSSNRNYLAWYQONPGQPPKLLIYWASTR
ESGVPDRFSGSGSGTDFTLTISLSLAEDVAVYYCQQYVSTPRTFGQGTKVEIK

Antibody U1-52

73 Heavy Chain DNA:

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTC
ACCTGCAGCTGTCTCTGGTGGCTCCATCAGCAGTGGTGGTTACTACTGGAGCTGGATCCGC
CAGCACCCAGGGAAGGGCCTGGAGTGGATGGGGAACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCCTCAAGAGTCGAGTTACCATATCAGTAGACAGCTCTGAGAACCAGTTC
TCCCTGAAGCTGAACTCTGTGACTGCCCGCGACACGGCCGTATATTACTGTGCGAGAGGG
GGAAGTGAACCAATTACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACG
GTCACCGTCTCCTC

74 Heavy Chain Protein:

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGGYWWSWIRQHPGKGLEWMGNIIYSGSTY
YNPSLKSRVTISVDTSENQFSLKLSVTAADTAVYYCARGGTGTNYIIYYGMDVWGQGT
VTVS

75 Light Chain DNA:

GAAATTGTGTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACC
CTCTCCTGCAGGGCCAGTCAGAGTGTAGCAGCAGCTACTTAGCCTGGTACCAGCAGAAA
CCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCAGCTGGGCCACTGGCATCCCA
AACAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAG
CCTGAAGATTTTGCAGTGTATTACTGTGTCAGCAGTATGGTAGCTCACCGCTCACTTTCGGC
CGAGGGACCAAGGTGGAGATCAAA

76 Light Chain Protein:

EIVLTQSPGTLSTLSPGERATLSCRASQSVSSSYLAWYQKPGQAPRLLIYGASSWATGIP
NRFSGSGSGTDFTLTISRLEPEDFAVYYCQYGSPLTFGGGTKVEIK

Antibody U1-61

77 Heavy Chain DNA:

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTC
ACCTGCAGCTGTCTCTGGTGTCTCCATCAGCAGTGGTGGTTACTACTGGAGCTGGATCCGC
CAGCACCCAGGATGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCCTCAAGAGTCGAGTCACCATATCAGAAGACACGTCTAAGAACCAGTTC
TCCCTGAAGCTGAGCTCTGTGACTGCCCGCGACACGGCCGTGTATTACTGTGCGAGAGAT
TCCGAGTCCGAGTATAGCAGCTCGTCGAACACTACGGTATGGACGTCTGGGGCCAAGGGACC
ACGGTCACCGTCTCCTC

78 Heavy Chain Protein:

QVQLQESGPGLVKPSQTLSTCTVSGVSISSGGYWWSWIRQHPGMGLEWIGYIIYSGSTY
YNPSLKSRVTISEDTSKNQFSLKLSVTAADTAVYYCARDSESEYSSSSNYGMDVWGQGT
VTVS

Antibody U1-61.1

79 Heavy Chain DNA:

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTC
ACCTGCAGCTGTCTCTGGTGTCTCCATCAGCAGTGGTGGTTACTACTGGAGCTGGATCCGC
CAGCACCCAGGATGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCCTCAAGAGTCGAGTCACCATATCAGAAGACACGTCTAAGAACCAGTTC
TCCCTGAAGCTGAGCTCTGTGACTGCCCGCGACACGGCCGTGTATTACTGTGCGAGAGAT
TCCGAGTCCGAGTATAGCAGCTCGTCGAACACTACGGTATGGACGTCTGGGGCCAAGGGACC

- ACGGTCACCGTCTCCTC
- 80 Heavy Chain Protein:
QVQLQESGPGLVKPSQTLSTCTVSGVSISSGGYIWSWIRQHPGMGLEWIGYIYYSGSTY
YNPSLKSRTVISEDTSKNQFSLKLSVTAADTAVYYCARDSESEYSSSSNYGMDVWGQGT
TVTVS
- 81 Light Chain DNA:
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCCTGCATCTGTAGGAGACAGAATCACC
ATCATTGCGCGGGCAAGTCAGACCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAGGTGGGGTCCCATCA
AGGTTTCAGTGGCAGTGTATCTGGGACAGATTTACCCCTCACCGTCAGCAGTCTGCAACCT
GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTAACCCGCTCACTTTGGGCGGA
GGGACCAAGGTGGAGATCAAA
- 82 Light Chain Protein:
DIQMTQSPSSLSASVGDRIITTCRASQTISYLNWYQQKPKAPKLLIYAASSLQGGVPS
RFSGSVSGTDFTLTVSSSLQPEDFATYYCQSYSNPLTFGGGTKEIK
- Antibody U1-62 (2.9.1)
- 83 Heavy Chain DNA:
GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAGCCCGGGGAGTCTCTGAAGATC
TCCGTGTAAGGGTCTGGATACAGTTTTACCAGCTACTGGATCGGCTGGGTGCGCCAGATG
CCCGGGAAAGGCCTGGAGTGGATGGGGATCATCTATCCTGGTGA CTCTGATACCAGATAC
AGCCCGTCTCTCCAAGGCCAGGTCAACATGTACGCCGACAAGTCCATCAGTACCGCCTAC
CTGCAGCTGAGCAGCCATGAAGGCCTCGGACACCGCCATGTATTACTGTGCGAGACAGAT
GGCTGGAACTACGTACATCACGGGTGATCGAGACGTCCTGGGGCCAAGGACCACGGTC
ACCGTCTCCTC
- 84 Heavy Chain Protein:
EVQLVQSGAEVKKPGESLKISCKSGSYSTSYWIGWVRQMPGKGLEWMGLIYPGDS DTRY
SPSFQGV TMSADKSISTAYLQLSSHEGLGHRHVL CTDGWKLRTSRVLET SWGQGT TV
TVS
- 85 Light Chain DNA:
GAAATTGTGTTGACGCAGTCTCCAGGCACCCCTGTCTTTGTCTCCAGGGGAAAGAGCCACC
CTCTCCTGCAGGGCCAGTCAGAGTGTTATCAGCATCTACTAGCCTGGTACCAGCAGAAA
CCTGGCCAGGCTCCAGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA
GACAGGTTCACTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAG
CCTGAAGATTTTGCAGTGTATTACTGTGTCAGCAGTATGGTAGCTCACCGTGCAGTTTGGC
CAGGGGACCAAACTGGAGATCAAA
- 86 Light Chain Protein:
EIVLTQSPGTLSPGERATLSCRASQSVISIYLA WYQQKPGQAPRLLIYGAS SRATGIP
DRFSGSGSGTDFTLTISRLEPEDFAVYYCQY GESSFCSFGQGTKLEIK
- Antibody U1-2
- 87 Heavy Chain DNA:
CAGGTGCAGCTGCAGGAGTCGGGCCCCAGGACTGGTGAAGCCTTCACAGACCCCTGTCCCTC
ACCTGCAGCTGTCTCTGGTGGCTCCATCAGCAGTGGTGATTACTACTGGAGCTGGATCCGC
CAGCACCACAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCCTCAGGAGTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
TCCCTGAAGCTGAGCTCTGTGACTGCCCGGACACGGCCGTGTATTACTGTGCGAGAGCG
GATTACGATTTTGGAGTGGTTATTTTGACTACTGGGGCCAGGGAACCCGTGGTCACCGTC
TCCTCA
- 88 Heavy Chain Protein:
QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDIYWSWIRQHPGKGLEWIGYIYYSGSTY
YNPSLRSRTVISVDTSKNQFSLKLSVTAADTAVYYCARADYDFWSGYFDYWGQGLTVT
SS

89 Light Chain DNA:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACCTTGCCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTGGTATCAGCAGATACCT
GGGAAAGCCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTTCAGCGGCAGTGGATCTGGGACAGAATTCACCTCTCACAATCAACAGCCTGCAGCCT
GAAGATTTTGCAACTTATTACTGTCTACAGCATAATGGTTACCCGTGGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAAC

90 Light Chain Protein:

DIQMTQSPSSLSASVGDRTTITCRASQGIKNDLGWYQQIPGKAPKRLIYAASSLQSGVPS
RFSGSGSGTEFTLTINSIQPEDFATYYCLQHNGYPWTFGGGTKVEIK

Antibody U1-7

91 Heavy Chain DNA:

CAGGTGCAGCTGCAGGAGTCCGGGCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTC
ACCTGCACCTGTCTCTGGTGGCTCCATCAGCAGTGGTGAATTACTACTGGAGCTGGATCCGC
CAGCACCCAGGGAAGGGCCTGGAGTGGATTGGATACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCCTCAAGAGTCGAGTTACCATATCAGTAGACACGCTCTAAGAACCAGTTC
TCCCTGAAGCTGAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGCG
GATTACGATTTTGGAGTGGTTATTTTGAATACTGGGGCCAGGGAACCCTGGTCAACGTC
TCCTCA

92 Heavy Chain Protein:

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDYYWSWIRQHPGKGLEWIGYIYYSGSTY
YNPSLKSRVTISVDTSKNQFSLKLSVTAADTAVYYCARADYDFWNGYFDYWGQGLVTV
SS

93 Light Chain DNA:

GACTTCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCCGGGCAAGTCAGGACATTCGAAATGATTTAGGCTGGTATCGGCAGAAACCT
GGGAAAGCCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTTCAGCGGCAGTGGATCTGGGACAGAATTCACCTCTCACAATCAGCAGCCTGCAGCCT
GAAGATTTTGCAACTTATTACTGTCTACAGCATAATAGTTACCCGTGGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAAC

94 Light Chain Protein:

DFQMTQSPSSLSASVGDRTTITCRASQDIRNDLGWYRQKPGKAPKRLIYAASSLQSGVPS
RFSGSGSGTEFTLTITSSIQPEDFATYYCLQHNSYPWTFGGGTKVEIK

Antibody U1-9

95 Heavy Chain DNA:

CAGGTGCAGCTGCAGGAGTCCGGGCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTC
ACCTGCACCTGTCTCTGGTGGCTCCATCAGCAGTGGTGAATTACTACTGGAGCTGGATCCGC
CAGCACCCAGGGAAGGGCCTGGAGTGGATTGGATACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCCTCAAGAGTCGAGTTACCATATCAATAGACACGCTCTAAGAACCAGTTC
TCCCTGAAGCTGAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGCG
GATTACGATTTTGGAAATGGTTATTTTGAATACTGGGGCCAGGGAACCCTGGTCAACGTC
TCCTCA

96 Heavy Chain Protein:

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDYYWSWIRQHPGKGLEWIGYIYYSGSFY
YNPSLKSRVTISIDTSKNQFSLKLSVTAADTAVYYCARADYDFWNGYFDYWGQGLVTV
SS

97 Light Chain DNA:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACCTTGCCCGGGCAAGTCAGGACATTAGAAATGATTTAGGCTGGTATCGGCAGAAACCT
GGGAAAGCCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTTCAGCGGCAGTGGATCTGGGACAGAATTCACCTCTCACAATCAGCAGCCTGCAGCCT

- GAAGATTTTGCAACTTATTACTGTCTACAGCATAATAGTTACCCGTGGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAA
- 98 Light Chain Protein:
DIQMTQSPSSLSASVGDRTTITCRASQDIENDLGWYRQKPGKAPKRLIYAASSLQSGVPS
RFSGSGSGTEFTLTISLQPEDFATYYCLQHNSYPWTFGQGTKVEIK
- Antibody U1-10
- 99 Heavy Chain DNA:
CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTACACAGACCCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGAATTACTACTGGAGCTGGATCCGC
CAGCACCCAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCCTCAAGAGTCGACTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
TCCCTGAAGCTGAGCTCTGTGACTGCCGCGACACGGCCGTGTATTACTGTGCGAGAGCA
GATTACGATTTTGGAGTGGTTACTTTGACTACTGGGCCCAGGGAACCCCTGGTCACCGTC
TCCTCA
- 100 Heavy Chain Protein:
QVQLQESGPGLVKPTQTLSTCTVSGGSISSGDYYWSWIRQHPGKLEWIGYIYYSGSTY
YNPSLKSRLTISVDTSKNQPSLKLSSVTAADTAVYYCARADYDFWSGYFDYWGQGLVTV
SS
- 101 Light Chain DNA:
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTTCAGCGGCAGTGGATCTGGGACAGAATTCACCTCTCACAATCAGCAGCCTGCAGCCT
GAAGATTTTGCAACTTATTACTGTCTACAGCATAATAATTACCCGTGGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAA
- 102 Light Chain Protein:
DIQMTQSPSSLSASVGDRTTITCRASQGIENDLGWYQQKPGKAPKRLIYAASSLQSGVPS
RFSGSGSGTEFTLTISLQPEDFATYYCLQHNNYPWTFGQGTKVEIK
- Antibody U1-12
- 103 Heavy Chain DNA
CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGACCCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTGGTGAATTACTACTGGAGCTGGATCCGC
CAGCACCCAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCCTCAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
TCCCTGAAGTTGAGCTCTGTGACTGCCGCGACACGGCCGTGTATTACTGTGCGAGAGCC
GATTACGATTTTGGAGTGGTTATTTGACTACTGGGCCCAGGGAACCCCTGCTCACCCTC
TCCTCA
- 104 Heavy Chain Protein:
QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDYYWSWIRQHPGKLEWIGYIYYSGSTY
YNPSLKSRLTISVDTSKNQPSLKLSSVTAADTAVYYCARADYDFWSGYFDYWGQGLVTV
SS
- 105 Light Chain DNA:
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTTCAGCGGCAGTGGATCTGGGACAGAATTCACCTCTCACAATCAGCAGCCTGCAGCCT
GAAGATTTTGCAACTTATTACTGTCTACAGCATAATAATTACCCGTGGACGTTTCGGCCAA
GGGACCAAGGTGGAAATCAAA
- 106 Light Chain Protein:
DIQMTQSPSSLSASVGDRTTITCRASQGIENDLGWYQQKPGKAPKRLIYAASSLQSGVPS
RFSGSGSGTEFTLTISLQPEDFATYYCLQHNNYPWTFGQGTKVEIK

Antibody U1- 13

107 Heavy Chain DNA:

CAGGTGCAGCTGCAGGAGTCGGGGCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGGTTACTACTGGAGCTGGATCCGC
CAGCAGCCAGGGAAGGGCCCTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCTCAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
TCCCTGAAGCTGAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGAG
GACGACCGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

108 Heavy Chain Protein:

QVQLQESGPGLVKPSQTLSTCTVSGGSISSEGGYVWSWIRQHPGKLEWIGYIYYSGSTY
YNPSLKSRVTISVDTSKNQPSLKLSSVTAADTAVYYCAREDDGMDVWGQGTITVTVSS

109 Light Chain DNA:

GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCC
ATTTCCCTGCAGGTCTAGTCAGAGCCTCCTGCATAGTAATGGATACAATAATTTGGAATGG
TACCTGCAGAAGCCAGGSCAGTCCCCACAGTTCATGATTTATTTGGGGTCTAATGGGGC
TCCGGGGTCCCTGACAGGTTCACTGGCAGTGGATCAGGCACAGATTTTACACTGAAAATC
AGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCAAGCTCTACAACTCCG
ATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA

110 Light Chain Protein:

DIVMTQSPSLSPVTPGEPASISCRSSQSLHNSNGYNILEWYLQKPGQSPQFMIYLGSNRA
SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPITFGQGTGLEIK

Antibody U1-14

111 Heavy Chain DNA:

CAGGTGCAGCTGCAGGAGTCGGGGCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGAATTACTACTGGAGCTGGATCCGC
CAGTACCCAGGGAAGGGCCCTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCTCAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
TCCCTGAAGCTGAGGTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGCG
GATTACGATTTTGGAGTGGTTATTTTGACTACTGGGGCCAGGGAACCCCTGGTCACCGTC
TCCTCA

112 Heavy Chain Protein:

QVQLQESGPGLVKPSQTLSTCTVSGGSISSEGDYYWSWIRQYPGKLEWIGYIYYSGSTY
YNPSLKSRVTISVDTSKNQPSLKLRSVTAADTAVYYCARADYDFWSGYFDYWGQGTITVTV
SS

113 Light Chain DNA:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTTCAGCGGCACTGCATCTGGGACAGAATTCACTCTCACAATCAGCAGCCTGCAGCCT
GAAGATTTTGCAACTTATTACTGTCTACAGCATAATACTTACCCGTGGACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAAC

114 Light Chain Protein:

DIQMTQSPSSLSASVGRVTITCRASQGIKNDLGWYQQKPKAPKRLIYAASSLQSGVPS
RFSGSGSGTEFTLTISLQPEDFATYYCLQHNTYFPTFGQGTKEIK

Antibody U1-15

115 Heavy Chain DNA:

CAGGTGCAGCTGCAGGAGTCGGGGCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCGTGAGCAGTGGTGGTTACTACTGGAGCTGGATCCGG
CAGCCCCCAGGGAAGGGACTGGAGTGGATTGGGTATATCTATTACAGTGGGAGCACCAAC
TACAACCCCTCCCTCAAGAGTCGAGTCACCATATCAGTAGACACGTCCAAGAACCAGTTC

- TCCCTGAAGCTGAGCTCTGTGACCGCTGCGGACACGGCCGTGTATTACTGTGCGAGAGAT
GGGGACGTGGATACAGCTATGGTCGATGCTTTTGATATCTGGGGCCAAGGACAATGGTC
ACCGTCTCCTCA
- 116 Heavy Chain Protein:
QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGGYYWSWIRQPPGKGLEWIGYIYYSGSTN
YNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDGDVDFTAMVDAFDIWGQGTNV
TVSS
- 117 Light Chain DNA:
GAAATTGTATTGACGCACTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACC
CTCTCCTGCAGGGCCAGTCAGAGTTTAAGCGGCAACTACTTAGCCTGGTACCAGCAGAAG
CCTGGCCAGGCTCCCAGGCTCATCTGTGGTGCATCCAGCAGGGCCACTGGCATCCCA
GACAGGTTCACTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCACAAGACTGGAG
CCTGAAGATTTTGCAGTGTATTACTGTGACAGTATGATAGGTCACCGCTCACTTTCGGC
GGAGGGACCAAGGTGGAGATCAAA
- 118 Light Chain Protein:
EIVLTQSPGTLTSLSPGERATLSCRASQSLSGNYLAWYQQKPGQAPRLIICGASSRATGIP
DRFSGSGSGTDFTLTITRLEPEDFAVYYCQQYDRSPLTFGGGTKEIK
- Antibody U1-19
- 119 Heavy Chain DNA:
CAGGTGCAGCTGCAGGAGTGGGGCCAGGACTGGTGAAGCCTTCACAGACCCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGATTACTACTGGAGCTGGATCCGC
CAGCACCACAGGGAAGGGCCCTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCTCAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
TCCCTGAAGCTGAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGGA
GATTACGATTTTTGGAGTGGAGAGTTTGACTACTGGGGCCAGGGAACCCCTGGTCACCGTC
TCCTCA
- 120 Heavy Chain Protein:
QVQLQESGPGLVKPSQTLSTCTVSGGSISSGYYWSWIRQHPGKGLEWIGYIYYSGSTY
YNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARGDYDFWSGEFDYWGQGTLLTV
SS
- Antibody U1-20
- 121 Heavy Chain DNA:
CAGGTGCAGCTGCAGGAGTGGGGCCAGGACTGGTGAAGCCTTCACAGACCCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGATTACTACTGGAGCTGGATCCGC
CAGCACCACAGGGAAGGGCCCTGGAGTGGATTGGGTACATCTATGACAGTGGGAGCACCTAC
TACAACCCGTCCTCAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
TCCCTGAAGCTGAGGTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGAT
CAGGGGCAGGACGGATACAGCTATGTTACGGCTACTACTACGGTATGGACGTCTGGGGC
CAAGGGACACGGTCACCGTCTCCTC
- 122 Heavy Chain Protein:
QVQLQESGPGLVKPSQTLSTCTVSGGSISSGYYWSWIRQHPGKGLEWIGYIYDSGSTY
YNPSLKSRVTISVDTSKNQFSLKLRSVTAADTAVYYCARDQGDGYSTGYGYYYGMDVWG
QGTFTVTS
- 123 Light Chain DNA:
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTCCCAGGCGAGTCAGGACATTAGCAATTATTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAACTCCTGATCTACGTTGCATCCAATTTGGAAACAGGGGTCCCATCA
AGGTTCACTGGAAGTGGATCTGGGACAGATTTTACTTTTACCATCAGCAGCCTGCAGCCT
GAAGATATTGCAACATATTACTGTCAACAGTGTGATAATCTCCCTCTCACTTTCGGCGGA
GGGACCAAGGTGGAGATCAAA
- 124 Light Chain Protein:

124 Light Chain Protein:
DIQMTQSPSSLSASVGDRTITCQASQDISNYLNWYQQKPGKAPKLLIYVASNLETGVPS
RFSGSGSGTDFTTFTISSLPEDIATYYCQQCDNLPLTFGGGTKVEIK

Antibody U1-21

125 Heavy Chain DNA:
CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGATTACTACTGGAGCTGGATCCGC
CAGCACCAGGGAAGGGCCTGGAGTGGATTGGATACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCCTCAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
TCCCTGAAGCTGAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGCG
GATTACGATTTTGGAGTGGTTATTTTGACTACTGGGGCCAGGGAACCCTGCTCACCGTC
TCCTC

126 Heavy Chain Protein:
QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDIYWSWIRQHPGKGLEWIGYIYYSGSTY
YNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARADYDFWSGYFDYWGQGLVTV
S

127 Light Chain DNA:
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGGACATTAGAAATGATTTAGGCTGGTATCGGCAGAAACCT
GGGAAAGCCCCCTAAGCGCCTGATCTATGCTGCATCCCGTTTGCAAAGTGGGGTCCCATCA
AGGTTTCAGCGGCAGTGGATCTGGGACAGAATTCACCTCTCAATCAGCAGCCTGCAGCCT
GAAGATTTTGCAACTTATTACTGTCTACAGCATAATAGTTACCCGTGGACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAAC

128 Light Chain Protein:
DIQMTQSPSSLSASVGDRTITCRASQDIRNDLGWYRQKPGKAPKRLIYAASRLQSGVPS
RFSGSGSGTEFTLTISSLPEDFATYYCLQHNSYPWTFGQGTKVEIK

Antibody U1-22

129 Heavy Chain DNA:
CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGATTACTACTGGAGCTGGATCCGC
CAGCACCAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCCTCAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
TCCCTGAAGCTGAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGCC
GATTACGATTTTGGAGTGGTTATTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTC
TCCTCA

130 Heavy Chain Protein:
QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDIYWSWIRQHPGKGLEWIGYIYYSGSTY
YNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARADYDFWSGYFDYWGQGLVTV
SS

131 Light Chain DNA:
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCAAATGGGGTCCCATCA
AGGTTTCAGCGGCAGTGGATCTGGGACAGAATTCACCTCTCAATCAGCAGCCTGCAGCCT
GAAGATTTTGCAACTTATTACTGTCTACAGCATAATAGTTACCCGTGGACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAAC

132 Light Chain Protein:
DIQMTQSPSSLSASVGDRTITCRASQDIRNDLGWYQQKPGKAPKRLIYAASSLQNGVPS
RFSGSGSGTEFTLTISSLPEDFATYYCLQHNSYPWTFGQGTKVEIK

Antibody U1-23

Antibody U1-23

133 Heavy Chain DNA:

CAGGTGCAGCTGCAGGAGTCGGGCCCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGATTACTACTGGAGCTGGATCCGC
CAGCACCCAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCTCAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
TCCCTGAAGCTGAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGCG
GATTACGATTTTTGGAGTGGTTATTTGACTACTGGGGCCAGGGAATCCTGGTCACCGTC
TCCTC

134 Heavy Chain Protein:

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDYYWSWIRQHPKGLEWIGYIYYSGSTY
YNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARADYDFWSGYFDYWGQGLVTV
S

135 Light Chain DNA:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCGCCTGATTTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTTCAGCGCAGTGGATCTGGGACAGAATTCACCTCTCACAATCAGCAGCCTGCAGCCT
GAAGATTTTGCAACTTATTACTGTCTACAGCATAATAGTTACCCGTGGACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAAC

136 Light Chain Protein:

DIQMTQSPSSLSASVGDRTVITCRASQGIRNDLGWYQQKPGKAPKRLIYAASSLQSGVPS
RFSGSGSGTEFTLTISSLQPEDFATYYCLQHNSTPWTFGQGTKVEIK

Antibody U1-24

137 Heavy Chain DNA:

CAGGTGCAGCTGCAGGAGTCGGGCCCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTGGTGATTACTACTGGAGCTGGATCCGC
CAGCACCCAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCTCAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
TCCCTGAAGTTGAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGCC
GATTACGATTTTTGGAATGGTTATTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTC
TCCTCA

138 Heavy Chain Protein:

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDYYWSWIRQHPKGLEWIGYIYYSGSTY
YNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARADYDFWNGYFDYWGQGLVTV
SS

139 Light Chain DNA:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTTCAGCGCAGTGGATCTGGGACAGAATTCACCTCTCACAATCAGCAGCCTGCAGCCT
GAAGATTTTGCAACTTATTACTGTCTACAGCATAATAATTACCCGTGGACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAAC

140 Light Chain Protein:

DIQMTQSPSSLSASVGDRTVITCRASQGIRNDLGWYQQKPGKAPKRLIYAASSLQSGVPS
RFSGSGSGTEFTLTISSLQPEDFATYYCLQHNSTPWTFGQGTKVEIK

Antibody U1-25

141 Heavy Chain DNA:

CAGGTGCAGCTGCAGGAGTCGGGCCCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGATTACTACTGGAGCTGGATCCGC
CAGCACCCAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTAC

TACAACCCGTCCTCAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
TCCCTGAAGCTGAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGCC
GATTACGATTTTTGGAGTGGTTATTTTGACTACTGGGGCCAGGGAACCCCTGGTCACCGTC
TCCTCA

142 Heavy Chain Protein:

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDYYWSWIRQHPGKGLEWIGYIYYSGSTY
YNPSLKSRTVISVDTSKNQFSLKLSSVTAADTAVYYCARADYDFWSGYFDYWGQGLVTV
SS

143 Light Chain DNA:

GACATCCAGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCAAATGGGGTCCCATCA
AGGTTTCAGCGGCAGTGGATCTGGGACAGAATTCACCTCTCACAATCAGCAGCCTGCAGCCT
GAAGATTTTGCAACTTATTACTGTCTACAGCATAATAGTTACCCGTGGACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAAC

144 Light Chain Protein:

DIQLTQSPSSLSASVGDRTTITCRASQGIKNDLGWYQQKPKAPKRLIYAASSLQNGVPS
RFSGSGSGTEFTLTISLQPEDFATYYCLQHNSYPWTFGQGTKVEIK

Antibody U1-26

145 Heavy Chain DNA:

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGACCCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGATTACTACTGGAGCTGGATCCGC
CAGTACCCAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCTCAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
TCCCTGAAGCTGGGCTCTGTGACTGCCGCGGACACGGCCGTGTATTTCTGTGCGAGAGCC
GATTACGATTTTTGGAGTGGTTATTTTGACTTCTGGGGCCAGGGAACCCCTGGTCACCGTC
TCCTC

146 Heavy Chain Protein:

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDYYWSWIRQYPGKGLEWIGYIYYSGSTY
YNPSLKSRTVISVDTSKNQFSLKLGSVTAADTAVYFCARADYDFWSGYFDYWGQGLVTV
S

147 Light Chain DNA:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTTCAGCGGCAGTGGATCTGGGACAGAATTCACCTCTCACAATCAGCAGCCTGCAGCCT
GAAGATTTTGCAACTTATTACTGTCTACAGCATAATGGTTACCCGTGGACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAAC

148 Light Chain Protein:

DIQMTQSPSSLSASVGDRTTITCRASQGIKNDLGWYQQKPKAPKRLIYAASSLQSGVPS
RFSGSGSGTEFTLTISLQPEDFATYYCLQHNGYPWTFGQGTKVEIK

Antibody U1-27

149 Heavy Chain DNA:

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGACCCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGATTACTACTGGAGCTGGATCCGC
CAGTACCCAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTAC
TACAACCCGTCCTCAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
TCCCTGAAGCTGGGCTCTGTGACTGCCGCGGACACGGCCGTGTATTTCTGTGCGAGAGCC
GATTACGATTTTTGGAGTGGTTATTTTGACTTCTGGGGCCAGGGAACCCCTGGTCACCGTC
TCCTC

150 Heavy Chain Protein:

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDYYWSWIRQYPGKGLEWIGYIYYSGSTY
YNPSLKSRVTISVDTSKNQFSLKLGSVTAADTAVYFCARADYDFWSGYFDFWGQGLTVTV
S

151 Light Chain DNA:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTCCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTTCAGCGGCAGTGGATCTGGGACAGAAATCACTCTCACAATCAGCAGCCTGCAGCCT
GAAGATTTTGCAACTTATTACTGTCTACAGCATAATGGTTACCCGTGGACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAAC

152 Light Chain Protein:

DIQMTQSPSSLSASVGDRTITCRASQGIKNDLGWYQQKPKAPKRLIYAASSLSQSGVPS
RFGSGSGTEFTLTISISLPEDFATYYCLQHNGYPWTFGQGTKVEIK

Antibody U1-28

153 Heavy Chain DNA:

CAGGTGCAGCTGCAGGAGTGGGGCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTGGTGAATTACTACTGGAGCTGGATCCGC
CAGCACCAGGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGAGCACCTAC
TACAACCGTCCCTCAAGAGTTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTT
TCCCTGAAGCTGAGCTCTGTGACTGCCGCGACACGGCCGTGTATTACTGTGCGAGAGCG
GATTACGATTTTTGGAGTGGTTATTTTGACTCCTGGGGCCAGGGAACCCTGGTCCCGTC
TCCTCA

154 Heavy Chain Protein:

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDYYWSWIRQHPGKGLEWIGYIYYSGSTY
YNPSLKSRVTISVDTSKNQFSLKLGSVTAADTAVYYCARADYDFWSGYFDSWGQGLTVTV
SS

155 Light Chain DNA:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTCCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTGGTATCAGCAGATACCT
GGGAAAGCCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTTCAGCGGCAGTGGATCTGGGACAGAAATCACTCTCACAATCAGCAGCCTGCAGCCT
GAAGATTTTGCAACTTATTACTGTCTACAGCATAATGGTTACCCGTGGACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAAC

156 Light Chain Protein:

DIQMTQSPSSLSASVGDRTITCRASQGIKNDLGWYQQIPGKAPKRLIYAASSLSQSGVPS
RFGSGSGTEFTLTISISLPEDFATYYCLQHNGYPWTFGQGTKVEIK

Antibody U1-31

157 Heavy Chain DNA:

CAGGTTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTC
TCCTGCAAGGCTTCTGGTTACACCTTTACCAACTATGGTATCAGCTGGGTGCGGCAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTACGATGGTTACAGAACTAT
GCACAGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGACCACTGCCTAC
ATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAGATGTT
CAAGACTACGGTGACTACGACTACTTTGACTACTGGGGCCAGGGAACCCTGGTCAACGTC
TCCTCA

158 Heavy Chain Protein:

QVQLVQSGAEVKKPGASVKVSCKASGYTFITNYGISWVRQAPGQGLEWMGWISAYDGYRNY
AQKLQGRVTMTTDTSTTTAYMELRSLRSDDTAVYYCARDVDYGDYDFDYWGQGLTVTV
SS

159 Light Chain DNA:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC

ATCACTTGCCGGGCAAGTCAGAGCATTAGCAGTTATTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAACCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGATTTCAGGGGCAGTGGATCTGGGACAGATTTCACTCTCAACATCAGCAGTCTGCAACCT
GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCATCACCTTCGGCCAA
GGGACACGACTGGAGATTAAA

- 160 Light Chain Protein:
DIQMTQSPSSLSASVGDRTTITCRASQSISSYLWYQQKPGKAPNLLIYAASSLQSGVPS
RFRSGSGTDFTLTISSLOPEDFATYYCQSYSTPITFGQTRLEIK

Antibody U1-32

- 161 Heavy Chain DNA:
CAGGTGCAGCTGCAGGAGTCGGGGCCAGGACTGGTGAAGCCTTTACAGACCCCTGTCCCTC
ACCTGCAGCTGTCTCTGGTGGCTCCATCAGCAGTGGTGATTACTACTGGAGCTGGATCCGC
CAGCAGCCAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGACCCACCTAC
TACAACCCGTCCCTCAAGAGTCCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
GCCCTGAAGCTGAACTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGCC
GATTACGATTTTTGGAGTGGTTATTTGACTACTGGGGCCAGGGAACCCCTGGTCACCGTC
TCCTCA

- 162 Heavy Chain Protein:
QVQLQESGPGLVKPLQLTSLTCTVSGGSISSGDIYWSWIRQHPGKGLEWIGYIYYSGITTY
YNPSLRSRVTTISVDTSKNQFALKLNSVTAADTAVYYCARADYDFWSGYFDYWGQGTILVTV
SS

- 163 Light Chain DNA:
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGGGCAATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTCAGCGCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTTCAGCGGCAGTGGATCTGGGACAGAAATCTCTCTCAAACTCTCCAGCCTGCAGCCT
GAAGATTTTGCAACTTATTACTGTCTACAGCATAATAGTTACCCGTGGACGTTTCGGCCAA
CGGACCAAGGTGGAAATCAAAC

- 164 Light Chain Protein:
DIQMTQSPSSLSASVGDRTTITCRAGQGIRNDLGWYQQKPGKAPQRLIYAASSLQSGVPS
RFRSGSGTDFSLTISSLOPEDFATYYCLQHSNYPWTFGQGTKVEIK

Antibody U1-35

- 165 Heavy Chain DNA:
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTC
TCCTGTGCAGCCTCTGGATTACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCT
CCAGGGAAGGGGCTGGAGTGGGTTTCATATATTAGTAGTAGTGGTAATAACATATACCAC
GCAGACTCTGTGAAGGGCCGATTACCATCTCCAGGGACAACGCCAAGAACTCACTGTAT
CTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAGAGA
TATAGTGGCTACGACGACCCCTGATGGTTTTTGATATCTGGGGCCAAGGGACAATGGTCACC
GTCTCTTCA

- 166 Heavy Chain Protein:
QVQLVESGGGLVKPGGSLRLSCAASGFTTFSDYYMSWIRQAPGKGLEWVSYIISSSGNNIYH
ADSVKGRFTISRDNKNSLYLQMNSLRLEDTAIVYYCARERYSGYDDPDGFDIWGQGTMTV
VSS

- 167 Light Chain DNA:
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCAGGCGAGTCAGGACATTAGCAACTATTAAAGTTGGTTTTTCAGCAGAAACCA
GGGAAAGCCCCCTAAGCTCCTGATCCACGATGCATCCAATTTGGAAACAGGGGTCCCTTCA
AGGTTTCAGTGGAAAGTGGATCTGGGACAGATTTTACTTTTACCATCAGCAGCCTGCAGCCT
GAAGATATTGCAACATATTACTGTCAACAGTATGATAATCCCCCGTCAGTTTTGGCCAG
GGGACCAAGCTGGAGATCAAA

168 Light Chain Protein:
DIQMTQSPSSLSASVGRVTITCQASQDISNYLSWFQOKPGKAPKLLIHDASHLETGVPS
RFSGSGSGTDFTFTISSLPEDIATYYCQQYDNPPCSFGQGTKLEIK

Antibody U1-36

169 Heavy Chain DNA:
CAGGTGCAGCTGCAGGAGTCGGGCCCCAGGACTGGTGAAGCCTTCACAGACCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTTATTACTACTGGAGCTGGATCCGC
CAGCACCAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGACCACCTAC
TACAATCCGTCCTTCAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTC
TCCCTGAAACTGAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGCC
GATTACGATTTTTGGAGTGGTCACTTTGACTACTGGGGCCAGGGAACCTGGTCACCGTC
TCCTCA

170 Heavy Chain Protein:
QVQLQESGPGLVKPSQTLSTCTVSGGSISSGYYWSWIRQHPGKGLEWIGYIYYSGETPY
YNPSFKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARADYDFWSGHFDYWGQGLVTV
SS

171 Light Chain DNA:
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCA
GGGAAAGCCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTTCAGCGGCAGTGGATCTGGGACAGAAATCACTCTCACAATCAGCAGCCTGCAGCCT
GAAGATTTTGCACCTTATTACTGTCTACAGCATAATAGTTACCCGTGGACGTTCCGGCCAA
GGGACCAAGGTGGAAATCAAA

172 Light Chain Protein:
DIQMTQSPSSLSASVGRVTITCRASQGIRNDLGWYQQKPGKAPKRLIYAASSLQSGVPS
RFSGSGSGTEFTLTISLQPEDFATYYCLOHNSYPWTFGQGTKVEIK

Antibody U1-37

173 Heavy Chain DNA:
CAGGTTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTC
TCCTGCAAGGCTTCTGGTTACACCTTTACCAGCTATGGTATCAGCTGGGTGCGACAGGCC
CCTGGACAAGGACTTGAGTGGATGGGATGGATCAGCGCTTACGATGGTCACACAACTAT
GCACAGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGAACACAGCCTAC
ATGGAGCTGAGGAGCCTGAGATCTGACGACACGCGCTTTATTACTGTGCGAGAGACCCC
CATGACTACAGTAACACGAGGCTTTTGACTTCTGGGGCCAGGGAACCTGGTCACCGTC
TCCTC

174 Heavy Chain Protein:
QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGWISAYDGHIN
AQKLQGRVTMTTDTSTNTAYMELRSLRSDDTAVYYCARDPHDYSNIEAFDFWGQGLVTV
S

175 Light Chain DNA
atgagggtcccctgctcagctcctggggctcctgctactctggctccgaggtgccagatgtg
acatccagatgacccagtcctccatccctcctgtctgcatctgtaggagacagagtcacat
cacttgccgggcaagtcagagcattagcagttatTTAAATTGGTATCAGCAGAAACCCAGGG
aaagcccctaacctcctgatctatgtctgcatccagtttgcaaagtgggggtcccataagat
tcagtggcagtggtctgggacagatttcaactctcccatcagcagtcctgcaacctgaaga
ttttgcaacttactactgtcaacagagttacagttaccccatcaccttcggccaagggaca
cgactggagattaaacgaactgtggctgcaaccatctgtcttcatcttcccgccatctgatg
agcagttgaaatctggaactgcctctgttgtgtgctgtgaataacttctatcccagaga
ggccaaagtacagtggaaggtggataacgcc

176 Light Chain Protein:

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPNLLIYAASSLQSGVPSR
FSGSGSGTDFTLTISLQPEDFATYYCQQSYSTPITFGQGRLEIK

Antibody U1-34

177 Heavy Chain DNA:

accatggactggacctggaggggtccttttcttgggtggcagcagcaacaggtgccactccca
ggttcagctgggtgcagtcctggagctgaggtgaagaagcctggggcctcagtgaaagtctcct
gcaaggcttctggttacacctttaccaactatggatcagctgggtgaggcagggcccttga
caagggcttgagtggatgggatggatcagcgcttacgatggttacagaaactatgcacagaa
gctccagggcagagtcaccatgaccacagacacatccacgaccactgcctacatggagctga
ggagcctgagatctgacgacacggccgtgtattactgtgcgagagatgttcaagactacgg
gactacgactactttgactactggggccagggaaccctgggtcaccgtctcctcagcttccac
caagggcccatcctgtcttccccctgggtgcctgtctcaggagcacctccgagagcacagccg
ccctgggtgcctgggtcaaggactacttccccgaaccg

178 Heavy Chain Protein

QVQLVQSGAEVKKPGASVKVSKASGYTFTNYGISWVRQAPGQGLEWMGWISAYDGYRNYA
QKLGQRVTMTDPTSTTTAYMELRSLRSDDTAVYYCARDVQDYGIDYFDYWGQGLTVTVSS

179 Light Chain DNA:

cagctcctggggctcctgtactctgggtccgaggtgccagatgtgacatccagatgaccc
agtctccatcctcctgtctgcacatctgtaggagacagagtcaccatcacttgcggggcaag
tcagagcattagcagttatttaattgggtatcagcagaaaccagggaagcccctaacctc
ctgatctatgctgcacccagtttgcaagtggtgggtcccatcaagattcagtggtgagtgga
ctgggacagatttcactctcaccatcagcagctctgcaacctgaagattttgcaacttacta
ctgtcaacagagttacagtacccccatcaccttcggccaagggaacagactggagattaaa
cgaactgtggctgcaccatctgtcttcatcttcccgcacatctgatgagcagttgaaatctg
gaactgcctctgttgtgtgcctgtgaataacttctatcccagagaggccaaagtacagtg
gaaggtggataacgcc

180 Light Chain Protein:

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPNLLIYAASSLQSGVPSR
FSGSGSGTDFTLTISLQPEDFATYYCQQSYSTPITFGQGRLEIK

Antibody U1-1

181 Heavy Chain DNA:

catctgtggttcttccctcctgtctgggtggcagctcccagatgggtcctgtcccaggtgcagc
tgcaggagtgcgggccaggactgggtgaagccttcacagaccctgtccctcactgcactgt
ctctggtggctccatcaacagtggtgattactactggagctggatccgccagcaccagg
aagggcctggagtggattgggtacatctattacagtgggagcaccctactacaaccctgcc
tcaagagtcgagttaccatattcagtagacacgtcttaagaaccagttctccctgaagctgag
ctctgtgactgcggcggaacggccgtgtattactgtgcgagagcagattacgatttttgg
agtgggttactttgactactggggccagggaaccctgggtcaccgtctcctcagcctccacca
agggcccatcgggtcttccccctgggcaccctcctccaagagcaccctctgggggacaaaggc
cctgg

182 Heavy Chain Protein

QVQLQESGPGLVKPSQTLSTCTVSGGSINSGDYYSWIRQHPGKGLEWIGYIYYSGSTYY
NPSLKSRTISVDTSKNQFSLKLSVTAADTAVYYCARADYDFWSGYFDYWGQGTLLTVSS

183 Light Chain DNA:

atgaggggtccctgctcagctcctggggctcctgctgctctgggtcccaggtgccaggtgtga
catccagatgacccagttccatccctcctgctcgcctctgtaggagacagagtcacccatca
cttgccgggcaagtcagggcattagaaatgatttaggctggatcagcagaaaccagggaaa
gcccctaagcgccctgatctatgctgcatccagtttgcaaagtggggtcccatcaagggttcag
cggcagtggtatctgggacagaattcactctcacaatcagcagcctgcagcctgaagattttg
caacttattactgtctacagcataatagttaccctggacgttcggccaagggaccaaggtg
gaaatcaaacgaactgtggctgcaccatctgtcttcatcttcccgcatctgatgagcagtt
gaaatctggaactgcctctgttggtgctgaataacttctatcccagagagggccaaaag
tacagtggaaggtggataacgc

184 Light Chain Protein

DIQMTQSPSSLSASVGDRTITCRASQGIKNDLGWYQQKPGKAPKRLIYAASSLQSGVPSR
FSGSGSGTEFTLTISSLQPEDFATYYCLOHNSYPWTFGQGTKVEIK

Antibody U1-3

185 Heavy Chain DNA:

tgggtcttctccttctgctggtggcagctcccagatgggtcctgtcccaggtgcagctgcagga
gtcggggcccaggactggtgaagccttcacagaccctgtccctcacctgcactgtctctgggtg
gctccatcagcagtggtggttactactggagctggatccgcccagcaccaggggaagggcctg
gagtggtattgggtacatctattacagtgaggacacctaactacaaccctgccctcaagagtcg
agttaccatatcagtagacacgtctaagaaccagttctccctgaagctgagctctgtgactg
ccgcgagacacggcgtgtattactgtgcgagagatggctatgatagtagtggttattaccac
ggctactttgactactggggccagggaaaccctggtcaccgtctcctcagcctccaccaaggg
cc

186 Heavy Chain Protein

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGGYYWSWIRQHPGKGLEWIGYIYYSGSTYY
NPSLKSRTISVDTSKNQFSLKLSVTAADTAVYYCARDGYDSSGYYHGYYFDYWGQGTLLTV
VSS

187 Light Chain DNA:

H3_130_1N1K

caggtcttcatcttctctgttgcctctggtgcctacggggacatcgtgatgacc
agtctccagactccctggctgtgtctctgggagagagggccaccatcaactgcaagtcag
ccagagtggtttatacagctccaacaataagaactacttagcttggtaccagcagaaacca
ggacagcctcctaagctgctcatttactgggcatctaccgggaatccggggtccctgacc
gattcagtggcagcgggtctgggacagatttactctcaccatcagcagcctgcaggctga
agatgtggcagtttattactgtcagcaatattatagtactccgctcacttccggcggaggg
accaaggtggagatcaaacgaactgtggctgcaccatctgtcttcatcttcccgccatctg
atgagcagttgaaatctggaactgcctctgttggtgctgctgaataacttctatcccag
agagggccaaagtagcagtggaaggtggataacgc

188 Light Chain Protein:

DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPLLIYWASTRE
SGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPLTFGGGTKVEIK

Antibody U1-4

H3_133_1N1G1

189 Heavy Chain DNA

ctgtggttcttctcctgctggtggcagctcccagatgggtcctgtcccaggtgcagctgca
ggagtcgggcccaggactggtgaagccttcacagaccctgtccctcacctgcactgtctctg
gtggctccatcagtagtggtgattactactggagctggatccgccagcaccaggggaagggc
ctggagtggtattgggtacatctattacagtgaggagcacctactacaaccctgccctcaagag
tcgagttaccataatcagtagacacgtctaagaaccagttctccctgaagttgagctctgtga
ctgccgggacacggccgtgtattactgtgagagccgattacgatttttgagtggttat
tttgactactggggccagggaaccctggtcacctctcctcagcctccaccaagggeccatc
ggtcttccccctggcaccctc

190 Heavy Chain Protein

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDYYWSWIRQHPGKLEWIGYIYYSGSTYY
NPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARADYDFWSGYFDYWGQGLVTVSS

191 Light Chain DNA

H3_133_1N1K

gtgcccgtcagcgccctggggctcctgctgctctggttcccaggtgccaggtgtgacatcc
agatgaccagctctccatcctcctgtctgcatctgtaggagacagagtcaccatcacttg
ccgggcaagtcagggcattagaaatgatttaggctggtatcagcagaaaccagggaaagcc
cctaagcgctgtatctatgctgcatccagtttgcaaagtgggtcccatcaaggttcagcg
gcagtggtatctgggacagaattcactctcacaatcagcagcctgcagcctgaagattttgc
aacttattactgtctacagcataataattaccctggtgacgttcggccaagggaaccaaggtg
gaaatcaaacgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagt
tgaaatctggaactg

192 Light Chain Protein

DIQMTQSPSSLSASVGDRVTITCRASQGIKNDLGWYQQKPKAPKRLIYAASSLQSGVPSRF
SGSGSGTEFTLTITSSLPEDFATYYCLQHNYPWTFGQGTKVEIK

Antibody U1-5

193 Heavy Chain DNA:

H3_138_1N1G1

tggttcttctctctgtgtggtggcagctcccagatgggtcctgtcccaggtgcagctgcagga
gtcgggcccaggactggtgaagccttcacagaccctgtccctcacctgcactgtctctggtg
gtccatcagcagtggtgattactactggagctggatccgccagcaccaggggaagggcctg
gagtggtattgggtacatctattacagtgaggagcacctactacaaccctgccctcaagagtcg
agttaccataatcagtagacacgtctaagaaccagttctccctgaagctgagctctgtgactg
ccggcgacacggccgtgtatttctgtgagagccgattacgatttttgagtggttatttt
gactactggggccagggaaccctggtcacctctcctcagcctccaccaagggcc

194 Heavy Chain Protein

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDYYWSWIRQHPGKLEWIGYIYYSGSTYYN
PSLKSRTISVDTSKNQFSLKLSSVTAADTAVYFCARADYDFWSGYFDYWGQGLVTVSS

195 Light Chain DNA:

H3_138_1N1K

atgaggggtccccgtcagctcctggggctcctgctgctctggttcccaggtgccaggtgtga
catccagatgaccagctctccatcctcctgtctgcatctgtaggagacagagtcaccatca
cttgccgggcaagtcagggcattagaaatgatttaggctggtatcagcagaaaccagggaaa

gcccctaagcgccctgatctatgctgcatccagtttgcaaagtggggtcccatcaagggttcag
cggcagtggtatctgggacagaattcactctcacaatcagcagcctgcagcctgaagattttg
caacttattactgtctacagcataatacttaccctggacgttcggccaagggaccaagggtg
gaaatcaaacgaactgtggctgcaccatctgtcttcattcttcccgccatctgatgagcagtt
gaaatctggaactgcctctgttgtgtgctgctgaataacttctatcccagagaggccaaag
tacagtggaaggtggataacgc

196 Light Chain Protein

DIQMTQSPSSLSASVGDRVTITCRASQGIKNDLGWYQQKPKAPKRLIYAASSLQSGVPS
RFSGSGSGTEFTLTISSLQPEDFATYYCLOHNTYPTTFGQGTKVEIK

Antibody U1-6

197 Heavy Chain DNA:

H3_162_1N1G1

tgggttcttctctgtggtggcagctcccagatgggtcctgtcccaggtgcagctgcagga
gtcggggcccaggactggtgaagccttcacagaccctgtccctcacctgcactgtctctgggtg
gctccatcagcagtggtgattactactggagctggatccgcccagcaccaggggaaggccctg
gagtggtattgggtacatctattacagtggtgagcacctactacaaccctccctcaagagctg
agttaccatatcagtagacacgtctaaagaaccagttctccctgaagctgagctctgtgactg
ccgcggaacagggccgtgtatttctgtgcgagagccgattacgatttttgggaatgggtatttt
gactactggggccagggaaccctggtcaccgtctcctcagcctccaccaagggccc

198 Heavy Chain Protein

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDYYSWIRQHPGKGLWIGYIYYSGSTY
YNPSLKSRTVISVDTSKNQFSLKLSSVTAADTAVYFCARADYDFWNGYFDYWGQGLTVTV
SS

199 Light Chain DNA:

H3_162_1N1K

atgaggggtcccgcctcagctcctggggctcctgctgctctggttcccaggtgccaggtgtga
catccagatgaccagctctccatcctccctgtctgcattctgtaggagacagagtcaccatca
cttgccggggcaagtcagggcattagaaatgatttaggctgggtatcagcagaaaccagggaaa
gcccctaagcgctgatctatgctgcttccagtttgcaaagtggggtcccatcaagggttcag
cggcagtggtatctgggacagaattcactctcacaatcagcagcctgcagcctgaagattttg
caacttattactgtctacagcataatacttaccctggacgttcggccaagggaccaagggtg
gaaatcaaacgaactgtggctgcaccatctgtcttcattcttcccgccatctgatgagcagtt
gaaatctggaactgcctctgttgtgctgctgaataacttctatcccagagaggccaaag
tacagtggaaggtggataacgcc

200 Light Chain Protein

DIQMTQSPSSLSASVGDRVTITCRASQGIKNDLGWYQQKPKAPKRLIYAASSLQSGVPS
RFSGSGSGTEFTLTISSLQPEDFATYYCLOHNTYPTTFGQGTKVEIK

Antibody U1-8

201 Heavy Chain DNA:

H3_174_1N1G1

ttgggtggcagcagctacaggcaccacgcccaggtccagctggtacagctctggggctgaggt
gaagaagcctggggcctcagtgaaaggtctcctgcaaggtttccggatacaccctcactgaat
tatccatgtactgggtgacaggtccttggaagggtctgagtggtggaggttttgat

cctgaagatggtgaaacaatctacgcacagaagtccagggcagagtcaccatgaccgagga
cacatctaragacacagcctacatggagctgagcagcctgagatctgaggacacggccgtgt
attactgtgcaactgggtggaactacgtctcttgactactggggccaggggaacctggtcacc
gtctctcagcctccaccaagggccc

202 Heavy Chain Protein

QVQLVQSGAEVKKPGASVKVSKVSGYTLTELSMYWVRQAPGKGLEWMGGFDPEDGETIYA
QKFQGRVTMTEDTSTDTAYMELSSLRSEDVAVYYCATGWNVYFDYWGQGTLLTVSS

203 Light Chain DNA:

H3_174_1N1K

ggatccagtggggatattgtgatgactcagtcctccactctccctgcccgtcaccctggaga
gcggccctccatctcctgcaggtccagtcagagcctcctgcatagtaattggatacaactatt
tggatttggtacctgcagaagccagggcagtcctccacagctcctgatctatttggattctcat
cgggcctccgggtccctgacaggttcagtggcagtggtcaggcacagattttacactgaa
aatcagcagagtgagggtgaggatgttgggggtttattactgcatgcaagctctacaaactc
cgctcactttcggcggagggaaccaaggtggagatcaaacgaactgtggctgcaccatctgtc
ttcatcttcccgcct

204 Light Chain Protein

DIVMTQSPFLSLPVTGPGEPAISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLDSHRA
SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPITFGGGTKVEIK

Antibody D1-11

205 Heavy Chain DNA:

H3_178_1N1G1

tggttcttccctctgtctggtggcagctcccagatgggtcctgtcccaggtgcagctgcagga
gtcgggcccaggactggtgaagccttcacagaccctgtccctcactgcactgtctctggtg
gtcccatcagcagtggtgattactactggagctggatccgccagcaccaggggaaggccctg
gagtggttgggtacatctattacagtgaggacactactacaaccctgcctcaagagtcg
agttaccatatacagtagacacgtctaagaaccagttctccctgaagctgagctctgtgactg
ccgcggacacggccgtgtatttctgtgagagccgattacgatttttggagtggttatttt
gactactggggccaggggaaccctgggtcacctctcctcagcctccaccaagggcccacgcag
tcttccccctgg

206 Heavy Chain Protein

QVQLQESGPGLVKPSQTLSTCTVSGGSTISSGDYYNSWIRQHPGKLEWIGYIYYSGSTY
YNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYFCARADYDFWSGYFDYWGQGTLLTV
SS

207 Light Chain DNA:

H3_178_1N1K

atgaggggtccccgtcagctcctggggctcctgtctgtctgtgttcccaggtgccaggtgtg
acatccagatgaccagtcctccatcctccctgtctgcatctgtaggagacagagtcaccat
cacttgccgggcaagtcagggcattagaaatgatttaggctgggtatcagcagaaaccaggg
aaagccccctaagcgcctgatctatgtctgcatccagtttgcaaagtgggggtcccatcaaggt
tcagcggcagtggtctgggacaaaattcactctcactatcagcagcctgcagcctgaaga
ttttgcaacttattactgtctacagcataatacttaccctggagcgttcggccaagggacc
aaggtggaaatcagacyaactgtggctgcaccatctgtcttcatcttcccgcctctgatg
agcagttgaaatctggaactgcctctgtgtgtgtgcctgtgtaataacttctatcccagaga
ggccaaagtcagtggaaggtggataacgcc

208 Light Chain Protein

DIQMTQSPSSLSASVGDRVTITCRASQGIKNDLGWYQQKPGKAPKRLIYAASSLQSGVP
SRFSGSGSGTKFTLTITSSLPEDFATYYCLOHNTYPWTFGQGTKVEIR

Antibody U1-16

209 Heavy Chain DNA:

H3_221_1N1G1

accatgaaacatctgtggttcttccctcctgctggtggcagctcccagatgggtcctgtccc
aggtgcagctgcaggagtcggggccaggactggtgaagccttcacagaccctgtccctcac
ctgcactgtctctggtggctccatcagcagtggtgat tactactggagctggatccgccaag
caccaggggaagggcctggagtggttgggtacatctattacagtgggagcacctaactaca
accggtccctcaagagtcgagttaccatatcagtagacacgtctaagaaccagttctccct
gaagctgagctctgtgactgcggcggaacggcctgtattactgtgcgagagcggattac
gatttttggagtggttattttgactactggggccagggaatcctggtcaccgtctcctcag
cctccaccaagggcccatcggtcttccccctggcaccctcctccaagaacacctctggggg
cacagcggccctgggtgctggtcaaggactacttccccgaaccggtgacgggtgtcctgg
aactcaggcgccctg

210 Heavy Chain Protein

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDYYWSWIRQHPGKGLEWIGYIYYSGSTYY
NPSLKSRTVISVDTSKNQFSLKLSSVTAADTAVYYCARADYDFWSGYFDYWGQILVTVSS

211 Light Chain DNA:

H3_221_1N1K

atgagggtccccgctcagctcctggggctcctgctgctctggttcccagggtgccagggtgt
gacatccagatgacccagctcctccatcctccctgtctgcatctgtaggagacagagtcacc
atcacttgcggggaagtcagggcattagaaatgatttaggctgggtatcagcagaaacca
gggaaagccccctaagcgctgatctatgctgcatccagtttgcaaagtgggtcccatca
aggttcagcggcagtggtatctgggacagaattcactctcacaatcagcagcctgcagcct
gaagattttgcaacttattactgtctacagcataatagttaccggtggacgttcggccaa
gggaccaaggtggaaatcaaacgaactgtggctgcaccatctgtcttcatcttcccgcca
tctgatgagcagttgaaatctggaactgcctctgttgtgtgctgtaataacttctat
cccagagaggccaaagtacagtggaaggtggataacgcc

212 Light Chain Protein

DIQMTQSPSSLSASVGDRVTITCRASQGIKNDLGWYQQKPGKAPKRLIYAASSLQSGVPSR
PSGSGSGTEFTLTITSSLPEDFATYYCLOHNSYPWTFGQGTKVEIK

Antibody U1-17

213 Heavy Chain DNA:

H3_224_1N1G1

tgggttcttcttctgctggtggcagctcccagatgggtcctgtcccagggtgcagctgcagg
agtcggggccaggactggtgaagccttcacagaccctgtccctcactgtctctgg
tggctccatcagcagtggtgattactactggagctggatccgccaagcaccaggggaagggc
ctggagtggtattggatacatctattacagtgggagcacctactacaattcgtccctcaaga
gtcgagttaccatatcagtagacacgtctaagaaccagttctccctgaagctgagctctgt
gactgcggcggaacggcctgtattactgtgcgagagcggattacgatttttggagtggt
tattttgactactggggccagggaaccctgggtcaccgtctcctcagcctccaccaagggcc
catcg

214 Heavy Chain Protein

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDYYWSWIRQHPGKGLEWIGYIYYSGSTYY
NSSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARADYDFWSGYFDYWGQGLVTVSS

215 Light Chain DNA:

H3_224_1N1K

gggtgccagggtgtgacatccagatgacccagtcctccatccctcctgtctgcatctgtaggag
acagagtcaccatcaacttgcgggcaagtcagggcattagaaatgatttaggctggatca
gcagaaacctgggaaagcccctaagcgctgatctatgctgcatccagtttgcaaagtggg
gtcccatcaagggttcagcggcagtgatctgggacagaattcactctcacaatcagcagcc
tgcagcctgaagattttgcaacttattactgtctacagcacaatagttacccgtggacgtt
cggccaagggaaccaagggtggaaatcaaacgaactgtggctgcaccatctgtcttcaccttc
ccgcc

216 Light Chain Protein

DIQMTQSPSSLSASVGDRVTITCRASQGIKNDLGWYQQKPKAPKRLIYAASSLQSGVPS
RFGSGSGTEFTLTISSLQPEDFATYYCLOHNSYPWTFGQGTKVEIK

Antibody U1-18

217 Heavy Chain DNA:

H3_227_1N1G1

agggttcttctctctgtgtgtggcagctcccagatgggtcctgtcccagggtgcagctgcagg
agtgcgggcccaggactgggtgaagccttcacagaccctgtccctcactgtctcttg
tggctccatcagcagtggtgattactactggagctggatccgccagcaccagggaagggc
ctggagtggtattggatacatctattacagtgaggagcacctactacaaccgctccctcaaga
gtcgagttaccatatcagtagacacgtcttaagaaccagttctccctgaagctgagctctgt
gactgccgcggacacggccgtgtattactgtgcgagagccgattacgatttttggagtgg
tattttgactactggggccagggaaccctgggtcaccgtctcctcagcctccaccaagggcc
catcggtcttccctcctggcaccctcctccaagagcacctctgggggacagcggccctggg
ctgcctgggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccct

218 Heavy Chain Protein

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDYYWSWIRQHPGKGLEWIGYIYYSGSTYY
NPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARADYDFWSGYFDYWGQGLVTVSS

219 Light Chain DNA:

H3_227_1N1K

atgagggtccccgctcagctcctggggctcctgctgctctgtgttcccagggtgccagggtgtga
catccagatgaccagctcctccatcctccctgtctgcatctgtaggagacagagtcaccatca
cttgcgggcaagtcagggcattagaaatgatttaggctgggtatcagcagaaaccaggga
gcccctaagcgctgatctatgctgcatccagtttgcaaagtgggtcccatcaagggttcag
cggcagtggtctgggacagaattcactctcacaatcagcagcctgcagcctgaagattttg
caacttattactgtctacagcataatagttacccgtggacgttcggccaagggaaccaagggtg
gaaatcaaacgaactgtggctgcaccatctgtcttcaccttcccgpcatctgatgagcagtt
gaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaag
tacagtggaaagggtggataacg

220 Light Chain Protein

DIQMTQSPSSLSASVGDRVTITCRASQGIKNDLGWYQQKPKAPKRLIYAASSLQSGVPS
RFGSGSGTEFTLTISSLQPEDFATYYCLOHNSYPWTFGQGTKVEIK

Antibody U1-33

221 Heavy Chain DNA:

H4_14_1N1G4

ctgtgggttcttctctgtgtggcagctcccagatgggtccctgtcccaggtgcagctgc
aggagtcggggcccaggactgggtgaagccttcacagaccctgtccctcaccctgcactgtctc
tgggtggctccatcagcagtggtgattactactggagctggatccgccagcaccaggggaag
ggcctggagtggtattgggtacatctattacagtgaggagcacctactacaaccctgccctca
agagtcgagttaccatgtcagtagacacgtcttaagaaccagttctccctgaagctgagctc
tgtgactgccgcggacacggcctgtattactgtgcgagagccgattacgatttttggagt
ggtcactttgactgtctggggccagggaaccctgggtaccgtctctcagcttccaccaagg
gccccatccgtcttccccc

222 Heavy Chain Protein

QVQLQESGPGLVKPSQTLSTCTVSGGSISSQDYWWSWIRQHPGKGLEWIGYIYYSGSTYY
NPSLKSRTVMSVDTSKNQFSLKLSSVTAADTAVYYCARADYDFWSGHFDCWGQGLTVTVSS

223 Light Chain DNA:

H4_14_1N1K

atgaggggtccccgctcagctccctggggctcctgtctgtctctgggtcccaggtgccaggtgtga
catccagatgaccagctccatccctccctgtctgtcatctgtaggagacagagtcaccatca
cttgccggggaagtcagggcattagagatgatttaggctggatcagcagaaaccagggaaa
gcccctaagcgccctgatctatgtgaatccagtttgcaaagtgggtcccatcaaggttcag
cggcagtggtatctgggacagaattcactctcacaatcagcagcctgcagcctgaagattttg
caacttattactgtctacagcatcatagttaccctgggacgttcggccaagggaccaaggtg
gaaatcaaacgaactgtggctgcaccatctgtcttcatcttcccgcc

224 Light Chain Protein

DIQMTQSPSSLSASVGDRTTTCRASQGIKDDLGWYQQKPKAPKRLIYAESSLSQSGVPSR
FSGSGSGTEFTLTISSLQPEDFATYYCLOEHSYPWTFGQGTKVEIK

Antibody U1-29

225 Heavy Chain DNA:

H4_107_1N1G4

tggctgagctgggttttccctcggttgcctcttttaagaggtgtccagtgctcaggtgcagctgg
tggagctctgggggaggcgtgggtccagcctgggaggtccctgagactctctgtgcagctc
tggattcaccttcaatagctatgacatgcaactgggtccgccaggctccaggcaaggggctg
gagtggtggcagttatatgggtatgatggaagtaataaatactatgcagactccgtgaagg
gccgattcaccatctctagagacaattccaagaacacgctgtatctgcaaataaacagcct
gagagccgaggacacggctgtgtattactgtgcgagagaccgcttgtgtactaatgggtgta
tgctatgaagactacgggtatggacgtctggggccaagggaccacggtcaccgtctcctcag
cttccaccaagggcccatccgtcttccccctggcgccctgtccaggagcaccctccgagag
cacagccgcctgggc

226 Heavy Chain Protein

QVQLVESGGGVVQPGRSRLRLSCAASGFTFNSYDMHWVRQAPGKLEWVAVIWDGSKYYA
DSVKGRTTISRDNKNTLYLQMNSLRAEDTAVYYCARDRLCTNGVCYEDYGMDVWGQTTV
TVSS

227 Light Chain DNA:

H4_107_1N1K

atgaggggtccctgtctcagctcctggggctcctgtctgtctctggctctcaggtgccagatgtga
catccagatgaccagctctccatccctccctgtctgtcatctgtaggagacagagtcaccatca

cttggcaggcgagtcaggacattagcaactatTTAAATTGGTATCAGCAGAAACCAGGGAAA
 gcccctaaggctcctgatctacgatgcatccaatttggaacaggggtcccatcaagggtcag
 tggaagtggatctgggacagatTTTACTTTCCCATCAGCAGCCTGCAGCCTGAAGATGTTG
 caacatattactgtcaacactatgatactctcccgctcactttcggcggagggaccaagggtg
 gagatcaaacgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagtt
 gaaatctggaactgcctctgttgtgtgctgtgaataacttctatcccagagaggccaaag
 tacagtgg

228 Light Chain Protein

DIQMTQSPSSLSASVGDRVITITCQASQDISNYLNWYQQKPGKAPKVLIIYDASNLETGVPSR
 FSGSGSGTDFFTISSLPEDVATYYCQHYDTLPLTFGGGTKVEIK

Antibody U1-30

229 Heavy Chain DNA:

H4_116_1_1N1G4

ggactgtgcaagaacatgaaacacctgtggttcttccctcctgctgggtggcagctcccagatg
 ggtcctgtcccaggtgcagctgcaggagtcggggccaggactgggtgaagcctttacagaccc
 tgtccctcactgcactgtctctggtggctccatcagcagtggtgattactactggagctgg
 atccgccagcaccaggggaaggcctggagtggttgggtacatctattacagtgggaccac
 ctactacaaccgctccctcaagagtogagttaccatatcagtagacacgtctaagaaccagt
 tcgcccctgaagctgaactctgtgactgcgcgggacacggccgtgtattactgtgcgagagcc
 gattacgatttttggagtggttatTTTGACTACTGGGGCCAGGGAACCCCTGGTCAACGCTCTC
 CTCAGCTTCCACCAAGGGCCCATCCGCTCTTCCCCCTGG

230 Heavy Chain Protein

QVQLQESGPGLVKPLQLTSLTCTVSGSISSGDYYSWIRQHPGKLEWIGYIYYSGTTY
 NPFLKSRVTISVDTSKNQFALKLNSVTAADTAVYYCARADYDFWSGYFDYWGQGLTVTVSS

231 Light Chain DNA:

H4_116_1_1N1K

atgagggtccctgctcagctcctggggctcctgctgctctgggttcccaggtgccaggtgtg
 acatccagatgaccagctctccatcctccctgtctgcatctgtaggagacagagtcaccat
 cacttgcggggcaggtcagggcattagaaatgatttaggctgggtatcagcagaaaccaggg
 aaagccctcagcgcctgactctatgctgcatccagtttgcaaagtggggctcccatcaaggt
 tcagcggcagtggaactctgggacagaattctctctcacaatctccagcctgcagcctgaaga
 ttttgcaacttaftactgtctacagcataatagttaccogtggacgttcggccaagggaacc
 aagggtggaatcaaacgaactgtggctgcaccatctgtcttcatcttcccgccatctgatg
 agcagttgaaatctggaactgcctctgttgtgtgctgtgaataacttctatcccagaga
 ggccaaagtacagtgggaaggtggataacgccttccaatcggg

232 Light Chain Protein

DIQMTQSPSSLSASVGDRVITITCRAGQGIRNDLGWYQQKPGKAPORLIYAASSLQSGVPSR
 FSGSGSGTEFSLTISLQPEDFATYYCLOHNSYPWTFGQGTKVEIK

SEQUENCE LISTING

5

Primer (SEQ ID NO: 233):
CGGGATCCATGTCCTAGCCTAGGGGC

10

Primer (SEQ ID NO: 234):
GCTCTAGATTAATGATGATGATGATGATGTTGTCCTAAA

Table of CDR Sequences

Ab chain	Pat. ID:	CDR1	CDR2	CDR3
heavy	U1-1	GGSISSGDYYWS	YIYYSGSTYYNPSLKS	ADYDFWSGYFDY
light		RASQIRNDLG	AASSLQS	LQHNYPWT
heavy	U1-2	GGSISSGDYYWS	YIYYSGSTYYNPSLRS	ADYDFWSGYFDY
light		RASQIRNDLG	AASSLQS	LQHNGYPWT
heavy	U1-3	GGSISSGGYYWS	YIYYSGSTYYNPSLKS	DGYDSSGYYHGYFDY
light		KSSQSVLYSSNNKNYLA	WASTRES	QQYYSTPLT
heavy	U1-4	GGSISSGDYYWS	YIYYSGSTYYNPSLKS	ADYDFWSGYFDY
light		RASQIRNDLG	AASSLQS	LQHNNYPWT
heavy	U1-5	GGSISSGDYYWS	YIYYSGSTYYNPSLKS	ADYDFWSGYFDY
light		RASQIRNDLG	AASSLQS	LQHNTYPWT
heavy	U1-6	GGSISSGDYYWS	YIYYSGSTYYNPSLKS	ADYDFWNGYFDY
light		RASQIRNDLG	AASSLQS	LQHNTYPWT
heavy	U1-7	GGSISSGDYYWS	YIYYSGSTYYNPSLKS	ADYDFWSGYFDY
light		RASQIRNDLG	AASSLQS	LQHNYPWT
heavy	U1-8	GYTLTELSMY	GPDPEGETIYAQKFOG	GWNYPFDY
light		RSSQSLLESNGYNYLD	LDSHRAS	MQALQTPIT
heavy	U1-9	GGSISSGDYYWS	YIYYSGSTYYNPSLKS	ADYDFWNGYFDY
light		RASQIRNDLG	AASSLQS	LQHNYPWT
heavy	U1-10	GGSISSGDYYWS	YIYYSGSTYYNPSLKS	ADYDFWSGYFDY
light		RASQIRNDLG	AASSLQS	LQHNNYPWT
heavy	U1-11	GGSISSGDYYWS	YIYYSGSTYYNPSLKS	ADYDFWSGYFDY
light		RASQIRNDLG	AASSLQS	LQHNTYPWT
heavy	U1-12	GGSISSGDYYWS	YIYYSGSTYYNPSLKS	ADYDFWSGYFDY
light		RASQIRNDLG	AASSLQS	LQHNNYPWT
heavy	U1-13	GGSISSGGYYWS	YIYYSGSTYYNPSLKS	EDDCMDV
light		RSSQSLLESNGYNYLE	LGSNRAS	MQALQTPIT
heavy	U1-14	GGSISSGDYYWS	YIYYSGSTYYNPSLKS	ADYDFWSGYFDY
light		RASQIRNDLG	AASSLQS	LQHNTYPWT

heavy		GGSVSSGGYYWS	YIYYSGSTYNNPSLKS	DGDVDTAMVDAFDI
	U1-15			
light		RASQSLSGNYLA	CASSRAT	QQYDRSPLT
heavy		GGSISSGDYYWS	YIYYSGSTYNNPSLKS	ADYDFWSGYFDY
	U1-16			
light		RASQIRNDLG	AASSLQS	LQHNSYPWT
heavy		GGSISSGDYYWS	YIYYSGSTYNNSSLKS	ADYDFWSGYFDY
	U1-17			
light		RASQIRNDLG	AASSLQS	LQHNSYPWT
heavy		GGSISSGDYYWS	YIYYSGSTYNNPSLKS	ADYDFWSGYFDY
	U1-18			
light		RASQIRNDLG	AASSLQS	LQHNSYPWT
heavy		GGSISSGDYYWS	YIYYSGSTYNNPSLKS	GDYDFWSGEFDY
	U1-19			
light		sequence not available		
heavy		GGSISSGGYYWS	YIYDSGSTYNNPSLKS	DQCQDGYEYGYGYYYGM
	U1-20			DV
light		QASQDISNYLN	VASNLET	QQCDNLPLT
heavy		GGSISSGDYYWS	YIYYSGSTYNNPSLKS	ADYDFWSGYFDY
	U1-21			
light		RASQIRNDLG	AASRLQS	LQHNSYPWT
heavy		GGSISSGDYYWS	YIYYSGSTYNNPSLKS	ADYDFWSGYFDY
	U1-22			
light		RASQIRNDLG	AASSLQN	LQHNSYPWT
heavy		GGSISSGDYYWS	YIYYSGSTYNNPSLKS	ADYDFWSGYFDY
	U1-23			
light		RASQIRNDLG	AASSLQS	LQHNSYPWT
heavy		GGSISSGDYYWS	YIYYSGSTYNNPSLKS	ADYDFWNGYFDY
	U1-24			
light		RASQIRNDLG	AASSLQS	LQHNNYPWT
heavy		GGSISSGDYYWS	YIYYSGSTYNNPSLKS	ADYDFWSGYFDY
	U1-25			
light		RASQIRNDLG	AASSLQN	LQHNSYPWT
heavy		GGSISSGDYYWS	YIYYSGSTYNNPSLKS	ADYDFWSGYFDF
	U1-26			
light		RASQIRNDLG	AASSLQS	LQHNGYPWT
heavy		GGSISSGDYYWS	YIYYSGSTYNNPSLKS	ADYDFWSGYFDF
	U1-27			
light		RASQIRNDLG	AASSLQS	LQHNGYPWT
heavy		GGSISSGDYYWS	YIYYSGSTYNNPSLKS	ADYDFWSGYFDS
	U1-28			
light		RASQIRNDLG	AASSLQS	LQHNGYPWT
heavy		GFTFNSYDMH	YIYDGSNKYYADSVKG	DELCTNGVCYEDYGMDV
	U1-29			
light		QASQDISNYLN	DASNLET	QHYDTLPLT
heavy		GGSISSGDYYWS	YIYYSGTYYNNPSLKS	ADYDFWSGYFDY
	U1-30			
light		RASQIRNDLG	AASSLQS	LQHNSYPWT

heavy	U1-31	GYTFTNYGIS	WISAYDGYRNYAQKLQG	DVQDYGDDYDFDY
light		RASQSISSYLN	AASSLQS	QGSYSTPIT
heavy	U1-32	GGSISSGDYYWS	YIYYSGTTYNPSLKS	ADYDFWSGYFDY
light		RAGQGIRNDLG	AASSLQS	LQHNSYPWT
heavy	U1-33	GGSISSGDYYWS	YIYYSGSTYYNPSLKS	ADYDFWSGHFDC
light		RASQGIRDDLG	AESSLQS	LQHNSYPWT
heavy	U1-34	GYTFTNYGIS	WISAYDGYRNYAQKLQG	DVQDYGDDYDFDY
light		RASQSISSYLN	AASSLQS	QGSYSTPIT
heavy	U1-35	GFTFSDYYMS	YISSSGNNIYHADSVKG	ERYSGYDDPDGFDI
light		QASQDISNYLS	DASNLET	QQYDNP PCS
heavy	U1-36	GGSISSGYYWS	YIYYSGTTYNPSFKS	ADYDFWSGHFDY
light		RASQGIRNDLG	AASSLQS	LQHNSYPWT
heavy	U1-37	GYTFTSYGIS	WISAYDGHTNYAQKLQG	DPHDYSNYEAFDF
light		RASQSISSYLN	AASSLQS	QGSYSTPIT
heavy	U1-38	GPSLSTSGVGVG	LIYWNDDKRYSPSLKS	RDEVRGFDY
light		RSSQSLVYSDGYTYLH	KVSNWDS	MQGAHWPT
heavy	U1-39	GFTVSSNYMS	VIYSSGSTYYADSVKG	GQWLDV
light		RSSQSLLHNGYNYLD	LGFHRAS	RQALQTPLT
heavy	U1-40	GGSISSGGYYWS	YIYSSGSTYYNPSLKS	DRELELYYYYYGMDV
light		RSSQSLLYNGYNYLD	LGSNRAS	MQALQTPLT
heavy	U1-41	GGSISSGGYYWS	YIYYSGSTYYNPSLKS	DRELEGYSNYYGVDV
light		RASQAISNYLN	AASSLQS	QQNNSLPIT
heavy	U1-42	GYSFTSYWIG	IIYPGDSDTRYSPSEQG	HENYGDYNY
light		RASQSIRSYLN	AASSLQS	QQSNGSPLT
heavy	U1-43	GGSISSGGYYWS	YIYYSGSTYYNPSLRS	DRERENDDYGDPQGMDV

light		RASQSISSYLH	AASSLQS	QSYSNPLT
heavy	U1-44	GYSFTSYWIG	IIWPGDSDTIYSPSFQG	HENYGDYNY
light		RASQSIRSYLN	AASSLQS	QSISSPLT
heavy	U1-45	GYTFTSYDIN	WMNPNSGDTGYAQVFQG	EGDLPYDYSYYEWFDP
light		RASQSISSYLH	AASSLQS	QSYSTPLT
heavy	U1-46	GDSVSSNSAAWN	RTYYRSKWYNDYAVSVK S	DLYDFWSGYPYYYGMDV
light		sequence not available		
heavy	U1-47	GDSVSSNSAAWN	RTYYRSKWYNDYAVSVK S	DYYGSGSFYYYYGMDV
light		RASQSISSYLH	AASNLS	QSYSTPRT
heavy	U1-48	GGSISSYYWS	HIYTSGSTNYNPSLKS	EAIFGVGPYYYYGMDV
light		sequence not available		
heavy	U1-49	GYTFTGYMH	WINPNIGGTNCAQKFG	GGRYSSWSYYYYGMDV
light		KSSQSLLSDGCTYLY	EVSNRFS	MQSMQLPIT
heavy	U1-50	GGSVSSGGYYWS	YIYYSGSTNYNPSLKS	GGDSNYEDYYYYGMDV
light		RASQSISSYLH	AASSLQS	QSYTSPIT
heavy	U1-51	GGSISSYYWS	YIYYSGSTNYNPSLKS	DSSYYDSSGYLYYYAM DV
light		KSSQSVLYSSNNKNYLA	WASTRES	QYYTTPLT
heavy	U1-52	GGSISSGGYYWS	NIYYSGSTNYNPSLKS	GGTGTNYYYYYGMDV
light		RASQSVSSSYLA	GASSWAT	QYQSSPLT
heavy	U1-53	GFTFSIYSMN	YISSSSSTIYYADSVKG	DREDFDAFDI
light		QASQDITNYLN	DASNLET	QCCENFPIT
heavy	U1-55.1	GGSVSSGGYYWN	YINYSGSTNYNPSLKS	DRELELYYYYYGMDV
light		will be same as U1-55		
heavy	U1-55	will be same as U1-55.1		
light		RSSQSLLYSNGYKYLD	LGSNRAS	MQALQTPIT
heavy	U1-57.1	will be same as U1-57		

light		RSSQSLLYSNGYKYLD	LGSNRAS	MQALQTPIT
heavy	U1-57	EGSVSSGGYYWN	YINYSGSTWYNPSLKS	DRELELYYYYYGMDV
light		will be same as U1-57.1		
heavy	U1-58	GFTFSSYGMH	VIWYDGSNKYYADSVKG	AARLDYYYYGMDV
light		RASQSINSYLN	GASGLQS	QQSYSSPLT
heavy	U1-59	GGSPSGYYWS	GINHSGSTWYNPSLKS	DKWTWYFDL
light		RSSQSVLYSSSNRNYLA	WASTRES	QQYYSTPRT
heavy	U1-61.1	GVSISSGGYYWS	YIYYSGSTYYNPSLKS	DSESEYSSBSNYGMDV
light		RASQTISSYLN	AASSLQG	QQSYSNPLT
heavy	U1-61	GVSISSGGYYWS	YIYYSGSTYYNPSLKS	DSESEYSSSSNYGMDV
light		will be the same as U1-61.1		
heavy	U1-62	GYSFTSYWIG	IIYPGDSDDTRYSPSFQG	QMAGNYYYYGMDV
light		RASQSVISIYLA	GASSRAT	QQYGSSPCS

Claims

5 1. An isolated binding protein that binds to HER-3,
comprising:

 a heavy chain amino acid sequence that comprises
at least one of the CDR's selected from the group consisting of (a) CDRH1's
10 as shown in SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30, 34, 36, 40, 42, 46, 50,
54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120,
122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170, 174, 178,
182, 186, 190, 194, 198, 202, 206, 210, 214, 218, 222, 226 and 230; (b)
CDRH2's as shown in SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30, 34, 36, 40,
15 42, 46, 50, 54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100, 104, 108, 112,
116, 120, 122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170,
174, 178, 182, 186, 190, 194, 198, 202, 206, 210, 214, 218, 222, 226 and
230; and (c) CDRH3's as shown in SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30,
34, 36, 40, 42, 46, 50, 54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100,
20 104, 108, 112, 116, 120, 122, 126, 130, 134, 138, 142, 146, 150, 154, 158,
162, 166, 170, 174, 178, 182, 186, 190, 194, 198, 202, 206, 210, 214, 218,
222, 226 and 230.

 2. An isolated binding protein that binds to HER-3,
25 comprising:

 a light chain amino acid sequence that comprises at
least one of the CDR's selected from the group consisting of: (d) CDRL1's
as shown in SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 38, 44, 48, 52, 56, 58,
30 64, 68, 72, 76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132,
136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192,
196, 200, 204, 208, 212, 216, 220, 224, 228 and 232; (e) CDRL2's as shown
in SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 38, 44, 48, 52, 56, 58, 64, 68,

72, 76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132, 136, 140,
144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200,
204, 208, 212, 216, 220, 224, 228 and 232; and (f) CDRL3's as shown in
SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 38, 44, 48, 52, 56, 58, 64, 68, 72,
5 76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132, 136, 140,
144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200,
204, 208, 212, 216, 220, 224, 228 and 232.

10 3. The isolated binding protein of Claim 1 or 2, wherein said
binding protein comprises:

a heavy chain amino acid sequence that comprises
at least one of the CDR's selected from the group consisting of (a) CDRH1's
as shown in SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30, 34, 36, 40, 42, 46, 50,
15 54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120,
122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170, 174, 178,
182, 186, 190, 194, 198, 202, 206, 210, 214, 218, 222, 226 and 230; (b)
CDRH2's as shown in SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30, 34, 36, 40,
42, 46, 50, 54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100, 104, 108, 112,
20 116, 120, 122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170,
174, 178, 182, 186, 190, 194, 198, 202, 206, 210, 214, 218, 222, 226 and
230; and (c) CDRH3's as shown in SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30,
34, 36, 40, 42, 46, 50, 54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100,
104, 108, 112, 116, 120, 122, 126, 130, 134, 138, 142, 146, 150, 154, 158,
25 162, 166, 170, 174, 178, 182, 186, 190, 194, 198, 202, 206, 210, 214, 218,
222, 226 and 230, and

a light chain amino acid sequence that comprises at least one of
the CDR's selected from the group consisting of: (d) CDRL1's as shown in
30 SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 38, 44, 48, 52, 56, 58, 64, 68, 72,
76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132, 136, 140,
144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200,
204, 208, 212, 216, 220, 224, 228 and 232; (e) CDRL2's as shown in SEQ

ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 38, 44, 48, 52, 56, 58, 64, 68, 72, 76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 216, 220, 224, 228 and 232; and (f) CDRL3's as shown in SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 38, 44, 48, 52, 56, 58, 64, 68, 72, 76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 216, 220, 224, 228 and 232.

4. The isolated binding protein of Claim 1 or 2, wherein said binding protein comprises a heavy chain amino acid sequence that comprises a CDRH1, a CDRH2, and a CDRH3 of any of SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30, 34, 36, 40, 42, 46, 50, 54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170, 174, 178, 182, 186, 190, 194, 198, 202, 206, 210, 214, 218, 222, 226 and 230, or a light chain amino acid sequence that comprises a CDRL1, a CDRL2, and a CDRL3 of any of SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 38, 44, 48, 52, 56, 58, 64, 68, 72, 76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 216, 220, 224, 228 and 232.

5. The isolated binding protein of Claim 3, wherein said binding protein comprises a heavy chain amino acid sequence that comprises a CDRH1, a CDRH2, and a CDRH3 of any of SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30, 34, 36, 40, 42, 46, 50, 54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170, 174, 178, 182, 186, 190, 194, 198, 202, 206, 210, 214, 218, 222, 226 and 230, and a light chain amino acid sequence that comprises a CDRL1, a CDRL2, and a CDRL3 of any of SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 38, 44, 48, 52, 56, 58, 64, 68, 72, 76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 216,

220, 224, 228 and 232.

6. The isolated binding protein of Claim 1, comprising:

5 a heavy chain amino acid sequence selected from the group
consisting of SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30, 34, 36, 40, 42, 46, 50,
54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120,
122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170, 174, 178,
182, 186, 190, 194, 198, 202, 206, 210, 214, 218, 222, 226 and 230.

10 7. The isolated binding protein of Claim 2 comprising:

a light chain amino acid sequence selected from the group
consisting of SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 38, 44, 48, 52, 56, 58,
64, 68, 72, 76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132,
136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192,
15 196, 200, 204, 208, 212, 216, 220, 224, 228 and 232.

8. The isolated binding protein of Claim 1, comprising:

a heavy chain amino acid sequence selected from the group
consisting of SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30, 34, 36, 40, 42, 46, 50,
20 54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120,
122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170, 174, 178,
182, 186, 190, 194, 198, 202, 206, 210, 214, 218, 222, 226 and 230; and
a light chain amino acid sequence selected from the group
consisting of SEQ ID NOs: 4, 8, 12, 16, 20, 24, 28, 32, 38, 44, 48, 52, 56, 58,
25 64, 68, 72, 76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132,
136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192,
196, 200, 204, 208, 212, 216, 220, 224, 228 and 232.

9. The isolated binding protein of Claim 1, comprising a

30 CDRH3 of any of SEQ ID NOs: 2, 6, 10, 14, 18, 22, 26, 30, 34, 36, 40, 42,
46, 50, 54, 60, 62, 66, 70, 74, 78, 80, 84, 88, 92, 96, 100, 104, 108, 112,
116, 120, 122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170,
174, 178, 182, 186, 190, 194, 198, 202, 206, 210, 214, 218, 222, 226 and

230.

10. The isolated binding protein according to Claim 9, comprising a light chain amino acid sequence of any of SEQ ID NOs: 4, 8,
5 12, 16, 20, 24, 28, 32, 38, 44, 48, 52, 56, 58, 64, 68, 72, 76, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 216, 220, 224, 228 and 232.

10 11. The isolated binding protein according of any one of Claims 1-9 comprising the heavy chain amino acid sequence of SEQ ID NO:42 and the light chain amino acid sequence of SEQ ID NO:44.

15 12. The isolated binding protein according of any one of Claims 1-9 comprising the heavy chain amino acid sequence of SEQ ID NO:54 and the light chain amino acid sequence of SEQ ID NO:56.

20 13. The isolated binding protein according of any one of Claims 1-9 comprising the heavy chain amino acid sequence of SEQ ID NO:70 and the light chain amino acid sequence of SEQ ID NO:72.

25 14. An isolated binding protein that binds to a three-dimensional structure formed by amino acid residues 1-160; 161-358; 359-575; 1-358; 359-604 of mature HER-3, particularly of mature human HER-3.

15. The isolated binding protein of any of Claims 1-14, wherein the binding protein is directed against the extracellular domain of HER-3.

30 16. The isolated binding protein of any one of Claims 1-15, wherein the binding of the binding protein to HER-3 reduces HER-3-mediated signal transduction.

17. The isolated binding protein of any one of Claims 1-15, wherein the binding of the binding protein to HER-3 reduces HER-3 phosphorylation.

5 18. The isolated binding protein of any one of Claims 1-15, wherein the binding of the binding protein to HER-3 reduces cell proliferation.

10 19. The isolated binding protein of any one of Claims 1-15, wherein the binding of the binding protein to HER-3 reduces cell migration.

15 20. The isolated binding protein of any one of Claims 1-15, wherein the binding of the binding protein to HER-3 increases the downregulation of HER-3.

21. The isolated binding protein of any one of Claims 1-20 which is an antibody.

20 22. The isolated binding protein of Claims 21, wherein the antibody is a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a humanized antibody, a human antibody, a chimeric antibody, a multispecific antibody, or an antibody fragment thereof.

25 23. The isolated binding protein of Claim 22, wherein the antibody fragment is a Fab fragment, a Fab' fragment, a F(ab')₂ fragment, a Fv fragment, a diabody, or a single chain antibody molecule.

30 24. The isolated binding protein of any one of Claims 1-23, wherein said isolated binding protein is of the IgG1-, IgG2-, IgG3- or IgG4-type.

25. The isolated binding protein of any one of Claims 1-

24, wherein the binding protein is coupled to a labelling group.

26. The isolated binding protein of Claim 25, wherein the labelling group is a radioisotope or radionuclide, a fluorescent group, an enzymatic group, a chemiluminescent group, a biotinyl group, or a predetermined polypeptide epitope.

27. The isolated binding protein of any one of Claims 1-24, wherein the binding protein is coupled to an effector group.

28. The isolated binding protein of Claim 27, wherein the effector group is a radioisotope or radionuclide, a toxin, or a therapeutic or chemotherapeutic group.

29. The isolated binding protein of Claim 28, wherein the therapeutic or chemotherapeutic group is selected from the group consisting of calicheamicin, auristatin-PE, geldanamycin, maytansine and derivatives thereof.

30. An isolated nucleic acid molecule encoding an binding protein of any one of Claims 1-29.

31. The isolated nucleic acid molecule of Claim 30, wherein the nucleic acid molecule is operably linked to a control sequence.

32. A vector comprising the nucleic acid molecule of Claim 30.

33. A vector comprising the nucleic acid molecule of Claim 31.

34. A host cell transformed with the vector of Claim 32.

35. A host cell transformed with the vector of Claim 33.

36. A process for preparing the isolated binding protein of any one of Claims 1-29, comprising the step of isolating said binding protein from a host cell

37. The process of Claim 36, wherein the host cell is a mammalian cell, a plant cell, a fungal cell, or a prokaryotic cell.

38. A pharmaceutical composition comprising as an active agent at least one isolated binding protein of any one of Claims 1-29, and a pharmaceutically acceptable carrier, diluent or adjuvant.

39. The composition of Claim 37 or 38 for therapeutic use.

40. The composition of Claim 37 or 38 for diagnostic use.

41. A method for treating or preventing a disease associated with HER-3 in a patient, comprising administering a pharmaceutically effective amount of a pharmaceutical composition of Claim 38 or 39 to a subject in need thereof.

42. The method of Claim 41, wherein the disease is a hyperproliferative disease.

43. The method of Claim 42, wherein said hyperproliferative disease is selected from the group consisting of breast cancer, gastrointestinal cancer, pancreas cancer, prostate cancer, ovarian cancer, stomach cancer, endometrial cancer, salivary gland cancer, lung cancer, kidney cancer, colon cancer, colorectal cancer, thyroid cancer, bladder cancer, glioma, melanoma, testis cancer, soft tissue sarcoma, head and neck cancer, other HER-3 expressing or overexpressing cancers, and formation of tumor metastases.

44. The method of Claim 42 or 43, wherein said hyperproliferative disease is associated with increased HER-3 phosphorylation, increased HER-2/HER-3 heterodimerization or an increased activity of PI₃-kinase, c-jun-terminal kinase, AKT, ERK2 and/or PYK2.

45. A method for diagnosing a disease associated with HER-3, comprising:

(a) contacting a sample with the binding protein of any one of Claims 1-26, under conditions suitable to allow binding of said binding protein to HER-3; and

(c) identifying binding of said binding protein to HER-3.

46. The method of Claim 45, wherein the disease is a hyperproliferative disease.

47. The method of Claim 46, wherein said hyperproliferative disease is selected from the group consisting of breast cancer, gastrointestinal cancer, pancreas cancer, prostate cancer, ovarian cancer, stomach cancer, endometrial cancer, salivary gland cancer, lung cancer, kidney cancer, colon cancer, colorectal cancer, thyroid cancer, bladder cancer, glioma, melanoma, other HER-3 expressing or overexpressing cancers, testis cancer, soft tissue sarcoma, head and neck cancer, and formation of tumor metastases.

48. The method of Claim 46 or 47, wherein said hyperproliferative disease is associated with increased HER-3 phosphorylation, increased HER-2/HER-3 heterodimerization or an increased activity of PI₃-kinase, c-jun-terminal kinase, AKT, ERK2 and/or PYK2.

49. A kit comprising the isolated binding protein of any one of Claims 1-28.

50. The kit of Claim 49, comprising a further therapeutic agent.

51. The kit of Claim 50 wherein the further therapeutic agent is an antineoplastic agent.

52. The kit of Claim 51, wherein the anti-neoplastic agent is an anti-tumor antibody or a chemotherapeutic agent.

Fig. 1

cell line	tissue	expression level	cell line	tissue	expression level
Hs578T	breast	++	RPMI-7951	melanoma	O/+
T47D	breast	++	MelJuso	melanoma	++
SKBr3	breast	+++	MelGerlach	melanoma	++
ZR 75-1	breast	++	C32	melanoma	+++
MDA-MB-435s	breast	+++	HT144	melanoma	+++
MCF-7	breast	++	SK-Mel2	melanoma	+++
BT474	breast	+++	MALME3	melanoma	+++
MDA-MB 453	breast	+++	Hs294T	melanoma	+++
MDA-MB 361	breast	++	A375p	melanoma	+++
HCT116	colon	+	SK-Mel3	melanoma	+++
HT29	colon	++	SK-Mel5	melanoma	++
LoVo	colon	+	KB	nasopharynx	+
CaCo-2	colon	+	SCC9	Squamous cell Carcinoma	
SW480	colon	++	SKOV3	ovary	+
A431	epidermoid	+	Capan-1	pancreas	+
HT1080	fibrosarcoma	O/+	Capan-2	pancreas	+
CaKi-1	kidney	O	Bx-PC-3	pancreas	+
CaKi-2	kidney	O	LNCap	prostate	++
Calu6	lung	O	DU145	prostate	+
A549	lung	O	PC-3	prostate	+
M19	melanoma	++	BM1604	prostate	++
M14	melanoma	+++	TSU	prostate	+

0=no expression; +=weak; ++=medium; +++=strong

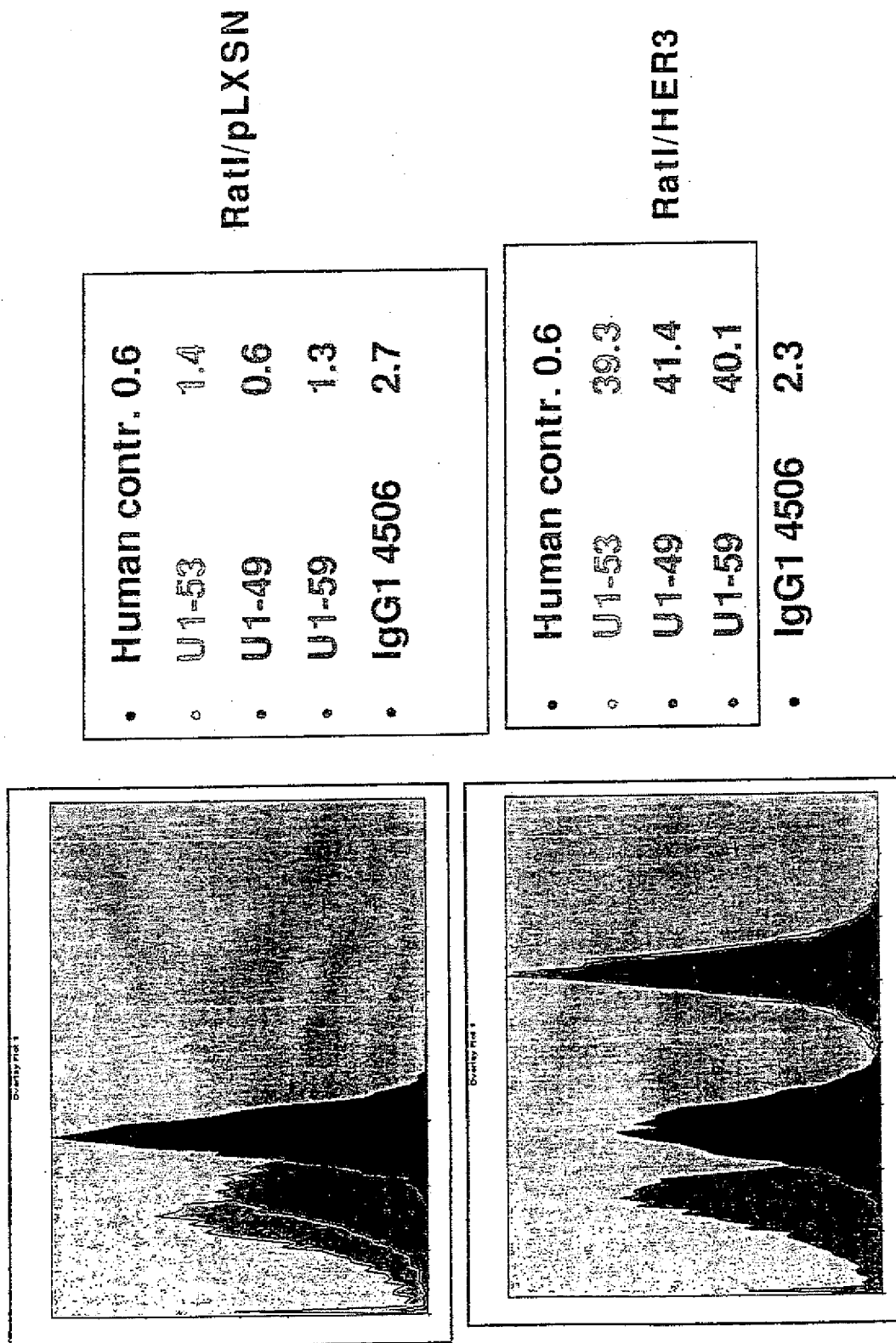


Fig. 3

antibody bins

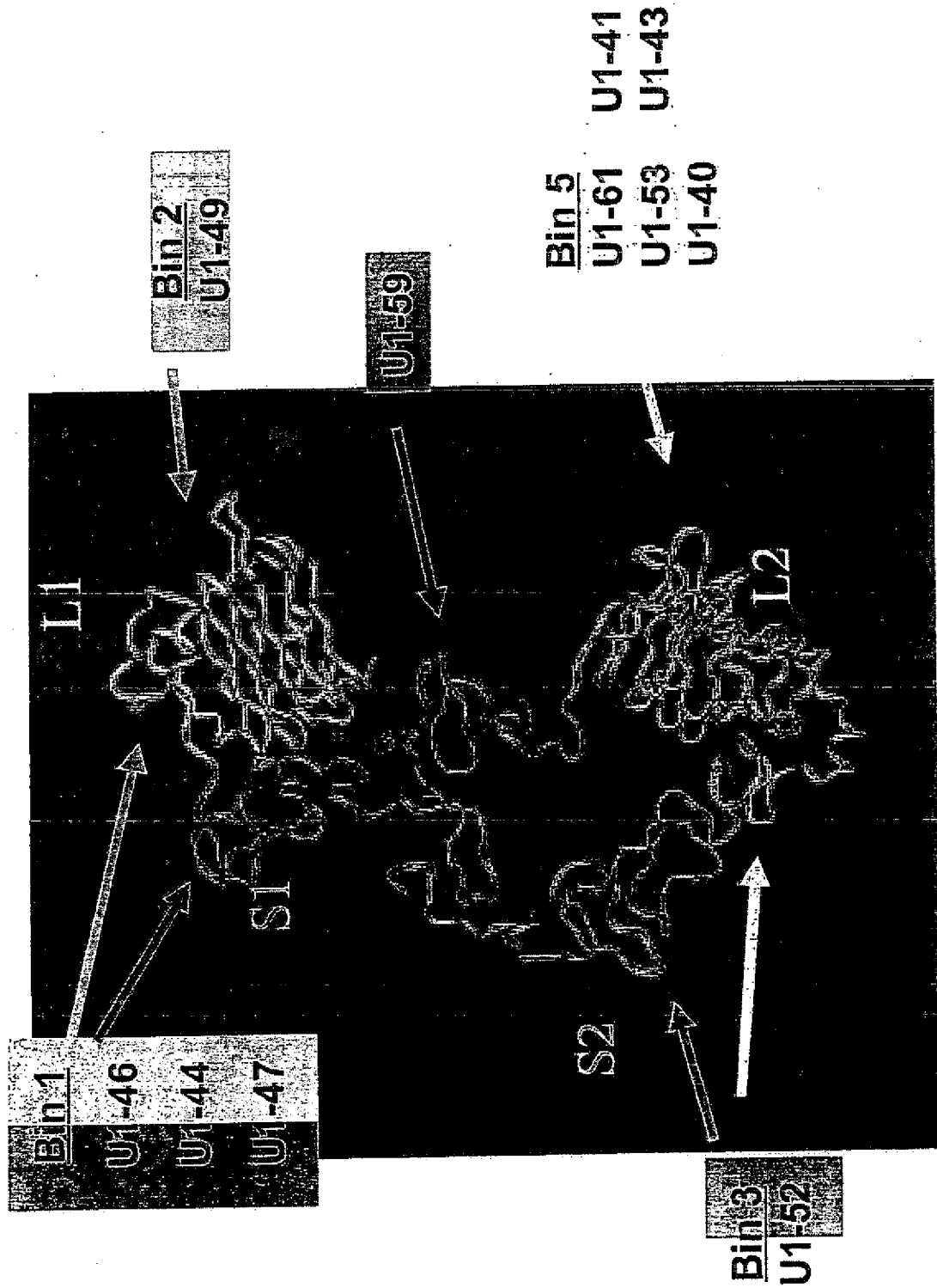


Fig. 4

FACS scatterhard

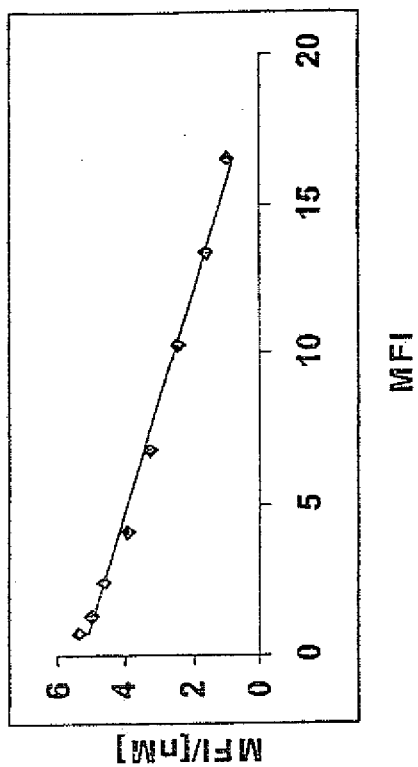
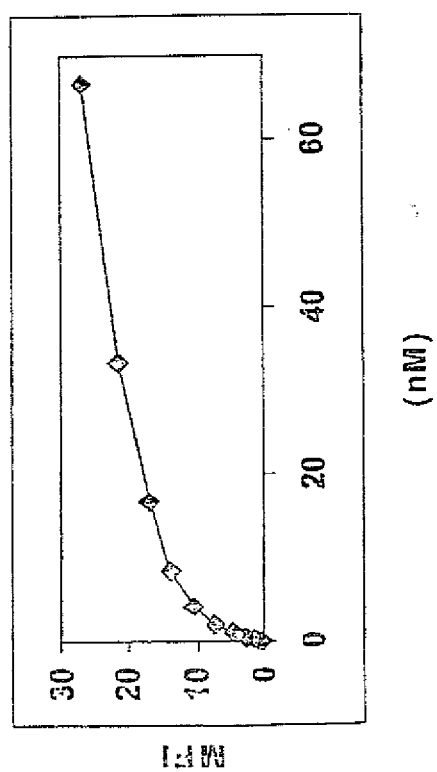


Fig. 5
internalization

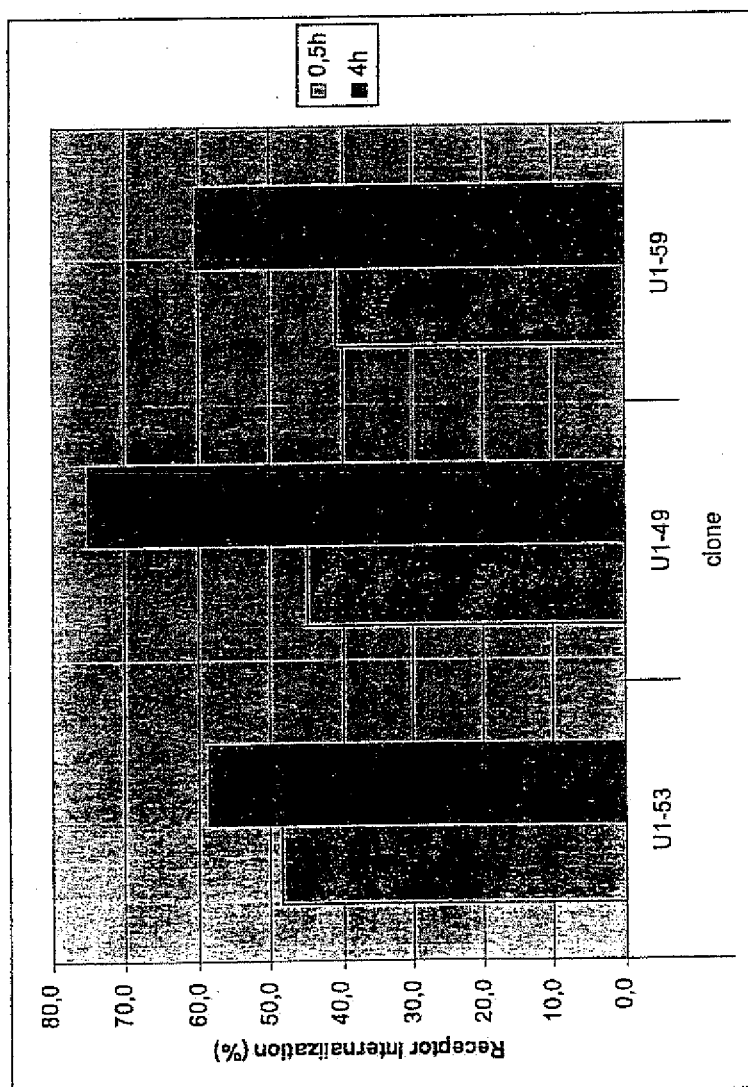
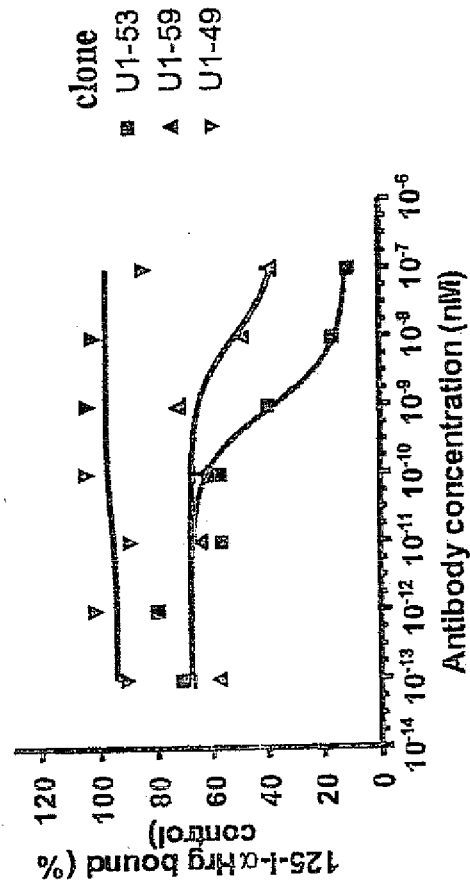


Fig. 6a

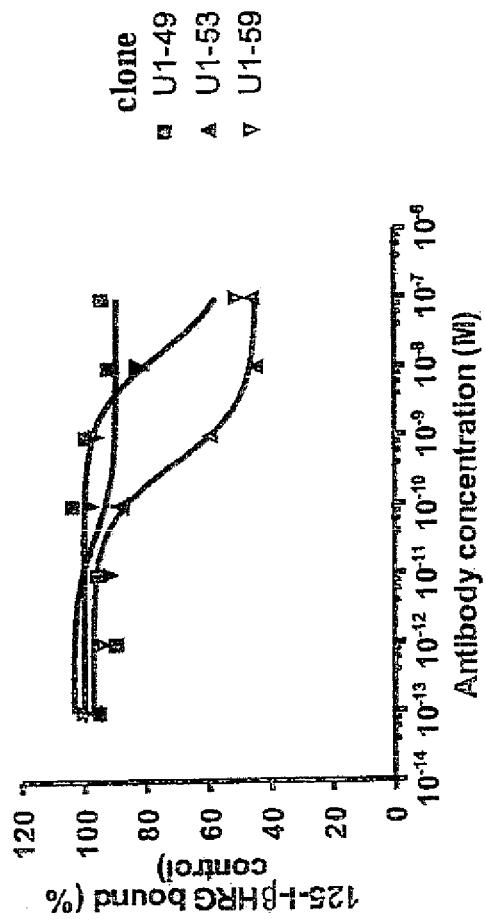
HRG blocking



clone	EC50 (nM)
U1-59	9,65
U1-49	-
U1-53	0,71

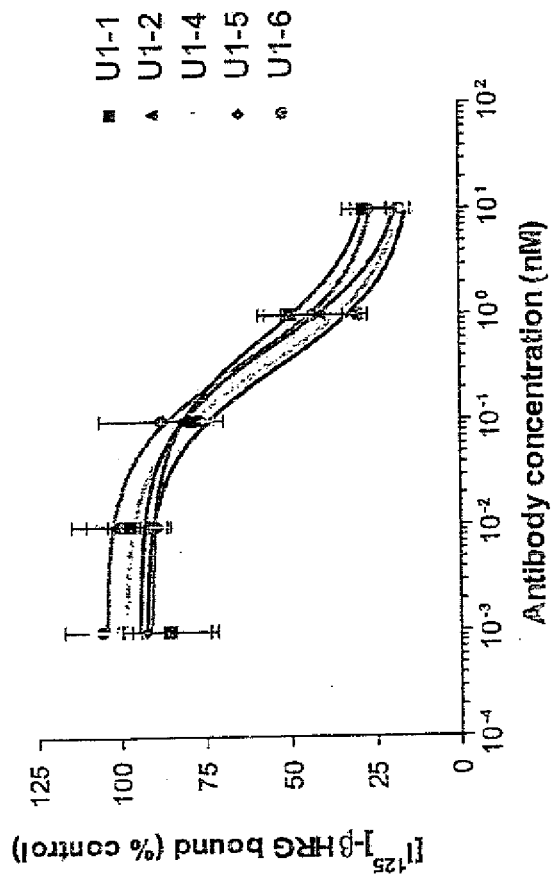
Fig. 6b

HRG blocking



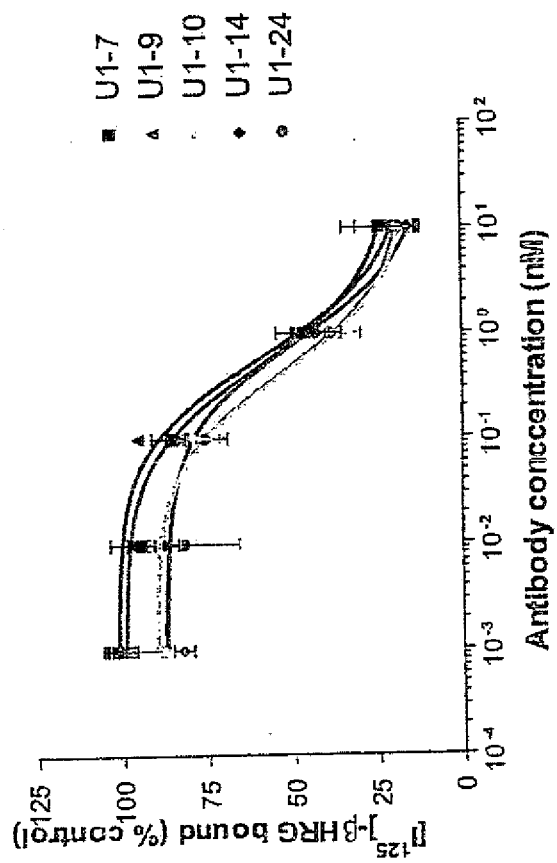
clone	EC50 (nM)
U1-59	32,1
U1-49	-
U1-53	0,49

Fig. 6c



clone	EC50 (nM)
U1-1	0.61
U1-2	0.51
U1-4	0.32
U1-5	0.33
U1-6	0.35

Fig. 6d



clone	EC50 (nM)
-------	-----------

U1-7	0.49
------	------

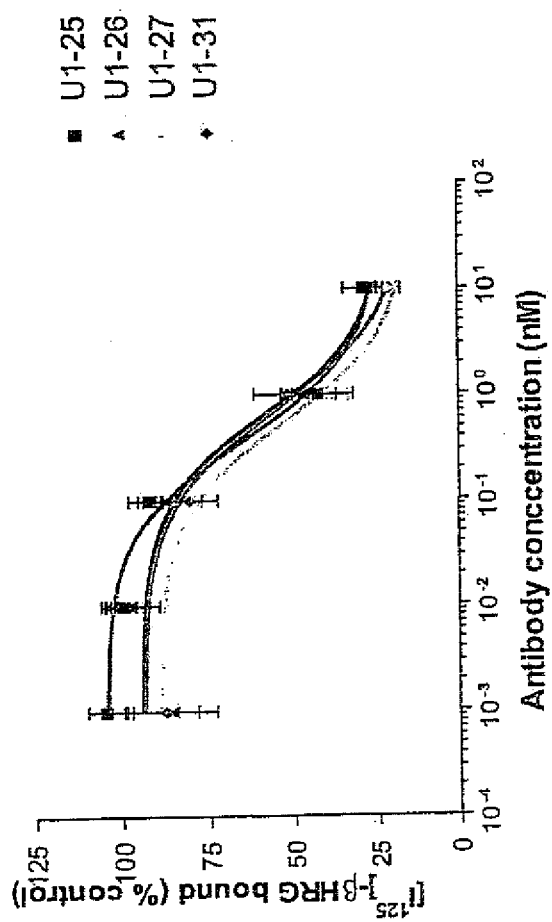
U1-9	0.60
------	------

U1-10	0.40
-------	------

U1-14	0.83
-------	------

U1-24	0.41
-------	------

Fig. 6e



clone	EC_{50} (nM)
U1-25	0.38
U1-26	0.60
U1-27	0.56
U1-31	0.77

Fig. 7a

HER3 tyrosine phosphorylation

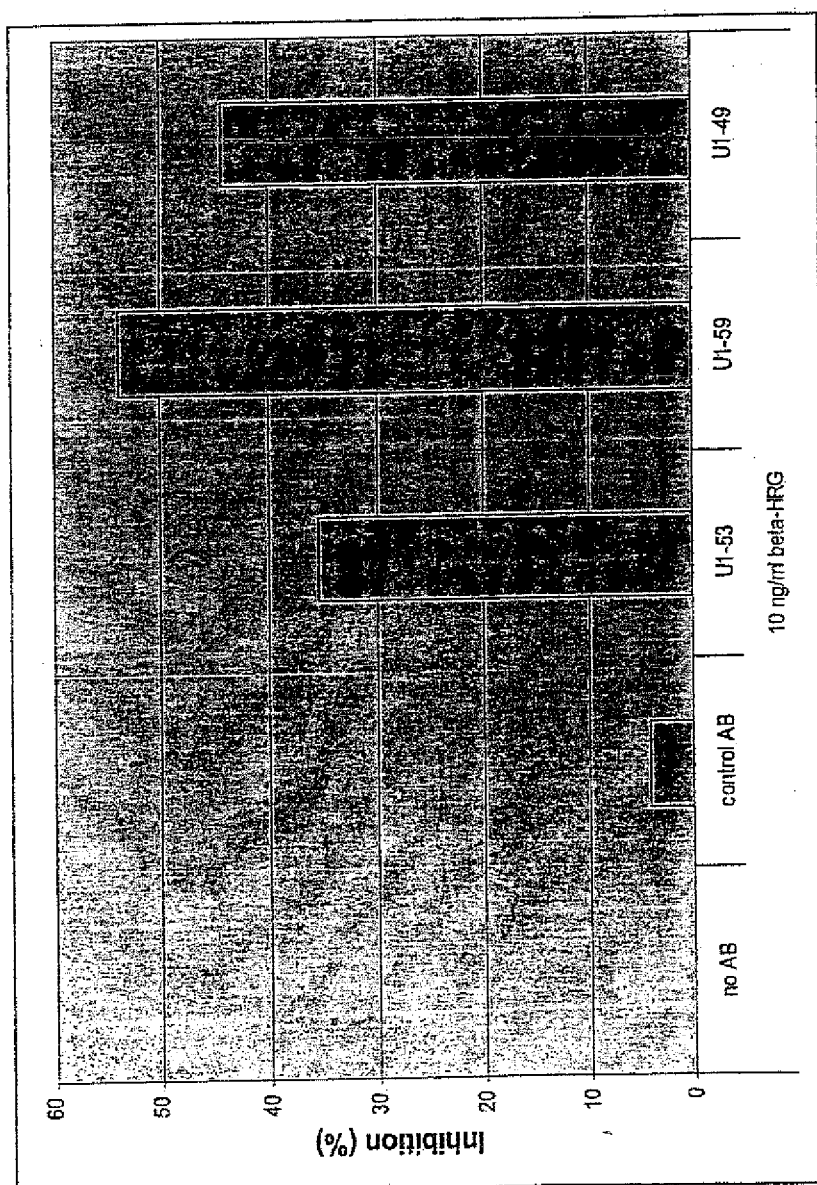
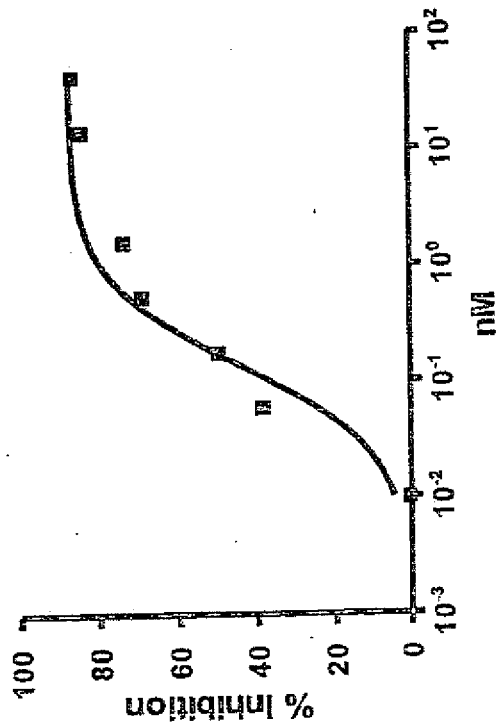


Fig. 7b

HER3 tyrosine phosphorylation

Inhibition of β -HRG induced HER3 phosphorylation by purified anti-HER3 antibody (clone U1-53)



EC50 | 0.1353

Fig. 8
MAP kinase

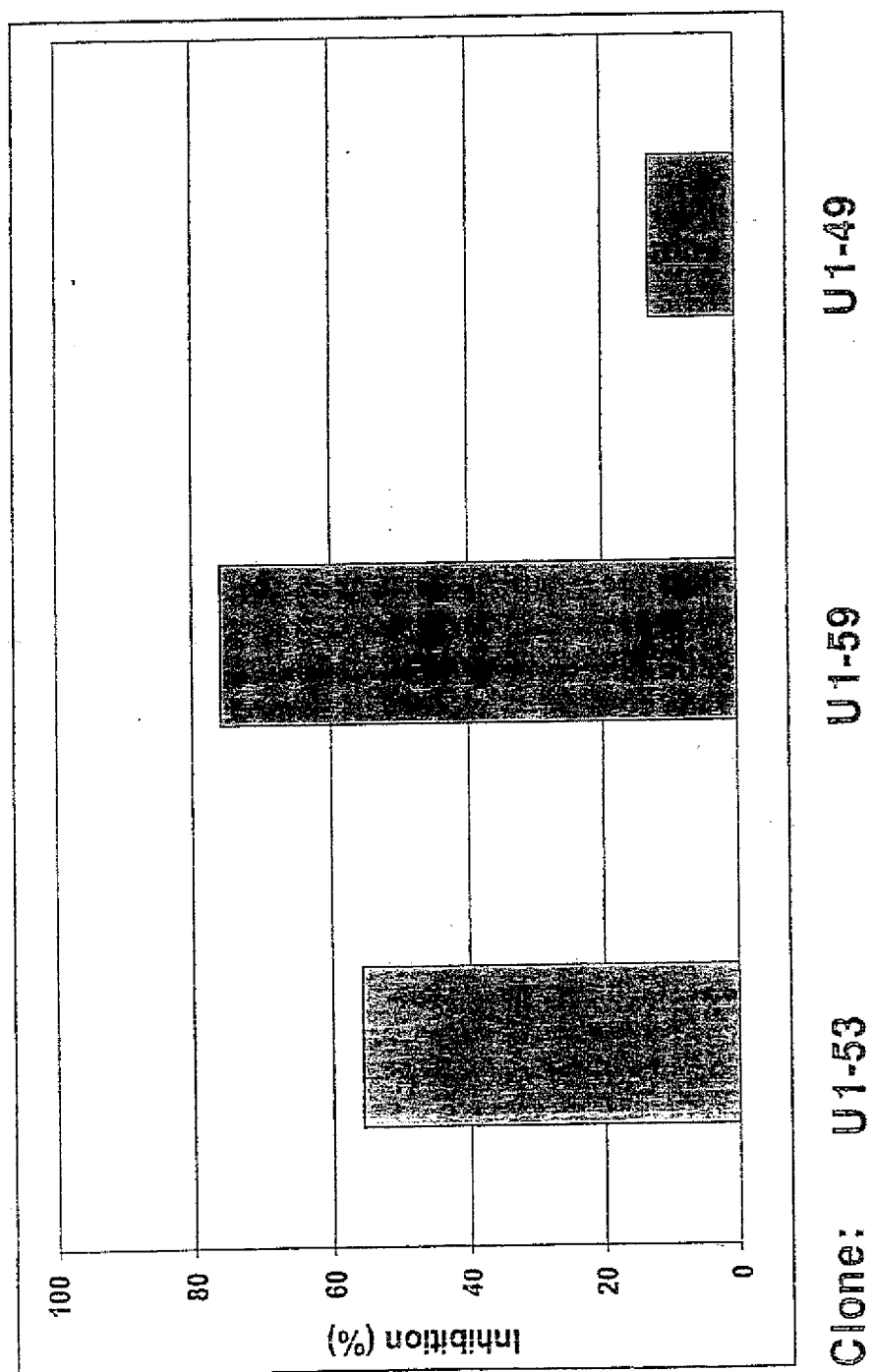


Fig. 9 ^{AKT}

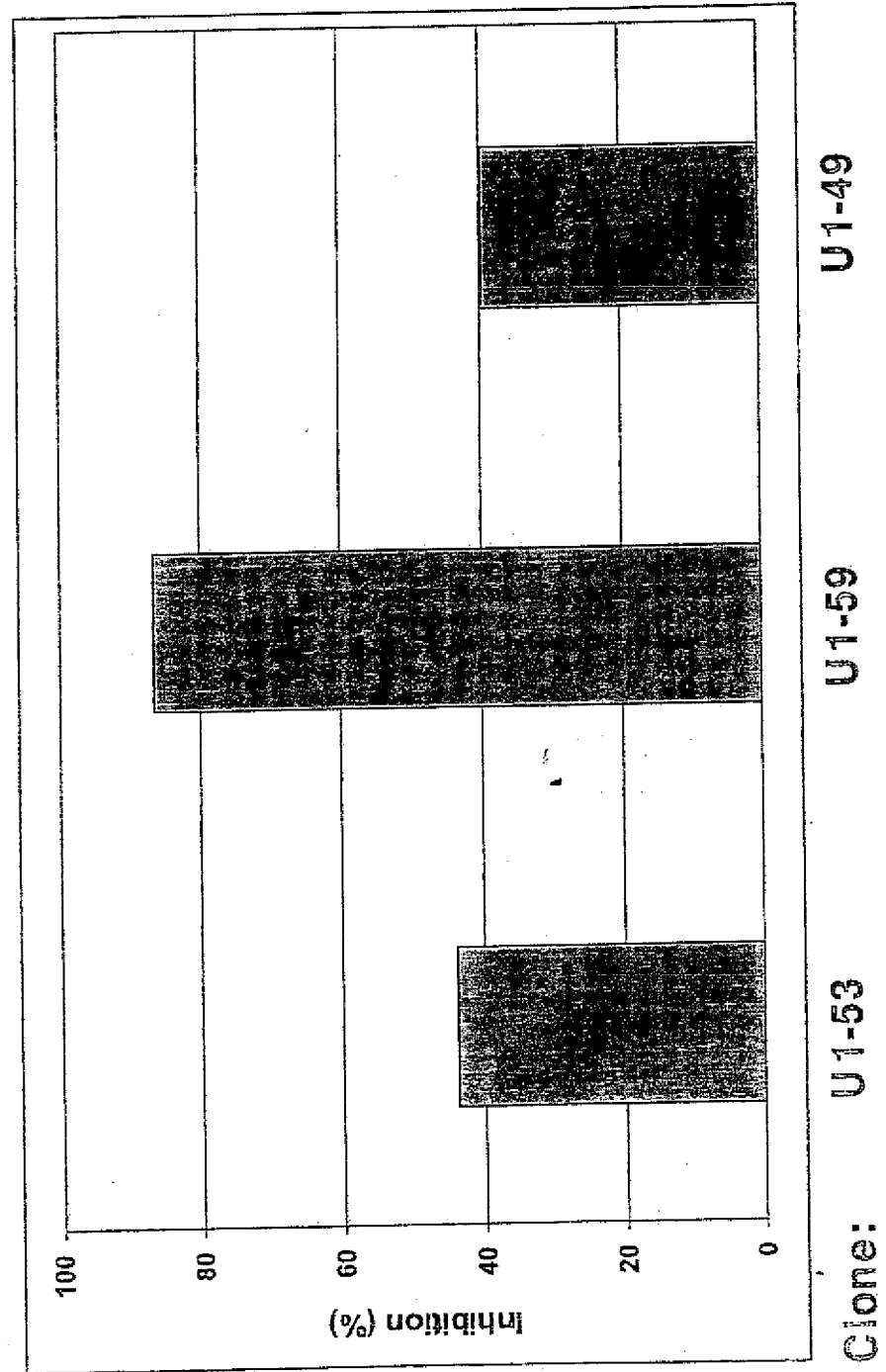


Fig. 10 proliferation

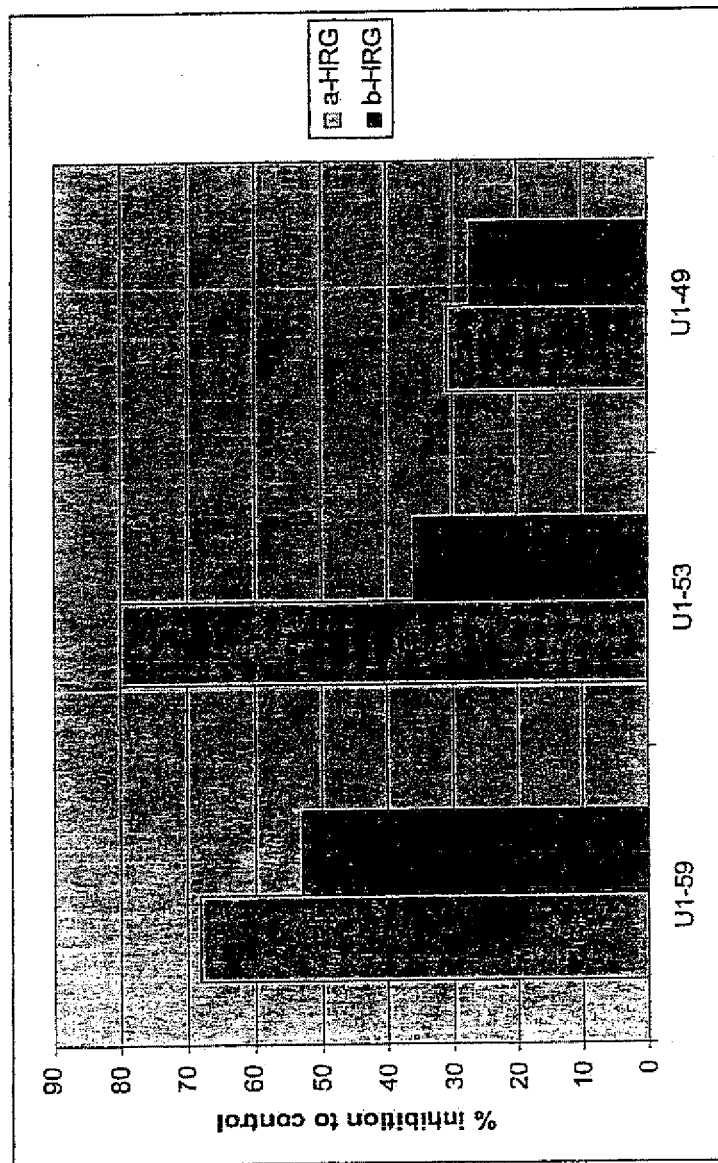


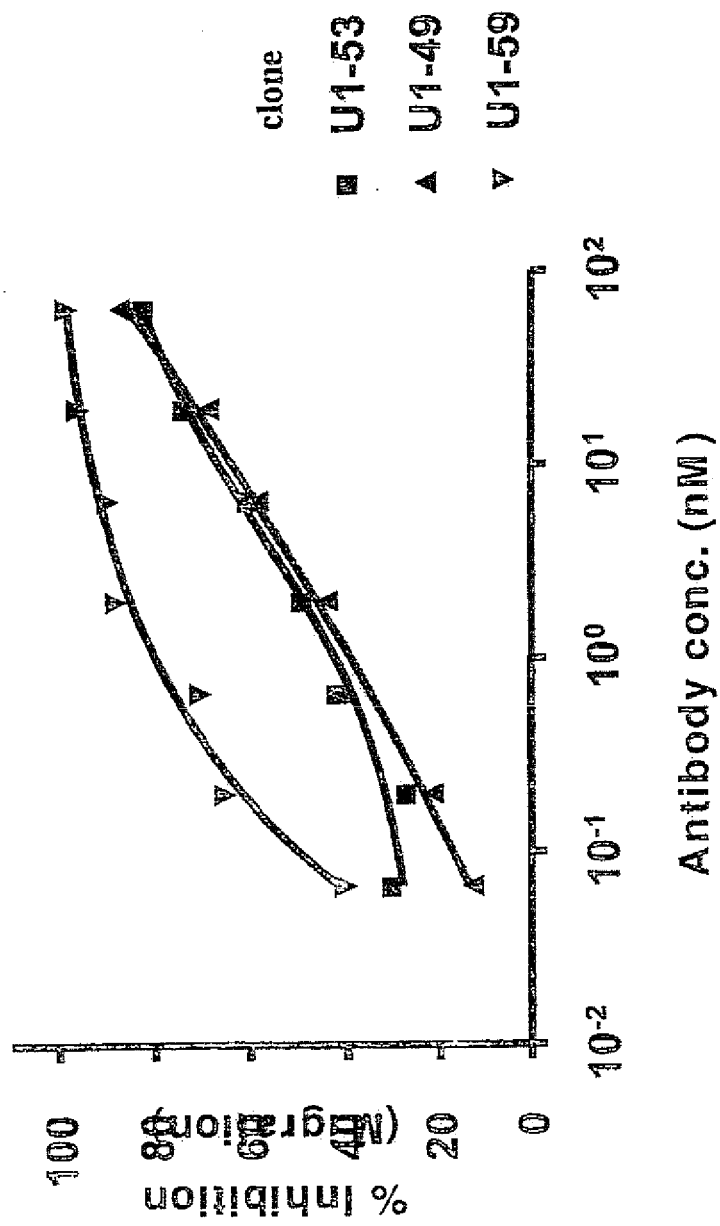
Fig. 11 migration

Fig. 12a
Soft Agar MB361

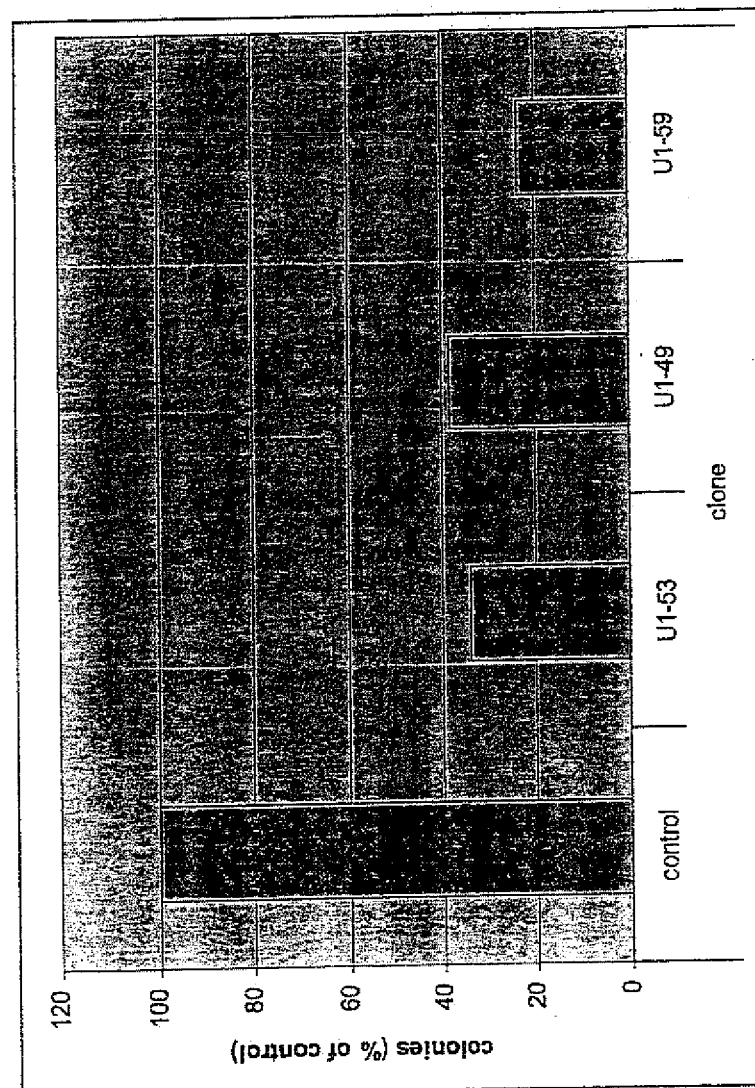


Fig. 12b
Soft Agar NCI

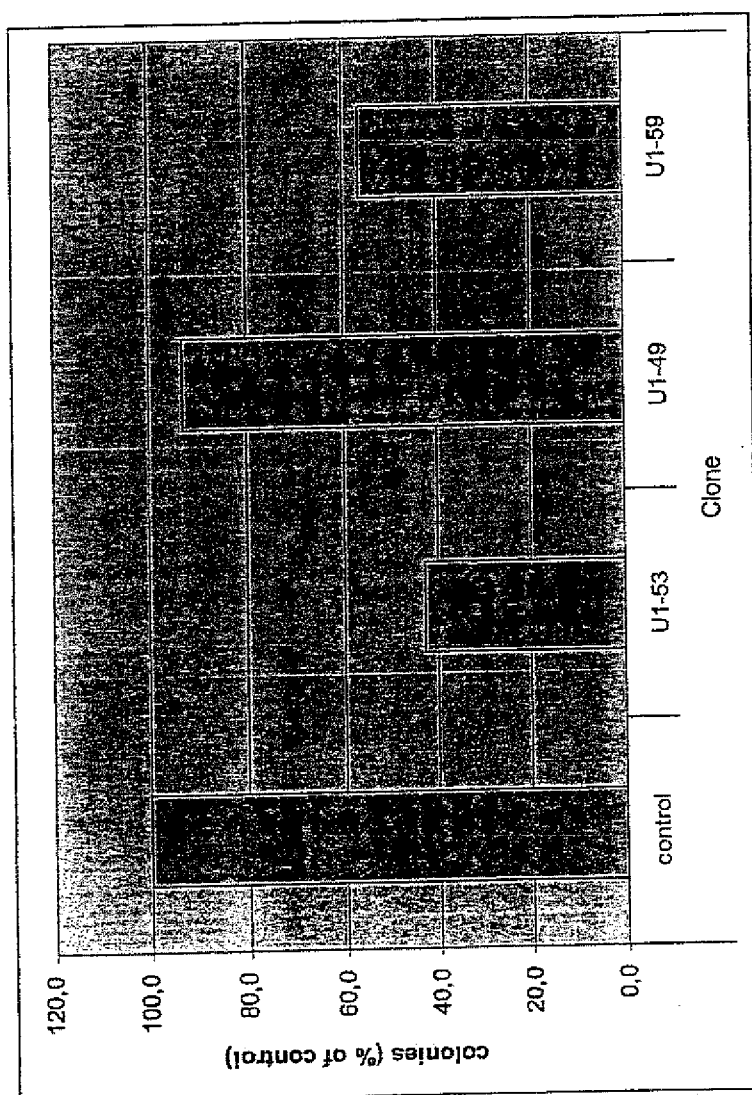


Fig. 12c

Soft Agar MKN-28

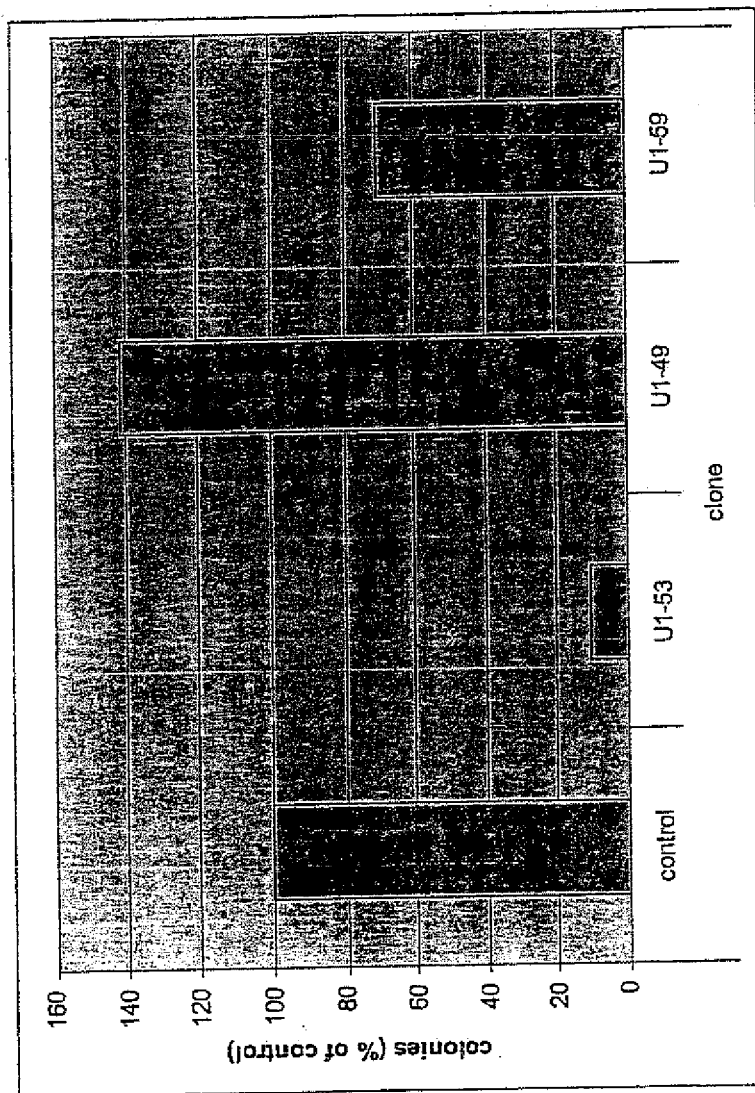


Fig. 12d
Soft Agar HT-144

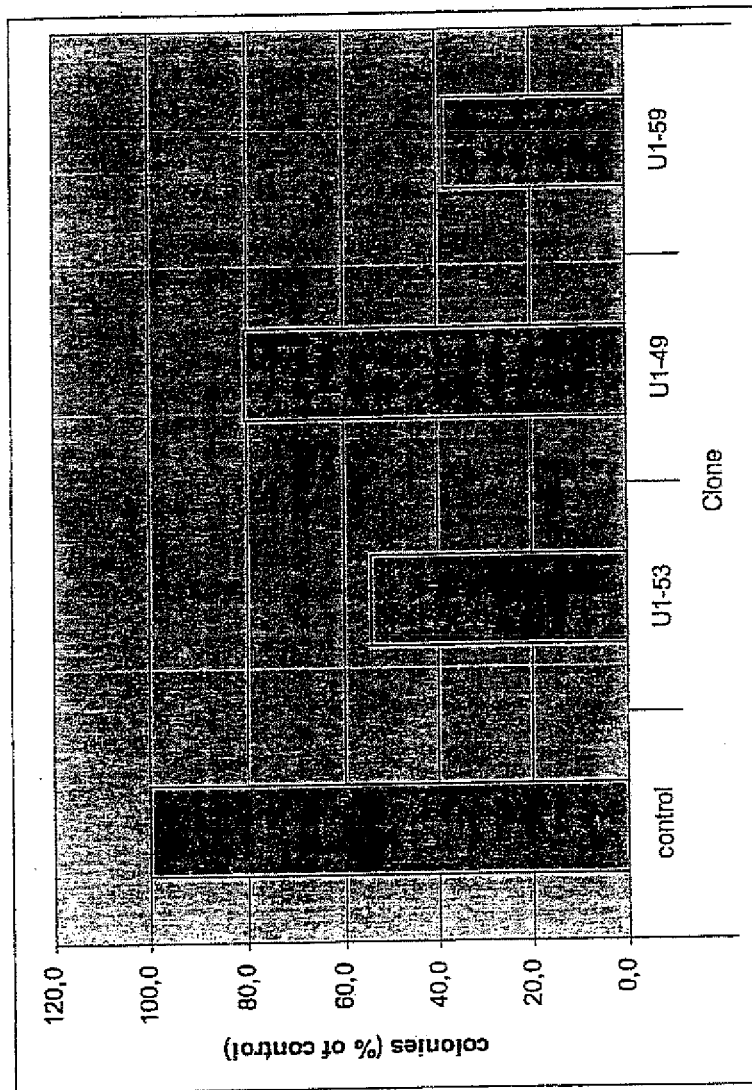


Fig. 12e
Soft Agar Skov-3

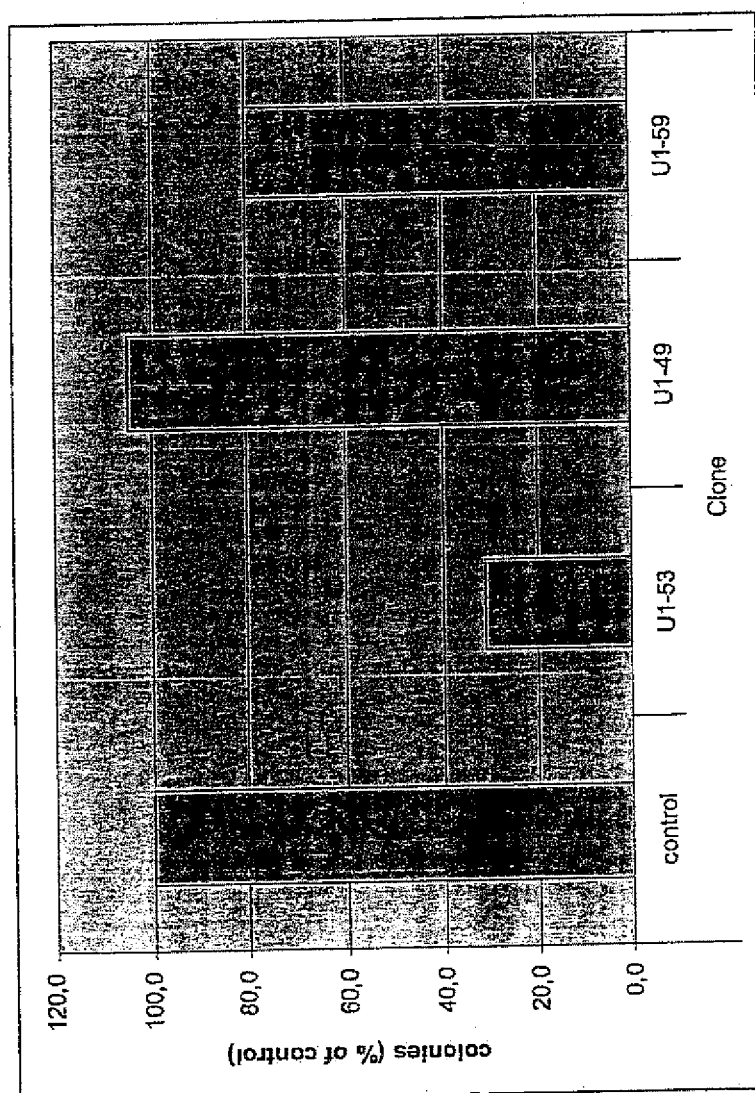


Fig. 12f
Soft Agar PPC1

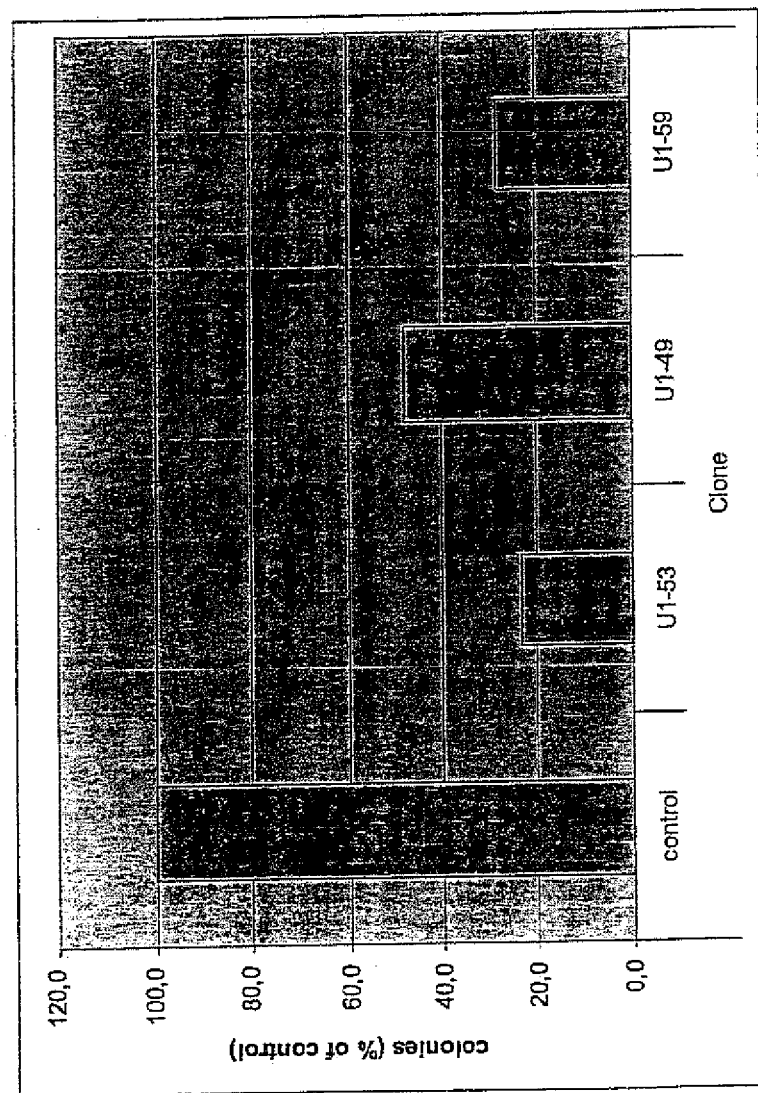


Fig. 12g
Soft Agar BX-PC3

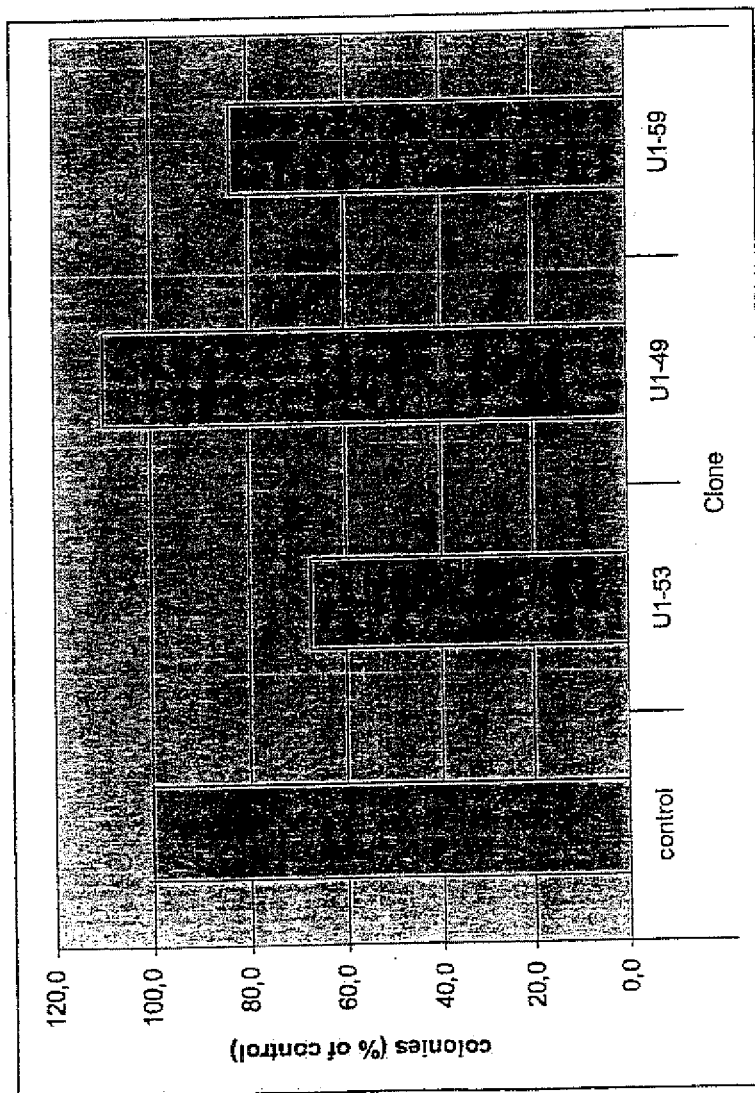


Fig. 12h
Soft Agar Δ549

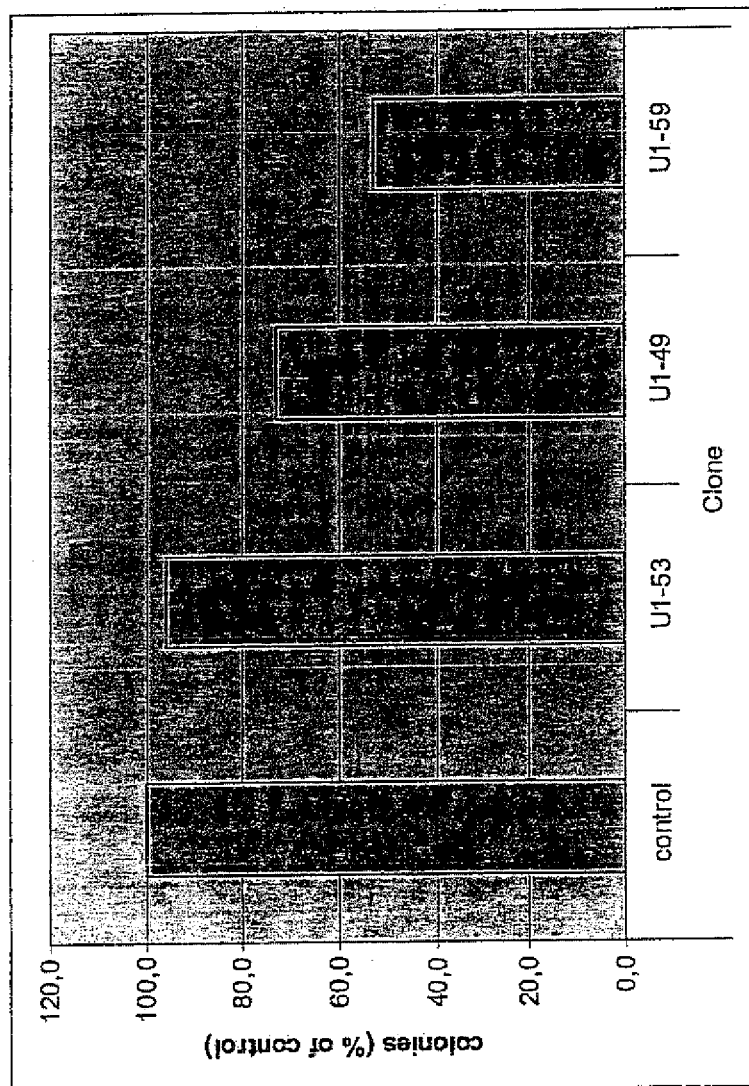


Fig. 12i
Soft Agar epidermoid

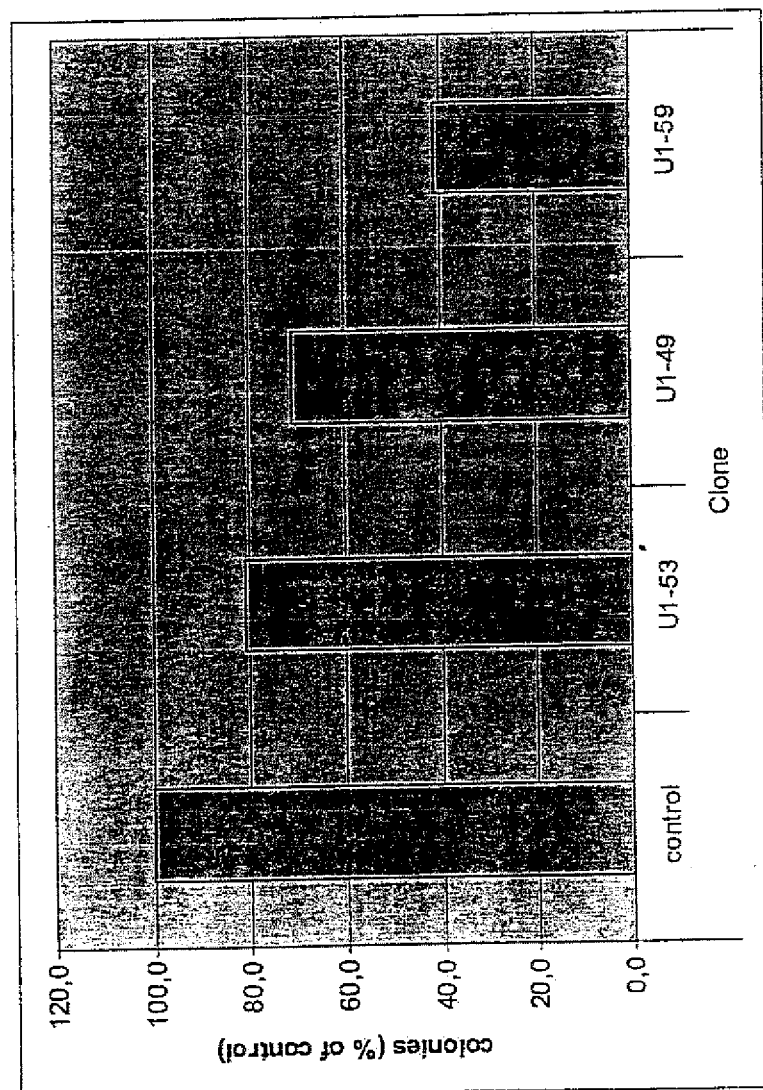


Fig. 13
in vivo T47D

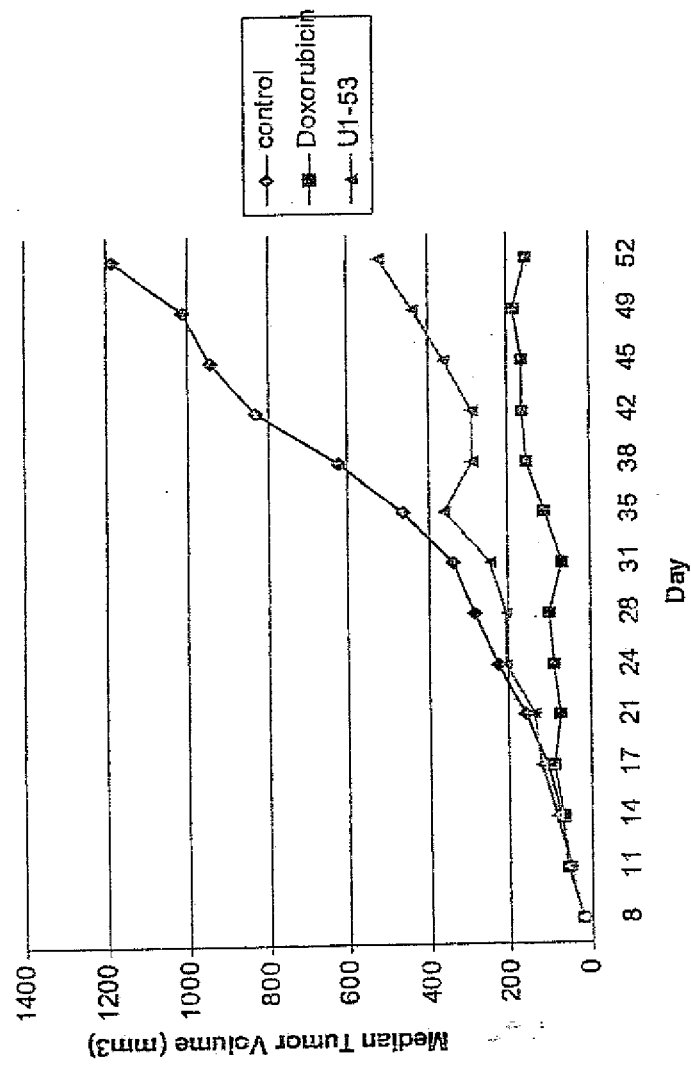


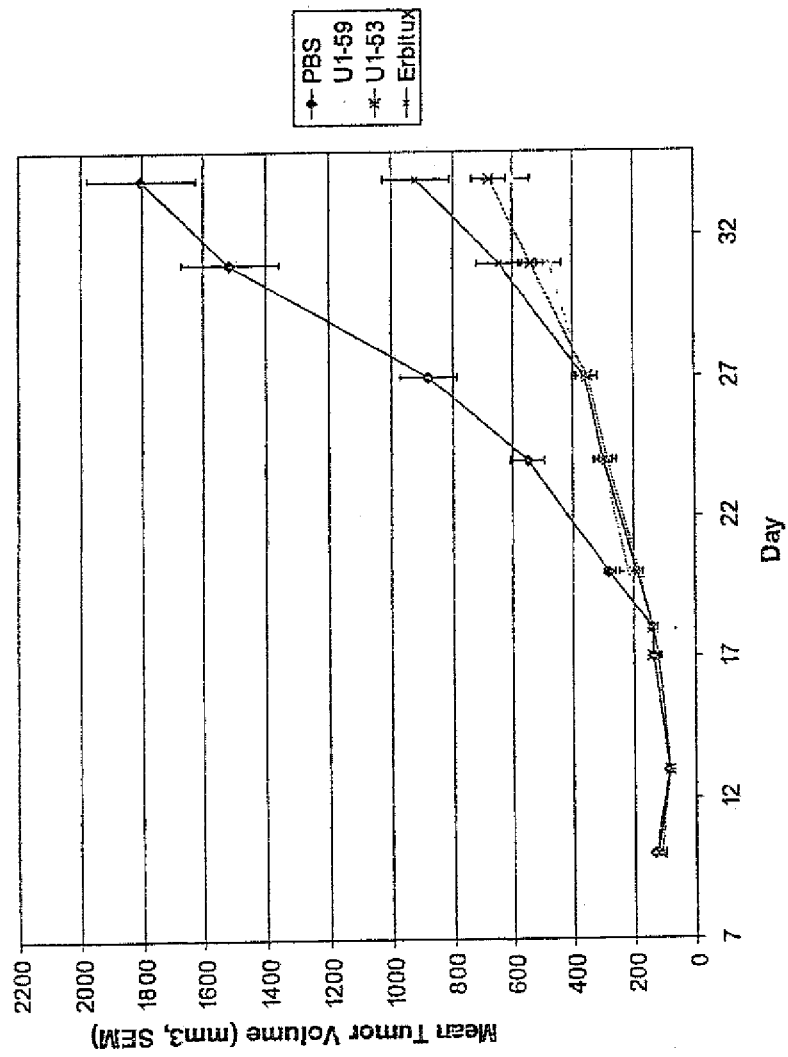
Fig. 14 BxPC3

Fig. 15

BxPC3 combination

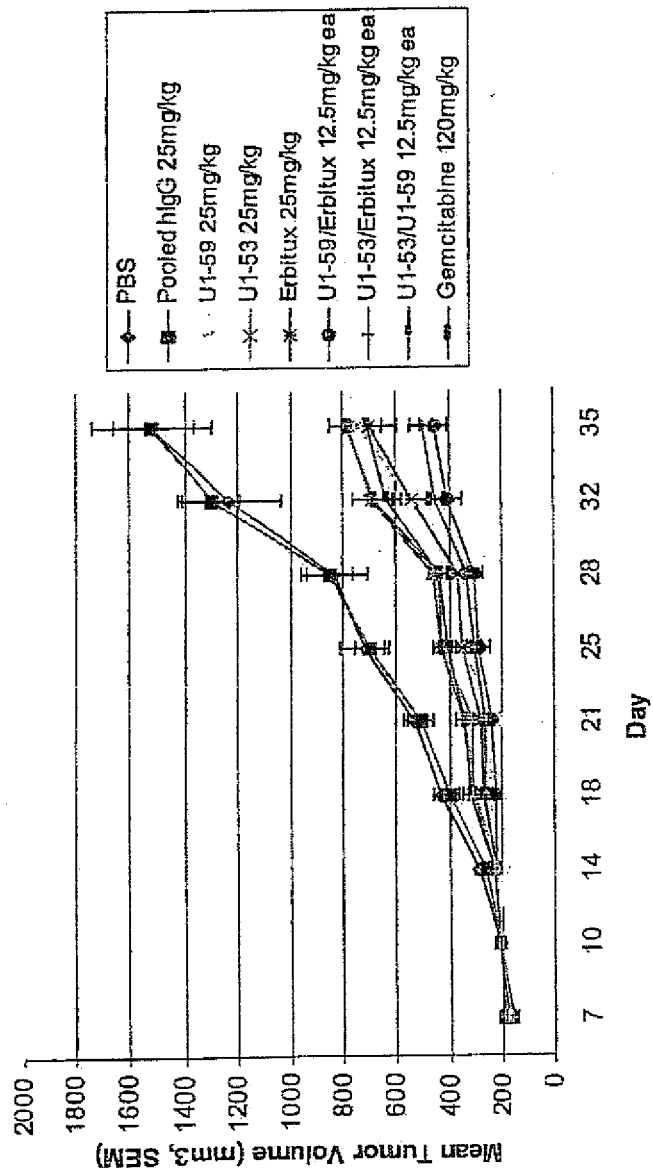


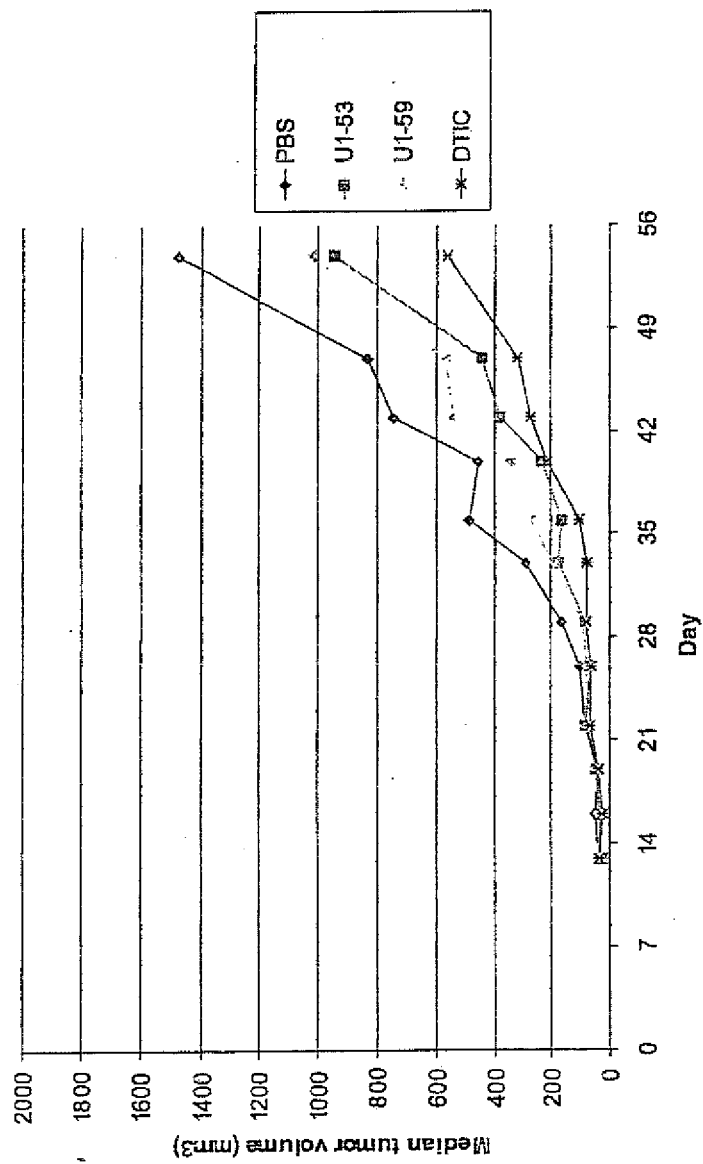
Fig. 16_{HT144}

Fig. 17

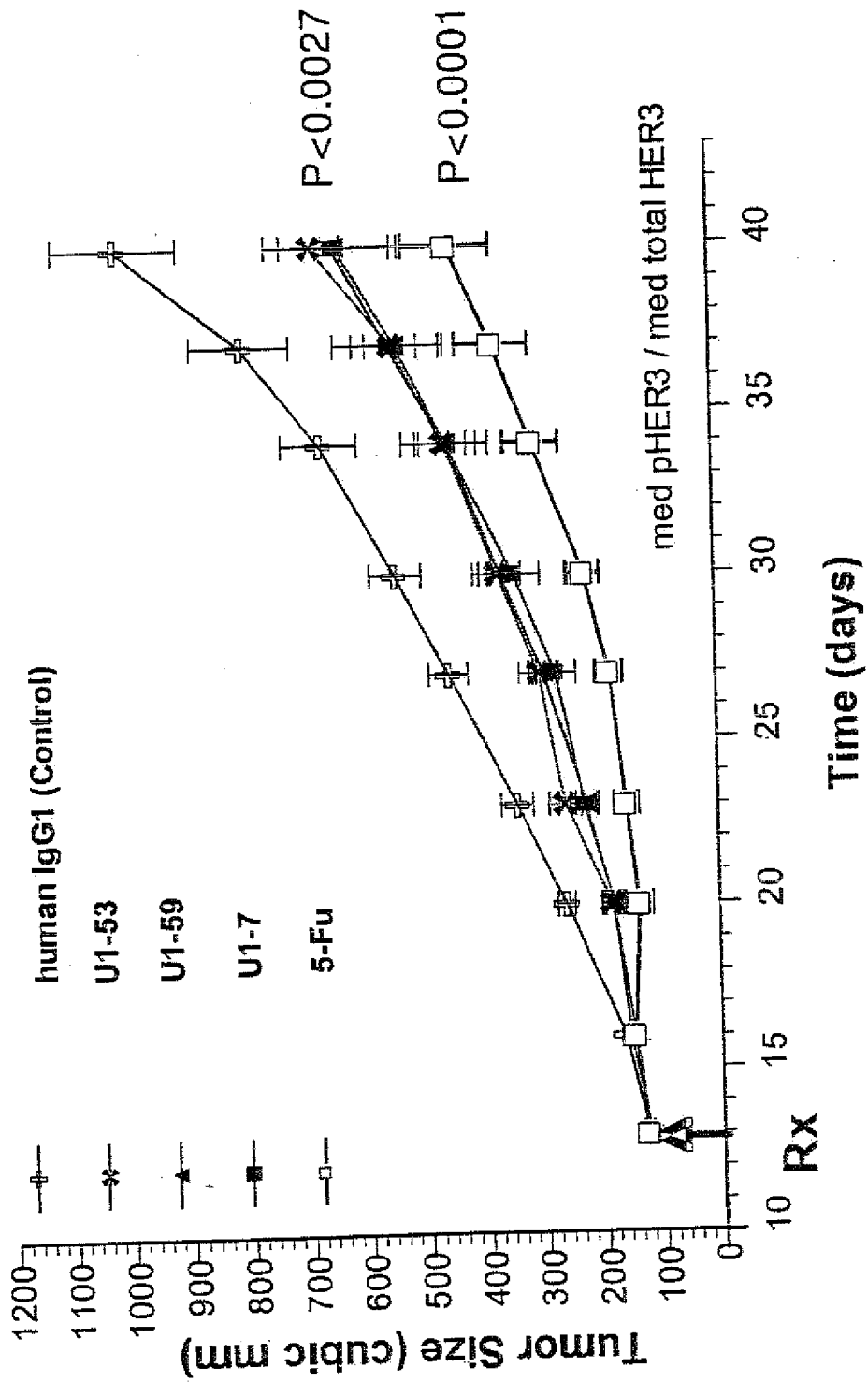


Fig. 18

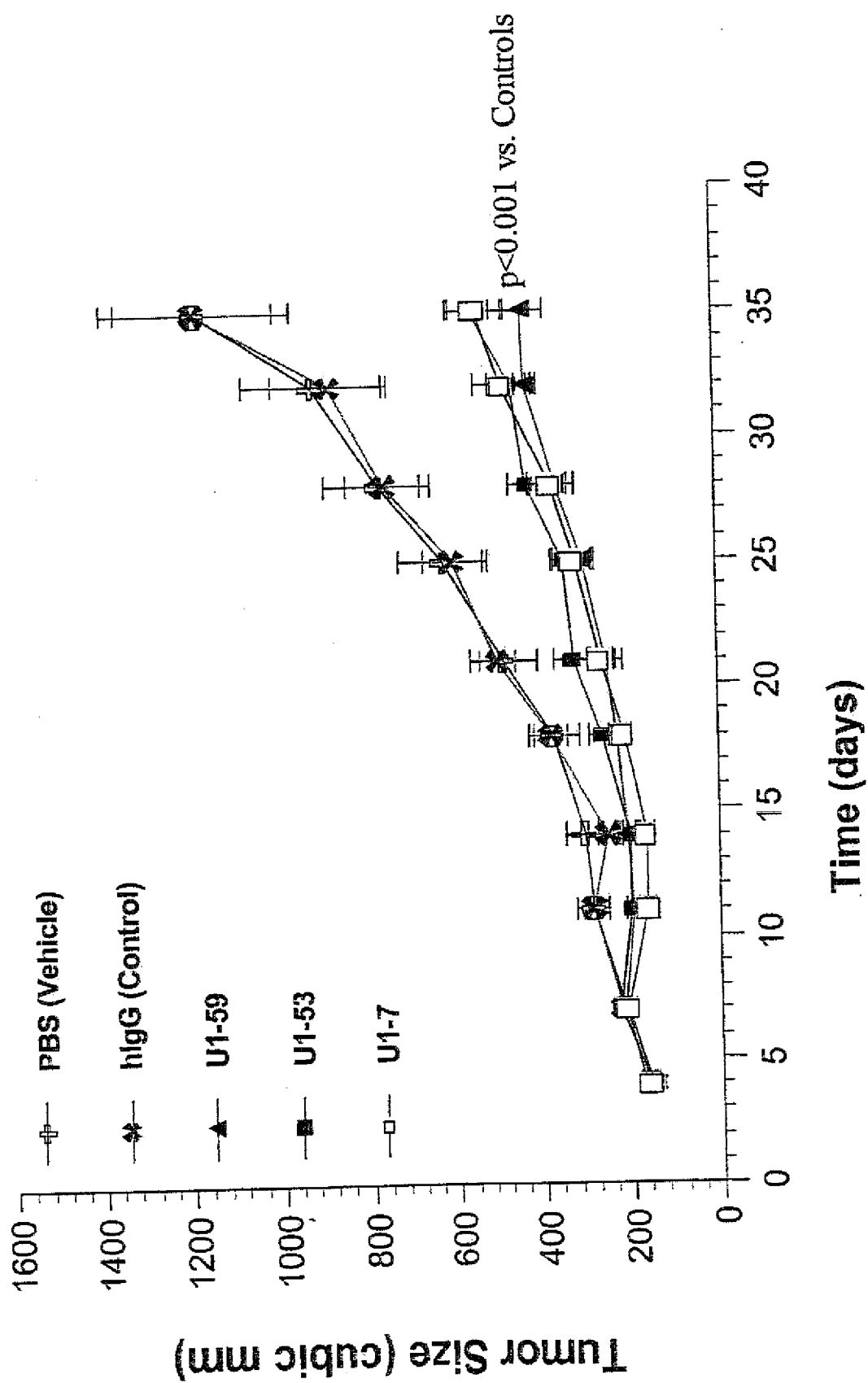


Fig. 19

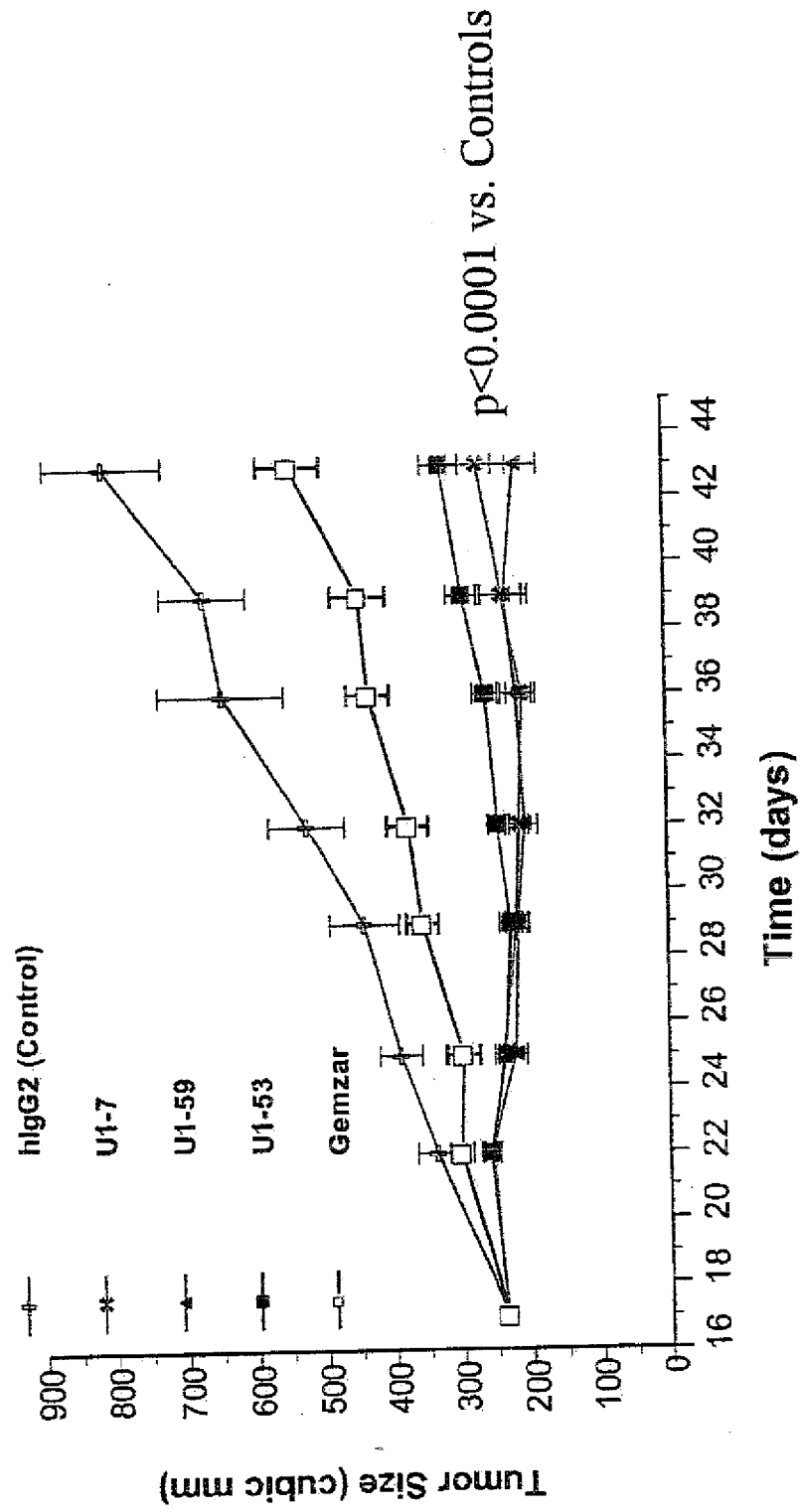


Fig. 20

