ANTI-IGFR1 ANTIBODY THERAPEUTIC COMBINATIONS

This application claims the benefit of U.S. Provisional Patent Application No. 60/524,732; filed November 21, 2003 which is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to therapeutic combinations comprising one or more anti-IGFR1 antibodies and one or more chemotherapeutic agents.

BACKGROUND OF THE INVENTION

The insulin-like growth factors, also known as somatomedins, include insulin-like growth factor-I (IGF-I) and insulin-like growth factor-II (IGF-II) (Klapper, *et al.*, (1983) Endocrinol. 112:2215 and Rinderknecht, *et al.*, (1978) Febs.Lett. 89:283). These growth factors exert mitogenic activity on various cell types, including tumor cells (Macaulay, (1992) Br. J. Cancer 65:311), by binding to a common receptor named the insulin-like growth factor receptor-1 (IGFR1) (Sepp-Lorenzino, (1998) Breast Cancer Research and Treatment 47:235). Interaction of IGFs with IGFR1 activates the receptor by triggering autophosphorylation of the receptor on tyrosine residues (Butler, *et al.*, (1998) Comparative Biochemistry and Physiology 121:19). Once activated, IGFR1, in turn, phosphorylates intracellular targets to activate cellular signaling pathways. This receptor activation is critical for stimulation of tumor cell growth and survival. Therefore, inhibition of IGFR1 activity represents a valuable potential method to treat or prevent growth of human cancers and other proliferative diseases.

Several lines of evidence indicate that IGF-I, IGF-II and their receptor IGFR1 are important mediators of the malignant phenotype. Plasma levels of IGF-I have been found to be the strongest predictor of prostate cancer risk (Chan, *et al.*, (1998) Science 279:563) and similar epidemiological studies strongly link plasma IGF-I levels with breast, colon and lung cancer risk.

Overexpression of Insulin-like Growth Factor Receptor-I has also been demonstrated in several cancer cell lines and tumor tissues. IGFR1 is overexpressed in 40% of all breast cancer cell lines (Pandini, *et al.*, (1999) Cancer Res. 5:1935) and in 15% of lung cancer cell lines. In breast cancer tumor tissue, IGFR1 is overexpressed 6-14 fold and IGFR1 exhibits 2-4 fold higher kinase activity as compared to normal tissue (Webster, *et al.*, (1996) Cancer Res. 56:2781 and Pekonen, *et al.*, (1998) Cancer Res. 48:1343).

Moreover, colorectal cancer tissue has been reported to exhibit strongly elevated IGFR1 levels (Weber *et al.*, Cancer 95(10):2086-95 (2002)). Analysis of primary cervical cancer cell cultures and cervical cancer cell lines revealed 3- and 5-fold overexpression of IGFR1, respectively, as compared to normal ectocervical cells (Steller, *et al.*, (1996) Cancer Res. 56:1762). Expression of IGFR1 in synovial sarcoma cells also correlated with an aggressive phenotype (*i.e.*, metastasis and high rate of proliferation; Xie, *et al.*, (1999) Cancer Res. 59:3588).

Acromegaly, a slowly developing disease, is caused by hypersecretion of growth hormone and IGF-I (Ben-Schlomo, *et al.*, (2001) Endocrin. Metab.Clin. North. Am. 30:565-583). Antagonism of IGFR1 function is helpful in treating the disease.

There are several antibodies, which are known in the art, which inhibit the activity of IGFR1. However, these are of relatively low therapeutic value. For example, α-IR3 (Kull, *et al.*, (1983) J. Biol. Chem. 258:6561), 1H7 (Li *et al.*, (1993) Biochem. Biophys. Res. Comm. 196.92-98 and Xiong *et al.*, (1992) Proc. Natl. Acad. Sci., U.S.A. 89:5356-5360; Santa Cruz biotechnology, Inc.; Santa Cruz, CA) and MAB391 (R&D Systems; Minneapolis, MN) are mouse monoclonal antibodies which interact with IGFR1 and inhibit its activity. Since these are mouse antibodies, their therapeutic utility in humans is limited. When an immunocompetent human subject is administered a dose of a murine antibody, the subject produces antibodies against the mouse immunoglobulin sequences. These human anti-mouse antibodies (HAMA) neutralize the therapeutic antibodies and may induce acute toxicity (*i.e.*, a HAMA response).

One method by which to avert a HAMA response is through the use of fully human antibodies which lack any foreign (*e.g.*, mouse) amino acid sequences. Although the use of fully-human antibodies is an effective method by which to reduce or prevent human host immune rejection of the therapeutic antibody, rejection of the fully-human antibody can occur. Human rejection of human antibodies may be referred to as a human anti-human antibody response (HAHA response). HAHA response can be mediated by factors such as the presence of rare, low occurrence amino acid sequences in the fully-human antibodies. For this reason, therapeutic antibodies can also be optimized by the inclusion of non-immunogenic or only weakly immunogenic human antibody framework sequences. Preferably, the sequences occur frequently in other human antibodies.

Although anti-IGFR1 antibodies are an effective means by which to treat medical conditions mediated by the receptor (*e.g.*, cancer or acromegaly), the efficacy of such treatments would be enhanced by use of one or more additional chemotherapeutic

agents. For example, an anti-IGFR1 antibody can be administered to a subject in association with a second anti-IGFR1 antibody or a small molecule IGFR1 antagonist. The present invention provides, *inter alia*, such treatments and compositions for use in the treatments.

SUMMARY OF THE INVENTION

The present invention provides a combination comprising (a) one or more binding compositions, such as any anti-IGFR1 antibody, preferably an isolated fully-human monoclonal antibody, preferably comprising a member selected from the group consisting of: (i) a light chain amino acid sequence which comprises CDR-L1 defined by SEQ ID NO: 5, CDR-L2 defined by SEQ ID NO: 6 and CDR-L3 defined by SEQ ID NO: 7; and (ii) a heavy chain amino acid sequence which comprises CDR-H1 defined by SEQ ID NO: 8 , CDR-H2 defined by SEQ ID NO: 9 and CDR-H3 defined by SEQ ID NO: 10; in association with (b) one or more chemotherapeutic agents and, optionally, a pharmaceutically acceptable carrier.

In one embodiment, a binding composition (*e.g.*, an isolated fully-human monoclonal antibody) comprises a light chain amino acid sequence which comprises CDR-L1 defined by SEQ ID NO: 5, CDR-L2 defined by SEQ ID NO: 6 and CDR-L3 defined by SEQ ID NO: 7; and a heavy chain amino acid sequence which comprises CDR-H1 defined by SEQ ID NO: 8 , CDR-H2 defined by SEQ ID NO: 9 and CDR-H3 defined by SEQ ID NO: 10. In an embodiment, a binding composition comprises a light chain immunoglobulin comprising mature LCF (amino acids 20-128 of SEQ ID NO: 2) and a heavy chain immunoglobulin comprising mature HCA (amino acids 20-137 of SEQ ID NO: 4).

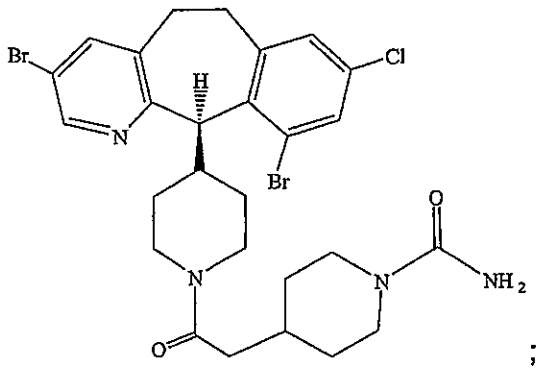
A binding composition can be any binding composition (*e.g.*, an isolated fully-human monoclonal antibody) set forth in U.S. Patent Application No. 10/443,466, filed May 22, 2003.

A chemotherapeutic agent can be one or more members selected from the group consisting of a taxane, a topoisomerase inhibitor, a signal transduction inhibitor, a cell cycle inhibitor, an IGF/IGFR1 system modulator, a farnesyl protein transferase (FPT) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a HER2 inhibitor, a vascular epidermal growth factor (VEGF) receptor inhibitor, a mitogen activated protein (MAP) kinase inhibitor, a MEK inhibitor, an AKT inhibitor, a, mTOR inhibitor, a pI3 kinase inhibitor, a Raf inhibitor, a cyclin dependent kinase (CDK) inhibitor, a microtubule

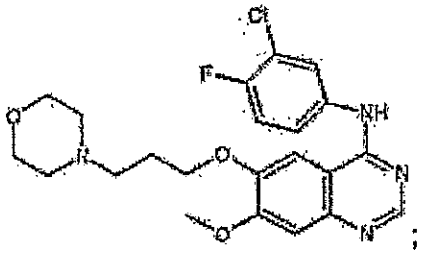
stabilizer, a microtubule inhibitor, a SERM/Antiestrogen, an aromatase inhibitor, an anthracycline, a proteasome inhibitor, an agent which inhibits insulin-like growth factor (IGF) production and/or an anti-sense inhibitor of IGFR1, IGF-1 or IGF2.

A taxane can be, for example, paclitaxel or docetaxel. A microtubule inhibitor can be, for example, vincristine, vinblastine, a podophyllotoxin, epothilone B, BMS-247550 or BMS-310705. An epidermal growth factor receptor (EGFR) inhibitor can be, for example, gefitinib, erlotinib, cetuximab, ABX-EGF, lapatanib, canertinib, EKB-569 or PKI-166. A farnesyl protein transferase inhibitor can be, for example, lonafarnib or tipifarnib (R155777). A selective estrogen receptor modulator (SERM)/antiestrogen can be, for example, tamoxifen, raloxifene, fulvestrant, acolbifene, pipendoxifene, arzoxifene, toremifene, lasofoxifene, bazedoxifene (TSE-424), idoxifene, HMR-3339 and ZK-186619. An anthracycline can be doxorubicin, daunorubicin or epirubicin. A HER2 inhibitor can be, for example, trastuzumab, HKI-272, CP-724714 or TAK-165. A topoisomerase inhibitor can be, for example, etoposide, topotecan, camptothecin or irinotecan.

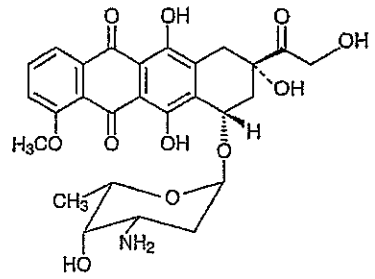
In one embodiment, the present invention comprises a combination comprising: (a) one or more binding compositions (*e.g.*, an isolated fully-human monoclonal antibody) comprising a light chain immunoglobulin comprising amino acids 20-128 of SEQ ID NO: 2 and a heavy chain immunoglobulin comprising amino acids 20-137 of SEQ ID NO: 4; in association with (b) one or more chemotherapeutic agents selected from:



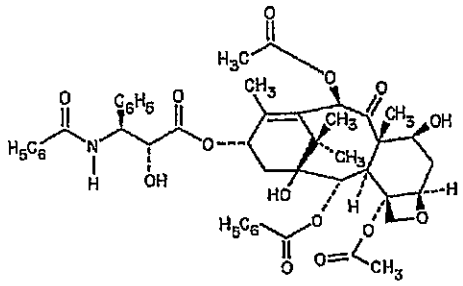
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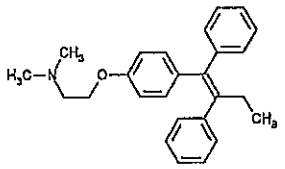
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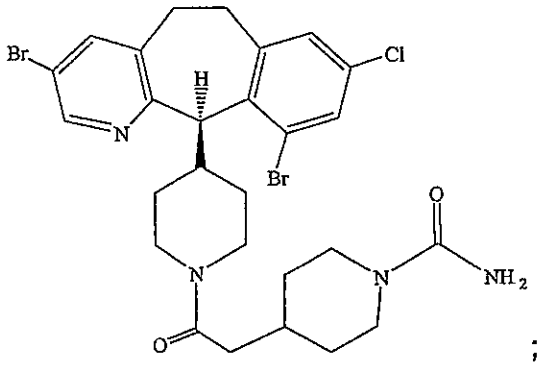
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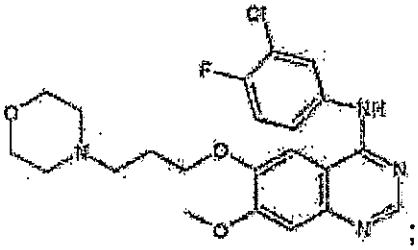
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Also provided by the present invention is a method for treating or preventing a medical condition in a subject, which medical condition is mediated by elevated expression or activity of Insulin-like Growth Factor Receptor-I, comprising administering (*e.g.*, by a parenteral or non-parenteral route), to the subject, a composition comprising a therapeutically effective amount of (a) one or more binding compositions (*e.g.*, an isolated fully-human monoclonal antibody), such as any anti-IGFR1 antibody, preferably comprising a member selected from the group consisting of: (i) a light chain amino acid sequence which comprises CDR-L1 defined by SEQ ID NO: 5, CDR-L2 defined by SEQ ID NO: 6 and CDR-L3 defined by SEQ ID NO: 7; and (ii) a heavy chain amino acid sequence which comprises CDR-H1 defined by SEQ ID NO: 8 , CDR-H2 defined by SEQ ID NO: 9 and CDR-H3 defined by SEQ ID NO: 10; optionally in association with (b) a therapeutically effective amount of one or more chemotherapeutic agents and, optionally, a pharmaceutically acceptable carrier. In an embodiment of the invention, the medical condition is treated with a therapeutically effective amount of any isolated anti-IGFR antibody or antigen binding fragment thereof of the invention alone.

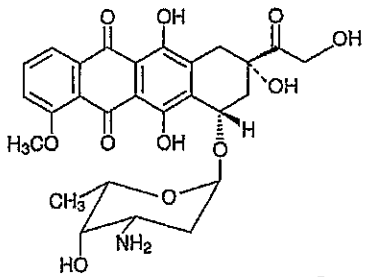
In one embodiment, the binding composition (*e.g.*, an isolated fully-human monoclonal antibody) comprises a light chain immunoglobulin comprising amino acids 20-128 of SEQ ID NO: 2 and a heavy chain immunoglobulin comprising amino acids of 20-137 of SEQ ID NO: 4. In one embodiment, a chemotherapeutic agent is one or more members selected from the group consisting of:

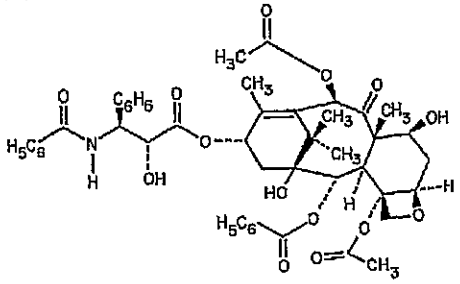


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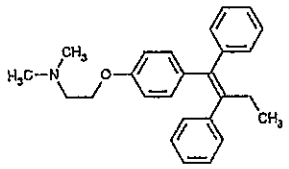
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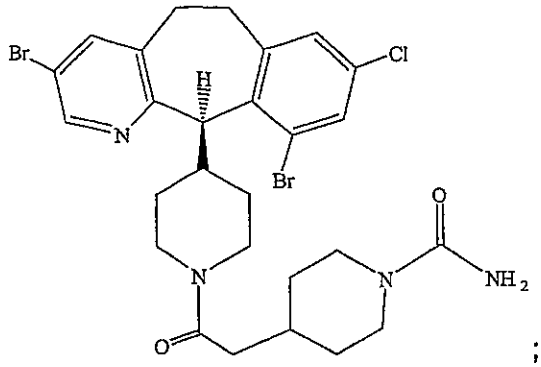
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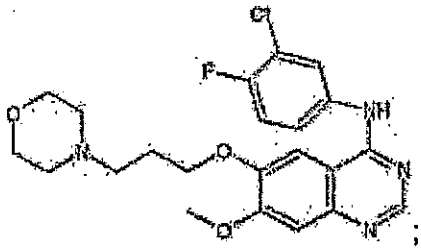


In one embodiment, the medical condition treated by a method of the present invention is selected from the group consisting of Rheumatoid Arthritis, Grave's disease, Multiple Sclerosis, Systemic Lupus Erythematosus, Hashimoto's Thyroiditis, Myasthenia Gravis, Auto-Immune Thyroiditis, Bechet's disease, acromegaly, bladder cancer, Wilm's cancer, ovarian cancer, pancreatic cancer, benign prostatic hyperplasia, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer, cervical cancer, synovial sarcoma, diarrhea associated with metastatic carcinoid, vasoactive intestinal peptide secreting tumors, gigantism, psoriasis, atherosclerosis, smooth muscle restenosis of blood vessels and inappropriate microvascular proliferation.

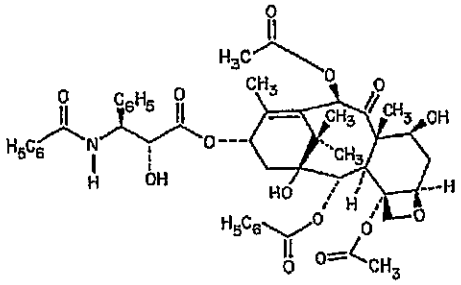
An embodiment of the present invention includes a method for treating or preventing a medical condition in a subject (*e.g.*, rheumatoid arthritis, Grave's disease, multiple sclerosis, systemic lupus erythematosus, Hashimoto's Thyroiditis, Myasthenia Gravis, auto-immune thyroiditis, Bechet's disease, acromegaly, bladder cancer, Wilm's cancer, ovarian cancer, pancreatic cancer, benign prostatic hyperplasia, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer, cervical cancer, synovial sarcoma, diarrhea associated with metastatic carcinoid, vasoactive intestinal peptide secreting tumors, gigantism, psoriasis, atherosclerosis, smooth muscle restenosis of blood vessels or inappropriate microvascular proliferation) comprising administering a combination comprising: (a) a therapeutically effective amount of one or more binding compositions (*e.g.*, an isolated fully-human monoclonal antibody) comprising a light chain immunoglobulin comprising amino acids 20-128 of SEQ ID NO: 2 and a heavy chain immunoglobulin comprising amino acids 20-137 of SEQ ID NO: 4; in association with (b) a therapeutically effective amount of one or more chemotherapeutic agents selected from:



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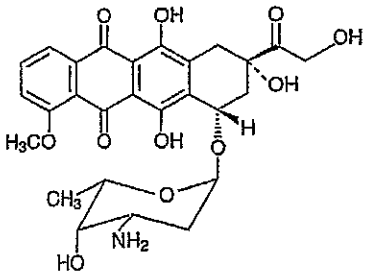


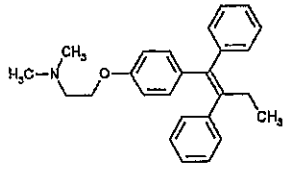
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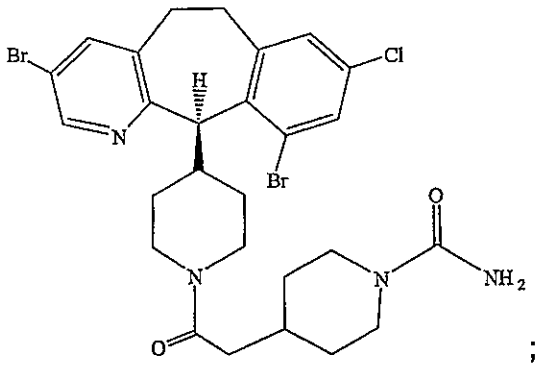




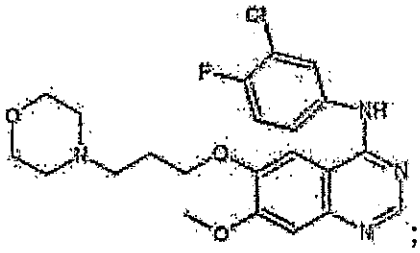
to the subject.

Also provided by the present invention is a method for inhibiting the growth or proliferation of any cell (*e.g.*, a cell *in vitro* or a cell *in vivo* (*e.g.*, in the body of a subject)), for example a malignant cell, including, but not limited to, an NCI-H322 cell, an A2780

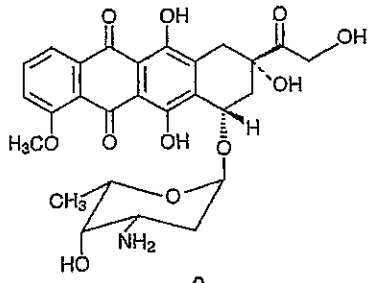
cell, an MCF7 cell, a non-small cell carcinoma lung cancer cell, a breast cancer cell, an ovarian cancer cell, a colorectal cancer cell, a prostate cancer cell, a pediatric cancer or a pancreatic cancer cell, comprising contacting the cell with a combination comprising (a) one or more binding compositions, such as any isolated anti-IGFR1 antibody, preferably an isolated fully-human monoclonal antibody, preferably comprising a member selected from the group consisting of: (i) a light chain amino acid sequence which comprises CDR-L1 defined by SEQ ID NO: 5, CDR-L2 defined by SEQ ID NO: 6 and CDR-L3 defined by SEQ ID NO: 7; and (ii) a heavy chain amino acid sequence which comprises CDR-H1 defined by SEQ ID NO: 8 , CDR-H2 defined by SEQ ID NO: 9 and CDR-H3 defined by SEQ ID NO: 10; in association with (b) one or more chemotherapeutic agents and, optionally, a pharmaceutically acceptable carrier. In one embodiment, a binding composition comprises a light chain immunoglobulin comprising amino acids 20-128 of SEQ ID NO: 2 and a heavy chain immunoglobulin comprising amino acids of 20-137 of SEQ ID NO: 4. In one embodiment, a chemotherapeutic agent is one or more members selected from the group consisting of:

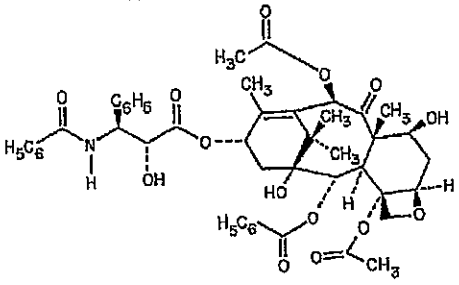


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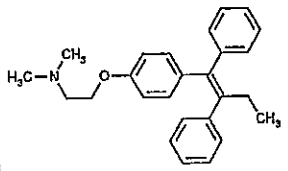


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The present invention also provides a kit comprising (a) one or more binding compositions (*e.g.*, an isolated fully-human monoclonal antibody) comprising a member selected from the group consisting of: a light chain amino acid sequence which comprises CDR-L1 defined by SEQ ID NO: 5, CDR-L2 defined by SEQ ID NO: 6 and CDR-L3 defined by SEQ ID NO: 7; and a heavy chain amino acid sequence which comprises CDR-H1 defined by SEQ ID NO: 8 or 12 , CDR-H2 defined by SEQ ID NO: 9 and CDR-H3 defined by SEQ ID NO: 10; in association with (b) one or more chemotherapeutic agents. The binding composition can be in a separate container from the chemotherapeutic agent.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides combinations and methods for treating medical conditions that are characterized by a high level of IGFR1 expression, ligand binding or activity or a high level of IGF-1 or IGF-2, such as cancer. The combinations of the invention, which can be used to treat the medical conditions, include one or more anti-IGFR1 antibodies (*e.g.*, an isolated fully-human monoclonal antibody) in association with one or more chemotherapeutic agents.

The combinations of the invention include the binding composition component and chemotherapeutic agent component "in association" with one another. The term "in

association" indicates that the components of the combinations of the invention can be formulated into a single composition for simultaneous delivery or formulated separately into two or more compositions (*e.g.*, a kit). Furthermore, each component of a combination of the invention can be administered to a subject at a different time than when the other component is administered; for example, each administration may be given non-simultaneously at several intervals over a given period of time. Moreover, the separate components may be administered to a subject by the same or by a different route (*e.g.*, orally, intravenously, intratumorally).

The compositions of the invention provide a particularly effective means for treating diseases mediated by IGFR1, IGF-1 and/or IGF-2. The therapeutic efficacy of both the binding composition of the invention and the chemotherapeutic agent(s), when administered in association, is far superior to that of either component alone.

The present invention includes any isolated nucleic acid or isolated polypeptide (*e.g.*, an isolated fully-human monoclonal antibody) which comprises one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7 or 8) of any of the nucleic acids or polypeptides (including mature fragments thereof) set forth, below, in Table 1.

Table 1. Summary of amino acid and nucleotide sequences of the invention.

Sequence	Sequence Identifier
19D12/15H12 light chain F (LCF) variable region polynucleotide sequence	SEQ ID NO: 1
19D12/15H12 light chain F variable region polypeptide sequence	SEQ ID NO: 2
19D12/15H12 heavy chain A (HCA) variable region polynucleotide sequence	SEQ ID NO: 3
19D12/15H12 heavy chain A variable region polypeptide sequence	SEQ ID NO: 4
19D12/15H12 light chain F CDR-L1 polypeptide sequence	SEQ ID NO: 5
19D12/15H12 light chain F CDR-L2 polypeptide sequence	SEQ ID NO: 6
19D12/15H12 light chain F CDR-L3 polypeptide sequence	SEQ ID NO: 7
19D12/15H12 heavy chain A CDR-H1 polypeptide sequence	SEQ ID NO: 8
19D12/15H12 heavy chain A CDR-H2 polypeptide sequence	SEQ ID NO: 9
19D12/15H12 heavy chain A CDR-H3 polypeptide sequence	SEQ ID NO: 10
Amino acid sequence of Insulin-like Growth Factor Receptor-I (IGFR1)	SEQ ID NO: 11
Alternative 19D12/15H12 heavy chain A	SEQ ID NO: 12

CDR-H1 polypeptide sequence	
19D12/15H12 light chain polypeptide sequence	SEQ ID NO: 13
19D12/15H12 heavy chain polypeptide sequence	SEQ ID NO: 14

Molecular Biology

In accordance with the present invention there may be employed conventional molecular biology, microbiology, and recombinant DNA techniques within the skill of the art. Such techniques are explained fully in the literature. See, *e.g.*, Sambrook, Fritsch & Maniatis, Molecular Cloning: A Laboratory Manual, Second Edition (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York (herein "Sambrook, *et al.*, 1989"); DNA Cloning: A Practical Approach, Volumes I and II (D.N. Glover ed. 1985); Oligonucleotide Synthesis (M.J. Gait ed. 1984); Nucleic Acid Hybridization (B.D. Hames & S.J. Higgins eds. (1985)); Transcription And Translation (B.D. Hames & S.J. Higgins, eds. (1984)); Animal Cell Culture (R.I. Freshney, ed. (1986)); Immobilized Cells And Enzymes (IRL Press, (1986)); B. Perbal, A Practical Guide To Molecular Cloning (1984); F.M. Ausubel, *et al.* (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, Inc. (1994).

A "polynucleotide", "nucleic acid" or "nucleic acid molecule" may refer to the phosphate ester polymeric form of ribonucleosides (adenosine, guanosine, uridine or cytidine; "RNA molecules") or deoxyribonucleosides (deoxyadenosine, deoxyguanosine, deoxythymidine, or deoxycytidine; "DNA molecules"), or any phosphoester analogs thereof, such as phosphorothioates and thioesters, in single stranded form, double-stranded form or otherwise.

A "polynucleotide sequence", "nucleic acid sequence" or "nucleotide sequence" is a series of nucleotide bases (also called "nucleotides") in a nucleic acid, such as DNA or RNA, and means any chain of two or more nucleotides.

A "coding sequence" or a sequence "encoding" an expression product, such as a RNA, polypeptide, protein, or enzyme, is a nucleotide sequence that, when expressed, results in production of the product.

The term "gene" means a DNA sequence that codes for or corresponds to a particular sequence of ribonucleotides or amino acids which comprise all or part of one or more RNA molecules, proteins or enzymes, and may or may not include regulatory DNA sequences, such as promoter sequences, which determine, for example, the conditions

under which the gene is expressed. Genes may be transcribed from DNA to RNA which may or may not be translated into an amino acid sequence.

"Amplification" of DNA as used herein may denote the use of polymerase chain reaction (PCR) to increase the concentration of a particular DNA sequence within a mixture of DNA sequences. For a description of PCR see Saiki, *et al.*, Science (1988) 239: 487. In a specific embodiment, the present invention includes a nucleic acid, which encodes an anti-IGFR1 antibody, an anti-IGFR1 antibody heavy or light chain, an anti-IGFR1 antibody heavy or light chain variable region, an anti-IGFR1 antibody heavy or light chain constant region or anti-IGFR1 antibody CDR (*e.g.*, CDR- L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2 or CDR-H3) which can be amplified by PCR.

As used herein, the term "oligonucleotide" refers to a nucleic acid, generally of at least 10 (*e.g.*, 10, 11, 12, 13 or 14), preferably at least 15 (*e.g.*, 15, 16, 17, 18 or 19), and more preferably at least 20 nucleotides (*e.g.*, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30), preferably no more than 100 nucleotides (*e.g.*, 40, 50, 60, 70, 80 or 90), that may be hybridizable to a genomic DNA molecule, a cDNA molecule, or an mRNA molecule encoding a gene, mRNA, cDNA, or other nucleic acid of interest. Oligonucleotides can be labeled, *e.g.*, by incorporation of ^{32}P-nucleotides, ^{3}H-nucleotides, ^{14}C-nucleotides, ^{35}S-nucleotides or nucleotides to which a label, such as biotin, has been covalently conjugated. In one embodiment, a labeled oligonucleotide can be used as a probe to detect the presence of a nucleic acid. In another embodiment, oligonucleotides (one or both of which may be labeled) can be used as PCR primers, either for cloning full length or a fragment of the gene, or to detect the presence of nucleic acids. Generally, oligonucleotides are prepared synthetically, preferably on a nucleic acid synthesizer.

The sequence of any nucleic acid (*e.g.*, a nucleic acid encoding an IGFR1 gene or a nucleic acid encoding an anti-IGFR1 antibody or a fragment or portion thereof) may be determined by any method known in the art (*e.g.*, chemical sequencing or enzymatic sequencing). "Chemical sequencing" of DNA may denote methods such as that of Maxam and Gilbert (1977) (Proc. Natl. Acad. Sci. USA 74:560), in which DNA is randomly cleaved using individual base-specific reactions. "Enzymatic sequencing" of DNA may denote methods such as that of Sanger (Sanger, *et al.*, (1977) Proc. Natl. Acad. Sci. USA 74:5463).

The nucleic acids herein may be flanked by natural regulatory (expression control) sequences, or may be associated with heterologous sequences, including promoters, internal ribosome entry sites (IRES) and other ribosome binding site sequences,

enhancers, response elements, suppressors, signal sequences, polyadenylation sequences, introns, 5'- and 3'- non-coding regions, and the like.

A "promoter" or "promoter sequence" is a DNA regulatory region capable of binding an RNA polymerase in a cell (*e.g.*, directly or through other promoter-bound proteins or substances) and initiating transcription of a coding sequence (*e.g.*, LCF or HCA). A promoter sequence is, in general, bounded at its 3' terminus by the transcription initiation site and extends upstream (5' direction) to include the minimum number of bases or elements necessary to initiate transcription at any level. Within the promoter sequence may be found a transcription initiation site (conveniently defined, for example, by mapping with nuclease S1), as well as protein binding domains (consensus sequences) responsible for the binding of RNA polymerase. The promoter may be operably associated with other expression control sequences, including enhancer and repressor sequences or with a nucleic acid of the invention. Promoters which may be used to control gene expression include, but are not limited to, cytomegalovirus (CMV) promoter (U.S. Patent Nos. 5,385,839 and 5,168,062), the SV40 early promoter region (Benoist, *et al.*, (1981) Nature 290:304-310), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto, *et al.*, (1980) Cell 22:787-797), the herpes thymidine kinase promoter (Wagner, *et al.*, (1981) Proc. Natl. Acad. Sci. USA 78:1441-1445), the regulatory sequences of the metallothionein gene (Brinster, *et al.*, (1982) Nature 296:39-42); prokaryotic expression vectors such as the β-lactamase promoter (Villa-Komaroff, *et al.*, (1978) Proc. Natl. Acad. Sci. USA 75:3727-3731), or the *tac* promoter (DeBoer, *et al.*, (1983) Proc. Natl. Acad. Sci. USA 80:21-25); see also "Useful proteins from recombinant bacteria" in Scientific American (1980) 242:74-94; and promoter elements from yeast or other fungi such as the *Gal 4* promoter, the *ADC* (alcohol dehydrogenase) promoter, *PGK* (phosphoglycerol kinase) promoter or the alkaline phosphatase promoter.

A coding sequence is "under the control of", "functionally associated with" or "operably associated with" transcriptional and translational control sequences in a cell when the sequences direct RNA polymerase mediated transcription of the coding sequence into RNA, preferably mRNA, which then may be trans-RNA spliced (if it contains introns) and, optionally, translated into a protein encoded by the coding sequence.

The terms "express" and "expression" mean allowing or causing the information in a gene, RNA or DNA sequence to become manifest; for example, producing a protein by activating the cellular functions involved in transcription and translation of a corresponding

gene. A DNA sequence is expressed in or by a cell to form an "expression product" such as an RNA (*e.g.*, mRNA) or a protein. The expression product itself may also be said to be "expressed" by the cell.

The terms "vector", "cloning vector" and "expression vector" mean the vehicle (*e.g.*, a plasmid) by which a DNA or RNA sequence can be introduced into a host cell, so as to transform the host and, optionally, promote expression and/or replication of the introduced sequence.

The term "transfection" or "transformation" means the introduction of a nucleic acid into a cell. These terms may refer to the introduction of a nucleic acid encoding an anti-IGFR1 antibody or fragment thereof into a cell. The introduced gene or sequence may be called a "clone". A host cell that receives the introduced DNA or RNA has been "transformed" and is a "transformant" or a "clone". The DNA or RNA introduced to a host cell can come from any source, including cells of the same genus or species as the host cell, or cells of a different genus or species.

The term "host cell" means any cell of any organism that is selected, modified, transfected, transformed, grown, or used or manipulated in any way, for the production of a substance by the cell, for example the expression or replication, by the cell, of a gene, a DNA or RNA sequence, a protein or an enzyme.

The term "expression system" means a host cell and compatible vector which, under suitable conditions, can express a protein or nucleic acid which is carried by the vector and introduced to the host cell. Common expression systems include *E. coli* host cells and plasmid vectors, insect host cells and Baculovirus vectors, and mammalian host cells and vectors. In a specific embodiment, IGFR1 or an antibody and antigen-binding fragment of the invention may be expressed in human embryonic kidney cells (HEK293). Other suitable cells include CHO (chinese hamster ovary) cells, HeLa cells and NIH 3T3 cells and NSO cells (non-Ig-producing murine myeloma cell line). Nucleic acids encoding an antibody or antigen-binding fragment of the invention, sIGFR1 (see *infra*) or IGFR1 may be expressed at high levels in an *E.coli*/T7 expression system as disclosed in U.S. Patent Nos. 4,952,496, 5,693,489 and 5,869,320 and in Davanloo, P., *et al.*, (1984) Proc. Natl. Acad. Sci. USA 81, 2035-2039; Studier, F. W., *et al.*, (1986) J. Mol. Biol. 189: 113-130; Rosenberg, A. H., *et al.*, (1987) Gene 56: 125-135; and Dunn, J. J., *et al.*, (1988) Gene 68: 259 which are herein incorporated by reference.

The present invention contemplates any superficial or slight modification to the amino acid or nucleotide sequences which correspond to the antibodies or antigen-

binding fragments of the invention. In particular, the present invention contemplates sequence conservative variants of the nucleic acids which encode the antibodies or antigen-binding fragments of the invention. "Sequence-conservative variants" of a polynucleotide sequence are those in which a change of one or more nucleotides in a given codon results in no alteration in the amino acid encoded at that position. Function-conservative variants of the antibodies of the invention are also contemplated by the present invention. "Function-conservative variants" are those in which one or more amino acid residues in a protein or enzyme have been changed without altering the overall conformation and function of the polypeptide, including, but, by no means, limited to, replacement of an amino acid with one having similar properties. Amino acids with similar properties are well known in the art. For example, polar/hydrophilic amino acids which may be interchangeable include asparagine, glutamine, serine, cysteine, threonine, lysine, arginine, histidine, aspartic acid and glutamic acid; nonpolar/hydrophobic amino acids which may be interchangeable include glycine, alanine, valine, leucine, isoleucine, proline, tyrosine, phenylalanine, tryptophan and methionine; acidic amino acids which may be interchangeable include aspartic acid and glutamic acid and basic amino acids which may be interchangeable include histidine, lysine and arginine.

The present invention includes anti-IGFR1 antibodies and fragments thereof which are encoded by nucleic acids as described in Table 1 as well as nucleic acids which hybridize thereto. Preferably, the nucleic acids hybridize under low stringency conditions, more preferably under moderate stringency conditions and most preferably under high stringency conditions and, preferably, exhibit IGFR1 binding activity. A nucleic acid molecule is "hybridizable" to another nucleic acid molecule, such as a cDNA, genomic DNA, or RNA, when a single stranded form of the nucleic acid molecule can anneal to the other nucleic acid molecule under the appropriate conditions of temperature and solution ionic strength (see Sambrook, *et al.*, *supra*). The conditions of temperature and ionic strength determine the "stringency" of the hybridization. Typical low stringency hybridization conditions include 55°C, 5X SSC, 0.1% SDS and no formamide; or 30% formamide, 5X SSC, 0.5% SDS at 42°C. Typical, moderate stringency hybridization conditions are similar to the low stringency conditions except the hybridization is carried out in 40% formamide, with 5X or 6X SSC and 0.1% SDS at 42°C. High stringency hybridization conditions are similar to low stringency conditions except the hybridization conditions are carried out in 50% formamide, 5X or 6X SSC at 42°C or, optionally, at a higher temperature (*e.g.*, 57 °C, 59 °C, 60 °C, 62 °C, 63 °C, 65°C or 68 °C). In general,

SSC is 0.15M NaC1 and 0.015M Na-citrate. Hybridization requires that the two nucleic acids contain complementary sequences, although, depending on the stringency of the hybridization, mismatches between bases are possible. The appropriate stringency for hybridizing nucleic acids depends on the length of the nucleic acids and the degree of complementation, variables well known in the art. The greater the degree of similarity or homology between two nucleotide sequences, the higher the stringency under which the nucleic acids may hybridize. For hybrids of greater than 100 nucleotides in length, equations for calculating the melting temperature have been derived (see Sambrook, *et al.*, *supra*, 9.50-9.51). For hybridization with shorter nucleic acids, *i.e.*, oligonucleotides, the position of mismatches becomes more important, and the length of the oligonucleotide determines its specificity (see Sambrook, *et al.*, *supra*, 11.7-11.8).

Also included in the present invention are nucleic acids comprising nucleotide sequences and polypeptides comprising amino acid sequences which are at least about 70% identical, preferably at least about 80% identical, more preferably at least about 90% identical and most preferably at least about 95% identical (*e.g.*, 95%, 96%, 97%, 98%, 99%, 100%) to the reference nucleotide and amino acid sequences of Table 1 when the comparison is performed by a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences. Polypeptides comprising amino acid sequences which are at least about 70% similar, preferably at least about 80% similar, more preferably at least about 90% similar and most preferably at least about 95% similar (*e.g.*, 95%, 96%, 97%, 98%, 99%, 100%) to any of the reference amino acid sequences of Table 1 when the comparison is performed with a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences, are also included in the present invention.

Sequence identity refers to exact matches between the nucleotides or amino acids of two sequences which are being compared. Sequence similarity refers to both exact matches between the amino acids of two polypeptides which are being compared in addition to matches between nonidentical, biochemically related amino acids. Biochemically related amino acids which share similar properties and may be interchangeable are discussed above.

The following references regarding the BLAST algorithm are herein incorporated by reference: **BLAST ALGORITHMS:** Altschul, S.F., *et al.*, (1990) J. Mol. Biol. 215:403-

410; Gish, W., *et al.*, (1993) Nature Genet. 3:266-272; Madden, T.L., *et al.*, (1996) Meth. Enzymol. 266:131-141; Altschul, S.F., *et al.*, (1997) Nucleic Acids Res. 25:3389-3402; Zhang, J., *et al.*, (1997) Genome Res. 7:649-656; Wootton, J.C., *et al.*, (1993) Comput. Chem. 17:149-163; Hancock, J.M. *et al.*, (1994) Comput. Appl. Biosci. 10:67-70; **ALIGNMENT SCORING SYSTEMS**: Dayhoff, M.O., *et al.*, "A model of evolutionary change in proteins." in Atlas of Protein Sequence and Structure, (1978) vol. 5, suppl. 3. M.O. Dayhoff (ed.), pp. 345-352, Natl. Biomed. Res. Found., Washington, DC; Schwartz, R.M., *et al.*, "Matrices for detecting distant relationships." in Atlas of Protein Sequence and Structure, (1978) vol. 5, suppl. 3." M.O. Dayhoff (ed.), pp. 353-358, Natl. Biomed. Res. Found., Washington, DC; Altschul, S.F., (1991) J. Mol. Biol. 219:555-565; States, D.J., *et al.*, (1991) Methods 3:66-70; Henikoff, S., *et al.*, (1992) Proc. Natl. Acad. Sci. USA 89:10915-10919; Altschul, S.F., *et al.*, (1993) J. Mol. Evol. 36:290-300; **ALIGNMENT STATISTICS**: Karlin, S., *et al.*, (1990) Proc. Natl. Acad. Sci. USA 87:2264-2268; Karlin, S., *et al.*, (1993) Proc. Natl. Acad. Sci. USA 90:5873-5877; Dembo, A., *et al.*, (1994) Ann. Prob. 22:2022-2039; and Altschul, S.F. "Evaluating the statistical significance of multiple distinct local alignments." in Theoretical and Computational Methods in Genome Research (S. Suhai, ed.), (1997) pp. 1-14, Plenum, New York.

Antibody Structure

In general, the basic antibody structural unit is known to comprise a tetramer. Each tetramer includes two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain may include a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain may define a constant region primarily responsible for effector function. Typically, human light chains are classified as kappa and lambda light chains. Furthermore, human heavy chains are typically classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. See generally, Fundamental Immunology Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)) (incorporated by reference in its entirety for all purposes).

The variable regions of each light/heavy chain pair form the antibody binding site. Thus, in general, an intact IgG antibody has two binding sites. Except in bifunctional or bispecific antibodies, the two binding sites are, in general, the same.

Normally, the chains all exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. The CDRs from the two chains of each pair are usually aligned by the framework regions, enabling binding to a specific epitope. In general, from N-terminal to C-terminal, both light and heavy chains comprise the domains FR1, CDR1, FR2 , CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is, generally, in accordance with the definitions of Sequences of Proteins of Immunological Interest, Kabat, *et al.*; National Institutes of Health, Bethesda, Md. ; 5th ed.; NIH Publ. No. 91-3242 (1991); Kabat (1978) Adv. Prot. Chem. 32:1-75; Kabat, *et al.*, (1977) J. Biol. Chem. 252:6609-6616; Chothia, *et al.*, (1987) J Mol. Biol. 196:901-917 or Chothia, *et al.*, (1989) Nature 342:878-883.

Binding Compositions

The binding compositions of the combinations of the present invention include any composition which binds specifically to IGFR1. A binding composition or agent refers to a molecule that binds with specificity to IGFR1, *e.g.*, in a ligand-receptor type fashion or an antibody-antigen interaction, *e.g.*, proteins which specifically associate with IGFR1, *e.g.*, in a natural physiologically relevant protein-protein interaction, either covalent or non-covalent. The term "binding composition" includes small organic molecules, nucleic acids and polypeptides, such as a full antibody (preferably an isolated monoclonal human antibody) or antigen-binding fragment thereof of the present invention (*e.g.*, antibody 19D12/15H12, antibody 19D12/15H12 LCF/HCA or any peptide set forth, above, in Table 1).

Antibodies and antigen binding fragments thereof, include, but are not limited to, monoclonal antibodies, polyclonal antibodies, bispecific antibodies, Fab antibody fragments, $F(ab)_2$ antibody fragments, Fv antibody fragments (*e.g.*, V_H or V_L), single chain Fv antibody fragments and dsFv antibody fragments. Furthermore, antibodies of the invention may be fully human antibodies or chimeric antibodies.

The combinations of the present invention include any antibody or antigen binding fragment thereof or any polynucleotide encoding such antibody or antigen-binding fragment thereof as set forth in U.S. Patent Application No. 10/443,466, filed May 22,

2003 and in WO 03/100008. Preferably, the antibody molecules are isolated monoclonal, fully human antibodies. Preferably the antibodies of the invention comprise one or more, more preferably all 6 CDRs comprising an amino acid sequence set forth in any one of SEQ ID NOs: 5-10. Preferably, an antibody of the invention includes mature 19D12/15H12 light chain F (LCF) (see SEQ ID NO: 2) paired with mature 19D12/15H12 heavy chain A (HCA) (see SEQ ID NO: 4) (*e.g.*, the monoclonal, fully-human antibody 19D12/15H12 LCF/HCA).

The amino acid and nucleotide sequences of preferred antibody chains are shown below. Dotted, underscored type indicates the signal peptide. Solid underscored type indicates the CDRs. Plain type indicates the framework regions. In one embodiment, the antibody chains are mature fragments which lack the signal peptide.

19D12/15H12 Light Chain-F (LCF; SEQ ID NO: 1)

ATG TCG CCA TCA CAA CTC ATT GGG TTT CTG CTG CTC TGG GTT CCA GCC TCC

AGG GGT GAA ATT GTG CTG ACT CAG AGC CCA GGT ACC CTG TCT GTG TCT CCA

GGC GAG AGA GCC ACC CTC TCC TGC CGG GCC AGT CAG AGC ATT GGT AGT AGC

TTA CAC TGG TAC CAG CAG AAA CCA GGT CAG GCT CCA AGG CTT CTC ATC AAG

TAT GCA TCC CAG TCC CTC TCA GGG ATC CCC GAT AGG TTC AGT GGC AGT GGA

TCT GGG ACA GAT TTC ACC CTC ACC ATC AGT AGA CTG GAG CCT GAA GAT TTC

GCA GTG TAT TAC TGT CAT CAG AGT AGT CGT TTA CCT CAC ACT TTC GGC CAA

GGG ACC AAG GTG GAG ATC AAA CGT ACA

(SEQ ID NO: 2)

M S P S Q L I G F L L L W V P A S

R G E I V L T Q S P G T L S V S P

G E R A T L S C R A S Q S I G S S

L H W Y Q Q K P G Q A P R L L I K

Y A S Q S L S G I P D R F S G S G

S G T D F T L T I S R L E P E D F

A V Y Y C H Q S S R L P H T F G Q

G T K V E I K R T

19D12/15H12 heavy chain-A (HCA; SEQ ID NO: 3)

ATG GAG TTT GGG CTG AGC TGG GTT TTC CTT GTT GCT ATA TTA AAA GGT GTC
CAG TGT GAG GTT CAG CTG GTG CAG TCT GGG GGA GGC TTG GTA AAG CCT GGG
GGG TCC CTG AGA CTC TCC TGT GCA GCC TCT GGA TTC ACC TTC AGT AGC TTT
GCT ATG CAC TGG GTT CGC CAG GCT CCA GGA AAA GGT CTG GAG TGG ATA TCA
GTT ATT GAT ACT CGT GGT GCC ACA TAC TAT GCA GAC TCC GTG AAG GGC CGA
TTC ACC ATC TCC AGA GAC AAT GCC AAG AAC TCC TTG TAT CTT CAA ATG AAC
AGC CTG AGA GCC GAG GAC ACT GCT GTG TAT TAC TGT GCA AGA CTG GGG AAC
TTC TAC TAC GGT ATG GAC GTC TGG GGC CAA GGG ACC ACG GTC ACC GTC TCC
TCA

(SEQ ID NO: 4)

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Leu Lys Gly Val
Gln Cys Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly
Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Ser
Val Ile Asp Thr Arg Gly Ala Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg
Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn
Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Leu Gly Asn
Phe Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
Ser

Three plasmids comprising a CMV promoter operably linked to the 15H12/19D12 LCF (κ) (variable region sequence set forth in SEQ ID NOs: 1 and 2), to the 15H12/19D12 HCA (γ4) (variable region sequence set forth in SEQ ID NOs: 3 and 4) or to the 15H12/19D12 HCA (γ1) (variable region sequence set forth in SEQ ID NOs: 3 and 4) has been deposited at the American Type Culture Collection (ATCC); 10801 University Boulevard; Manassas, Virginia 20110-2209 on May 21, 2003. The deposit name and the ATCC accession numbers for the plasmids are set forth below:

CMV promoter-15H12/19D12 HCA (γ4)-

Deposit name: "15H12/19D12 HCA (γ4)";

ATCC accession No.: PTA-5214;

CMV promoter-15H12/19D12 HCA (γ1)-

Deposit name: "15H12/19D12 HCA (γ4)";

ATCC accession No.: PTA-5216;

CMV promoter-15H12/19D12 LCF (κ)-

Deposit name: "15H12/19D12 LCF (κ)";

ATCC accession No.: PTA-5220.

All restrictions on access to the plasmids deposited in ATCC will be removed upon grant of a patent.

Each of the above-referenced plasmids constitutes part of the present invention. Further, the nucleic acid located within each expression cassette, along with the immunoglobulin variable region therein, along with the mature, processed version thereof (*i.e.*, lacking the signal sequence), particularly, SEQ ID NO: 3, mature HCA (nucleotides 58-411 of SEQ ID NO: 3), SEQ ID NO: 1 or mature LCF (nucleotides 58-384 of SEQ ID NO: 1), optionally including an immunoglobulin constant region, along with any polypeptide encoded by any of the foregoing nucleic acids, including mature or unprocessed chains, optionally including an immunoglobulin constant region, is a part of the present invention. Moreover, any antibody or antigen-binding fragment thereof comprising one of the encoded polypeptides is part of the present invention.

The scope of the present invention includes antibody variable regions of the present invention (*e.g.*, any variable region, mature or unprocessed, indicated in Table 1) linked to any immunoglobulin constant region. If a light chain variable region is linked to a constant region, preferably it is a κ chain. If a heavy chain variable region is linked to a constant region, preferably it is a γ1, γ2, γ3 or γ4 constant region, more preferably, γ1, γ2 or γ4 and even more preferably γ1 or γ4.

The anti-IGFR1 antibody molecules of the invention preferably recognize human IGFR1, preferably a soluble fragment of IGFR1 (*i.e.*, sIGFR1) such as amino acids 30-902 or SEQ ID NO: 11; however, the present invention includes antibody molecules which recognize IGFR1 from different species, preferably mammals (*e.g.*, mouse, rat, rabbit, sheep or dog).

The present invention also includes an anti-IGFR1 antibody (e.g., LCF/HCA) or antigen-binding fragments thereof which are complexed with IGFR1 or any fragment thereof (*e.g.*, sIGFR1, such as amino acids 30-902 of SEQ ID NO: 11) or with any cell which is expressing IGFR1 or any portion or fragment thereof on the cell surface (*e.g.*, HEK293 cells stably transformed with human *IGFR1* or MCF7 (*e.g.*, ATCC Cell Line No.

HTB-22)). Such complexes may be made by contacting the antibody or antibody fragment with IGFR1 or the IGFR1 fragment.

In a preferred embodiment, fully-human monoclonal antibodies directed against IGFR1 are generated using transgenic mice carrying parts of the human immune system rather than the mouse system. These transgenic mice, which may be referred to, herein, as "HuMAb" mice, contain a human immunoglobulin gene miniloci that encodes unrearranged human heavy (μ and γ) and κ light chain immunoglobulin sequences, together with targeted mutations that inactivate the endogenous μ and κ chain loci (Lonberg, N., *et al.*, (1994) Nature 368(6474): 856-859). Accordingly, the mice exhibit reduced expression of mouse IgM or κ, and in response to immunization, the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity human IgGκ monoclonal antibodies (Lonberg, N., *et al.*, (1994), *supra*; reviewed in Lonberg, N. (1994) Handbook of Experimental Pharmacology 113:49-101; Lonberg, N., *et al.*, (1995) Intern. Rev. Immunol. 13:65-93, and Harding, F., *et al.*, (1995) Ann. N. Y Acad. Sci 764:536-546). The preparation of HuMab mice is commonly known in the art and is described, for example, in Taylor, L., *et al.*, (1992) Nucleic Acids Research 20:6287-6295; Chen, J., *et al.*, (1993) International Immunology 5: 647-656; Tuaillon, *et al.*, (1993) Proc. Natl. Acad. Sci USA 90:3720-3724; Choi, *et al.*, (1993) Nature Genetics 4:117-123; Chen, J., *et al.*, (1993)EMBO J. 12: 821- 830; Tuaillon, *et al.*, (1994) J Immunol. 152:2912-2920; Lonberg, *et al.*, (1994) Nature 368(6474): 856-859; Lonberg, N. (1994) Handbook of Experimental Pharmacology 113:49-101; Taylor, L., *et al.*, (1994) International Immunology 6: 579-591; Lonberg, N., *et al.*, (1995) Intern. Rev. Immunol. Vol. 13: 65-93; Harding, F., *et al.*, (1995) Ann. N.Y Acad. Sci 764:536-546; Fishwild, D., *et al.*, (1996) Nature Biotechnology 14: 845-851 and Harding, *et al.*, (1995) Annals NY Acad. Sci. 764:536-546; the contents of all of which are hereby incorporated by reference in their entirety. See further, U.S. Patent Nos. 5,545,806; 5, 569,825; 5,625,126; 5,633,425; 5,789,650; 5,877,397; 5,661,016; 5,814,318; 5,874, 299; 5,770,429 and 5,545,807; and International Patent Application Publication Nos. WO 98/24884; WO 94/25585; WO 93/12227; WO 92/22645 and WO 92/03918 the disclosures of all of which are hereby incorporated by reference in their entity.

To generate fully human, monoclonal antibodies to IGFR1, HuMab mice can be immunized with an antigenic IGFR1 polypeptide, preferably amino acids 30-902 of SEQ ID NO: 11, as described by Lonberg, N., *et al.*, (1994) Nature 368(6474): 856-859; Fishwild, D., *et al.*, (1996) Nature Biotechnology 14: 845-851 and WO 98/24884.

Preferably, the mice will be 6-16 weeks of age upon the first immunization. For example, a purified preparation of IGFR1 or sIGFR1 can be used to immunize the HuMab mice intraperitoneally. The mice can also be immunized with whole HEK293 cells which are stably transfected with an *IGFR1* gene. An "antigenic IGFR1 polypeptide" may refer to an IGFR1 polypeptide of any fragment thereof, preferably amino acids 30-902 of SEQ ID NO: 11, which elicits an anti-IGFR1 immune response, preferably in HuMab mice.

In general, HuMAb transgenic mice respond well when initially immunized intraperitoneally (IP) with antigen in complete Freund's adjuvant, followed by every other week IP immunizations (usually, up to a total of 6) with antigen in incomplete Freund's adjuvant. Mice can be immunized, first, with cells expressing IGFR1 (*e.g.*, stably transfected HEK293 cells), then with a soluble fragment of IGFR1 (*e.g.*, amino acids 30-902 of SEQ ID NO: 11) and continually receive alternating immunizations with the two antigens. The immune response can be monitored over the course of the immunization protocol with plasma samples being obtained by retroorbital bleeds. The plasma can be screened for the presence of anti-IGFR1 antibodies, for example by ELISA, and mice with sufficient titers of immunoglobulin can be used for fusions. Mice can be boosted intravenously with antigen 3 days before sacrifice and removal of the spleen. It is expected that 2-3 fusions for each antigen may need to be performed. Several mice can be immunized for each antigen. For example, a total of twelve HuMAb mice of the HC07 and HC012 strains can be immunized.

Hybridoma cells which produce the monoclonal, fully human anti-IGFR1 antibodies may be produced by methods which are commonly known in the art. These methods include, but are not limited to, the hybridoma technique originally developed by Kohler, *et al.*, (1975) (Nature 256:495-497), as well as the trioma technique (Hering, *et al.*, (1988) Biomed. Biochim. Acta. 47:211-216 and Hagiwara, *et al.*, (1993) Hum. Antibod. Hybridomas 4:15), the human B-cell hybridoma technique (Kozbor, *et al.*, (1983) Immunology Today 4:72 and Cote, *et al.*, (1983) Proc. Natl. Acad. Sci. U.S.A 80:2026-2030), and the EBV-hybridoma technique (Cole, *et al.*, in Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc., pp. 77-96, 1985). Preferably, mouse splenocytes are isolated and fused with PEG to a mouse myeloma cell line based upon standard protocols. The resulting hybridomas may then be screened for the production of antigen-specific antibodies. For example, single cell suspensions of splenic lymphocytes from immunized mice may by fused to one-sixth the number of P3X63- Ag8.653 nonsecreting mouse myeloma cells (ATCC, CRL 1580) with 50% PEG. Cells may be plated at

approximately 2 x 10^5 cells/mL in a flat bottom microtiter plate, followed by a two week incubation in selective medium containing 20% fetal Clone Serum, 18% "653" conditioned media, 5% origen (IGEN), 4 mM L-glutamine, 1 mM L-glutamine, 1 mM sodium pyruvate, 5mM HEPES, 0.055 mM 2-mercaptoethanol, 50 units/ml penicillin, 50 mg/ml streptomycin, 50 mg/ml gentamycin and 1X HAT (Sigma; the HAT is added 24 hours after the fusion). After two weeks, cells may be cultured in medium in which the HAT is replaced with HT. Individual wells may then be screened by ELISA for human anti-IGFR1 monoclonal IgG antibodies. Once extensive hybridoma growth occurs, medium can be observed usually after 10-14 days. The antibody secreting hybridomas may be replated, screened again, and if still positive for human IgG, anti-IGFR1 monoclonal antibodies, can be subcloned at least twice by limiting dilution. The stable subclones may then be cultured *in vitro* to generate small amounts of antibody in tissue culture medium for characterization.

The anti-IGFR1 antibodies and antigen-binding fragments thereof of the present invention may also be produced recombinantly (*e.g.*, in an *E.coli*/T7 expression system as discussed above). In this embodiment, nucleic acids encoding the antibody molecules of the invention (*e.g.*, V_H or V_L) may be inserted into a pET-based plasmid and expressed in the *E.coli*/T7 system. There are several methods by which to produce recombinant antibodies which are known in the art. One example of a method for recombinant production of antibodies is disclosed in U.S. Patent No. 4,816,567, which is herein incorporated by reference. Transformation can be by any known method for introducing polynucleotides into a host cell. Methods for introduction of 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, biolistic injection and direct microinjection of the DNA into nuclei. In addition, nucleic acid molecules may be introduced into mammalian cells by viral vectors. Methods of transforming cells are well known in the art. See, for example, U.S. Patent Nos. 4,399,216; 4,912,040; 4,740,461 and 4,959,455.

Anti-IGFR1 antibodies can also be synthesized by any of the methods set forth in U.S. Patent No. 6,331,415.

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). These include, *inter alia*, Chinese hamster ovary (CHO) cells, NSO,

SP2 cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*e.g.*, Hep G2), A549 cells, 3T3 cells, HEK-293 cells and a number of other cell lines. Mammalian host cells include human, mouse, rat, dog, monkey, pig, goat, bovine, horse and hamster cells. Cell lines of particular preference are selected through determining which cell lines have high expression levels. Other cell lines that may be used are insect cell lines, such as Sf9 cells, amphibian cells, bacterial cells, plant cells and fungal cells. When recombinant expression vectors encoding the heavy chain or antigen-binding portion thereof, the light chain and/or antigen-binding portion thereof are introduced into mammalian host cells, the antibodies are produced by culturing the host cells for a period of time sufficient to allow for expression of the antibody in the host cells or, more preferably, secretion of the antibody into the culture medium in which the host cells are grown.

Antibodies can be recovered from the culture medium using standard protein purification methods. Further, expression of antibodies of the invention (or other moieties therefrom) from production cell lines can be enhanced using a number of known techniques. For example, the glutamine synthetase gene expression system (the GS system) is a common approach for enhancing expression under certain conditions. The GS system is discussed in whole or part in connection with European Patent Nos. 0 216 846, 0 256 055, and 0 323 997 and European Patent Application No. 89303964.4.

It is likely that antibodies expressed by different cell lines or in transgenic animals will have different glycosylation from each other. However, all antibodies encoded by the nucleic acid molecules provided herein, or comprising the amino acid sequences provided herein are part of the instant invention, regardless of the glycosylation of the antibodies.

The term "monoclonal antibody," as used herein, refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Monoclonal antibodies are advantageous in that they may be synthesized by a hybridoma culture, essentially uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being amongst a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. As mentioned above, the monoclonal antibodies to be used in accordance with the present invention

may be made by the hybridoma method first described by Kohler, *et al.*, (1975) Nature 256: 495.

A polyclonal antibody is an antibody which was produced among or in the presence of one or more other, non-identical antibodies. In general, polyclonal antibodies are produced from a B-lymphocyte in the presence of several other B-lymphocytes which produced non-identical antibodies. Usually, polyclonal antibodies are obtained directly from an immunized animal.

A bispecific or bifunctional antibody is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. See, *e.g.*, Songsivilai, *et al.*, (1990) Clin. Exp. Immunol. 79: 315-321, Kostelny, *et al.*, (1992) J Immunol. 148:1547- 1553. In addition, bispecific antibodies may be formed as "diabodies" (Holliger, *et al.*, (1993) PNAS USA 90:6444-6448) or as "Janusins" (Traunecker, *et al.*, (1991) EMBO J. 10:3655-3659 and Traunecker, *et al.*, (1992) Int. J. Cancer Suppl. 7:51-52).

The term "fully human antibody" refers to an antibody which comprises human immunoglobulin protein sequences only. A fully human antibody may contain murine carbohydrate chains if produced in a mouse, in a mouse cell or in a hybridoma derived from a mouse cell. Similarly, "mouse antibody" refers to an antibody which comprises mouse immunoglobulin sequences only.

The present invention includes "chimeric antibodies"- an antibody which comprises a variable region of the present invention fused or chimerized with an antibody region (*e.g.*, constant region) from another, non-human species (*e.g.*, mouse, horse, rabbit, dog, cow, chicken). These antibodies may be used to modulate the expression or activity of IGFR1 in the non-human species.

"Single-chain Fv" or "sFv" antibody fragments have the V_H and V_L domains of an antibody, wherein these domains are present in a single polypeptide chain. Generally, the sFv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the sFv to form the desired structure for antigen binding. Techniques described for the production of single chain antibodies (U.S. Patent Nos. 5,476,786; 5,132,405 and 4,946,778) can be adapted to produce anti-IGFR1-specific single chain antibodies. For a review of sFv see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore eds. Springer-Verlag, N.Y., pp. 269-315 (1994).

"Disulfide stabilized Fv fragments" and "dsFv" refer to antibody molecules comprising a variable heavy chain (V_H) and a variable light chain (V_L) which are linked by a disulfide bridge.

Antibody fragments within the scope of the present invention also include $F(ab)_2$ fragments which may be produced by enzymatic cleavage of an IgG by, for example, pepsin. Fab fragments may be produced by, for example, reduction of $F(ab)_2$ with dithiothreitol or mercaptoethylamine. A Fab fragment is a V_L-C_L chain appended to a V_H-C_{H1} chain by a disulfide bridge. A $F(ab)_2$ fragment is two Fab fragments which, in turn, are appended by two disulfide bridges. The Fab portion of an $F(ab)_2$ molecule includes a portion of the F_c region between which disulfide bridges are located.

An F_V fragment is a V_L or V_H region.

Depending on the amino acid sequences of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are at least five major classes of immunoglobulins: IgA, IgD, IgE, IgG and IgM, and several of these may be further divided into subclasses (isotypes), *e.g.* IgG-1, IgG-2, IgG-3 and IgG-4; IgA-1 and IgA-2.

The anti-IGFR1 antibody molecules of the invention may also be conjugated to a chemical moiety. The chemical moiety may be, *inter alia*, a polymer, a radionuclide or a cytotoxic factor. Preferably the chemical moiety is a polymer which increases the half-life of the antibody molecule in the body of a subject. Suitable polymers include, but are not limited to, polyethylene glycol (PEG) (*e.g.*, PEG with a molecular weight of 2kDa, 5 kDa, 10 kDa, 12kDa, 20 kDa, 30kDa or 40kDa), dextran and monomethoxypolyethylene glycol (mPEG). Lee, *et al.*, (1999) (Bioconj. Chem. 10:973-981) discloses PEG conjugated single-chain antibodies. Wen, *et al.*, (2001) (Bioconj. Chem. 12:545-553) disclose conjugating antibodies with PEG which is attached to a radiometal chelator (diethylenetriaminpentaacetic acid (DTPA)).

The antibodies and antibody fragments of the invention may also be conjugated with labels such as ^{99}Tc, ^{90}Y, ^{111}In, ^{32}P, ^{14}C, ^{125}I, ^{3}H, ^{131}I, ^{11}C, ^{15}O, ^{13}N, ^{18}F, ^{35}S, ^{51}Cr, ^{57}To, ^{226}Ra, ^{60}Co, ^{59}Fe, ^{57}Se, ^{152}Eu, ^{67}CU, ^{217}Ci, ^{211}At, ^{212}Pb, ^{47}Sc, ^{109}Pd, ^{234}Th, and ^{40}K, ^{157}Gd, ^{55}Mn, ^{52}Tr and ^{56}Fe.

The antibodies and antibody fragments of the invention may also be conjugated with fluorescent or chemilluminescent labels, including fluorophores such as rare earth chelates, fluorescein and its derivatives, rhodamine and its derivatives, isothiocyanate, phycoerythrin, phycocyanin, allophycocyanin, o-phthaladehyde, fluorescamine, ^{152}Eu,

dansyl, umbelliferone, luciferin, luminal label, isoluminal label, an aromatic acridinium ester label, an imidazole label, an acridimium salt label, an oxalate ester label, an aequorin label, 2,3-dihydrophthalazinediones, biotin/avidin, spin labels and stable free radicals.

The antibody molecules may also be conjugated to a cytotoxic factor such as diptheria toxin, *Pseudomonas aeruginosa* exotoxin A chain , ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins and compounds (*e.g.*, fatty acids), dianthin proteins, *Phytolacca americana* proteins PAPI, PAPII, and PAP-S, *momordica charantia* inhibitor, curcin, crotin, *saponaria officinalis* inhibitor, mitogellin, restrictocin, phenomycin, and enomycin.

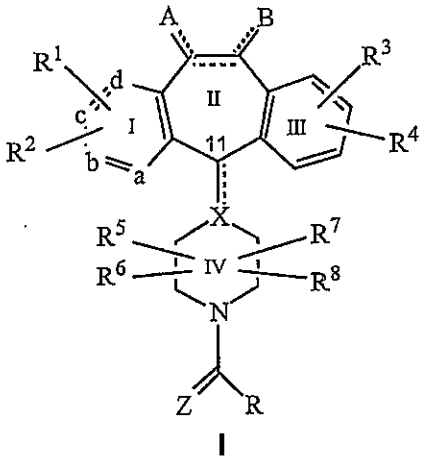
Any method known in the art for conjugating the antibody molecules of the invention to the various moieties may be employed, including those methods described by Hunter, *et al.*, (1962) Nature 144:945; David, *et al.*, (1974) Biochemistry 13:1014; Pain, *et al.*, (1981) J. Immunol. Meth. 40:219; and Nygren, J., (1982) Histochem. and Cytochem. 30:407. Methods for conjugating antibodies are conventional and very well known in the art.

Chemotherapeutic Agents

The present invention includes combinations and methods comprising one or more binding compositions, such as an anti-IGFR1 antibody or antigen-binding fragment thereof in association with one or more chemotherapeutic agents. A chemotherapeutic agent provides a therapeutic effect which is helpful in the treatment of any medical condition being treated by administration of a binding composition of the invention (*e.g.*, LCF/HCA). For example, if a binding composition is administered to treat cancer in a subject (*e.g.*, human), the chemotherapeutic agent(s) provide an additional anti-cancer therapeutic effect or some other therapeutic effect which will improve the subject's treatment outcome. The chemotherapeutic agent component of a combination of the invention can operate by any mechanism (*i.e.*, by the same mechanism by which the binding composition acts or by a different mechanism). Chemotherapeutic agents in the combinations and methods of the present invention include, but are, by no means, limited to, signal transduction inhibitors, cell cycle inhibitors, IGF/IGFR1 system modulators (*e.g.*, inhibitors or activators), farnesyl protein transferase (FPT) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, HER2 inhibitors, vascular epidermal growth factor (VEGF) receptor inhibitors, mitogen activated protein (MAP) kinase inhibitors, MEK

inhibitors, AKT inhibitors, mTOR inhibitors, pI3 kinase inhibitors, Raf inhibitors, cyclin dependent kinase (CDK) inhibitors, microtubule stabilizers, microtubule inhibitors, SERMs/Antiestrogens, aromatase inhibitors, anthracyclines, proteasome inhibitors and agents which inhibit insulin-like growth factor (IGF) production and anti-sense inhibitors of IGFR1, IGF-1 or IGF2.

FPT inhibitors including tricyclic amide compounds such as those disclosed in U.S. Patent No. 5,719,148 or in U.S. Patent No. 5,874,442 can be combined with an anti-IGFR antibody. For example, any compound represented by formula I, below, may be included in the combinations of the invention:



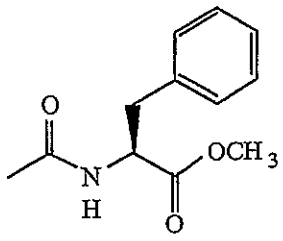
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or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or NR^9 wherein R^9 is O^-, $-CH_3$ or $-(CH_2)_nCO_2H$ wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR^1 or CR^2; or

each of a, b, c, and d are independently selected from CR^1 or CR^2;

each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{10}$ (*e.g.*, $-OCH_3$), $-COR^{10}$, $-SR^{10}$ (*e.g.*, $-SCH_3$ and $-SCH_2C_6H_5$), $-S(O)_tR^{11}$ (wherein t is 0, 1 or 2, e.g., $-SOCH_3$ and $-SO_2CH_3$), -SCN, $-N(R^{10})_2$, $-NR^{10}R^{11}$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, -CN, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, $-NR^{10}COOR^{11}$,



,

$-SR^{11}C(O)OR^{11}$ (e.g., $-SCH_2CO_2CH_3$), $-SR^{11}N(R^{75})_2$ wherein each R^{75} is independently selected from H and $-C(O)OR^{11}$ (e.g., $-S(CH_2)_2NHC(O)O$-t-butyl and $-S(CH_2)_2NH_2$), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio (e.g., alkyl substituted tetrazol5-ylthio such as 1-methyl-tetrazol-5-ylthio), alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, $-OR^{10}$ or $-CO_2R^{10}$;

R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring (Ring III);

R^5, R^6, R^7 and R^8 each independently represents H, $-CF_3$, $-COR^{10}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-OR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$, $-NR^{10}COOR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{11}$, $-CO_2R^{10}$, OPO_3R^{10} or one of R^5, R^6, R^7 and R^8 can be taken in combination with R^{40} as defined below to represent $-(CH_2)_r-$ wherein r is 1 to 4 which can be substituted with lower alkyl, lower alkoxy, $-CF_3$ or aryl, or R^5 is combined with R^6 to represent =O or =S and/or R^7 is combined with R^8 to represent =O or =S;

R^{10} represents H, alkyl, aryl, or aralkyl (e.g., benzyl);

R^{11} represents alkyl or aryl;

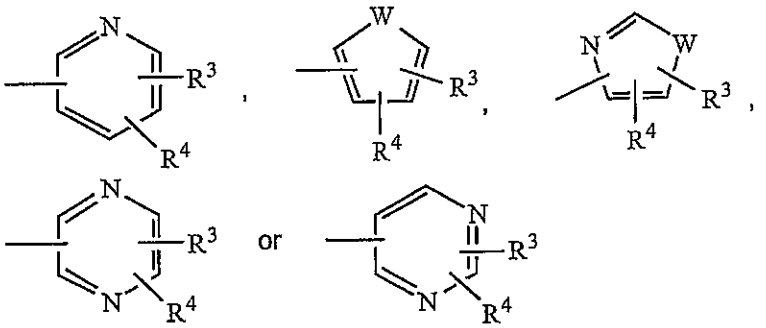
X represents N, CH or C, which C may contain an optional double bond (represented by the dotted line) to carbon atom 11;

the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent $-R^{10}$, halo, $-OR^{11}$, $-OCO_2R^{11}$ or $-OC(O)R^{10}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, $-(OR^{11})_2$; H and halo,

dihalo, alkyl and H, $(alkyl)_2$, -H and $-OC(O)R^{10}$, H and $-OR^{10}$, =O, aryl and H, $=NOR^{10}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4;

R represents R^{40}, R^{42}, R^{44}, or R^{54}, as defined below;

R^{40} represents H, aryl, alkyl, cycloalkyl, alkenyl, alkynyl or -D wherein -D represents

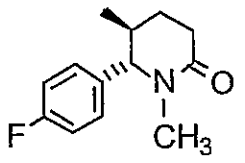
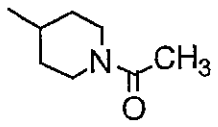
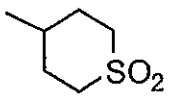
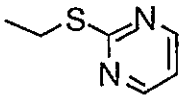


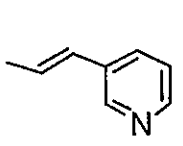
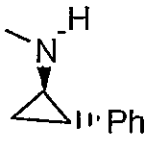
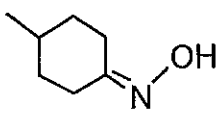
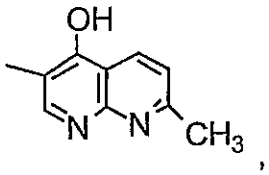
wherein R^3 and R^4 are as previously defined and W is O, S or NR^{10} wherein R^{10} is as defined above; said R^{40} cycloalkyl, alkenyl and alkynyl groups being optionally substituted with from 1-3 groups selected from halo, $-CON(R^{10})_2$, aryl, $-CO_2R^{10}$, $-OR^{12}$, $-SR^{12}$, $-N(R^{10})_2$, $-N(R^{10})CO_2R^{11}$, $-COR^{12}$, $-NO_2$ or D, wherein -D, R^{10} and R^{11} are as defined above and R^{12} represents R^{10}, $-(CH_2)_mOR^{10}$ or $-(CH_2)_qCO_2R^{10}$ wherein R^{10} is as previously defined, m is 1 to 4 and q is 0 to 4; said alkenyl and alkynyl R^{40} groups not containing -OH, -SH or

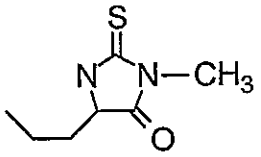
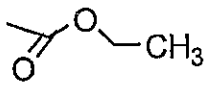
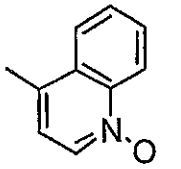
-N(R^{10})$_2$ on a carbon containing a double or triple bond respectively; or

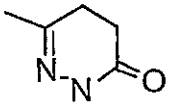
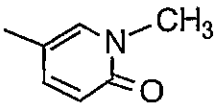
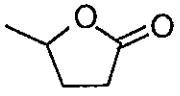
R^{40} represents phenyl substituted with a group selected from -SO_2NH_2, -$NHSO_2CH_3$, -SO_2NHCH_3, -SO_2CH_3, -$SOCH_3$, -SCH_3, or -$NHSO_2CF_3$, preferably, said group is located in the para (p-) position of the phenyl ring; or

R^{40} represents a group selected from

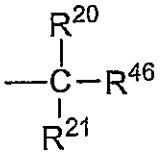

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R^{42} represents



wherein R^{20}, R^{21} and R^{46} are each independently selected from the group consisting of:

(1) H;

(2) -$(CH_2)_qSC(O)CH_3$ wherein q is 1 to 3 (*e.g.*, -$CH_2SC(O)CH_3$);

(3) -$(CH_2)_qOSO_2CH_3$ wherein q is 1 to 3 (*e.g.*, -$CH_2OSO_2CH_3$);

(4) -OH;

(5) -CS(CH_2)$_w$(substituted phenyl) wherein w is 1 to 3 and the substitutents on said substituted phenyl group are the same substitutents as described below for said substituted phenyl (*e.g.*, -C-S-CH_2-4-methoxyphenyl);

(6) -NH_2;

(7) -NHCBZ (wherein CBZ stands for carbonylbenzyloxy--*i.e.*, CBZ represents -C(O)$OCH_2C_6H_5$);

(8) -NHC(O)OR^{22} wherein R^{22} is an alkyl group having from 1 to 5 carbon atoms (*e.g.*, R^{22} is t-butyl thus forming -NHBOC wherein BOC stands for tert-butyloxycarbonyl--i.e., BOC represents -C(O)$OC(CH_3)_3$), or R^{22} represents phenyl substituted with 1 to 3 alkyl groups (*e.g.*, 4-methylphenyl);

(9) alkyl (*e.g.*, ethyl);

(10) -(CH_2)$_k$phenyl wherein k is 1 to 6, usually 1 to 4 and preferably 1 (e.g., benzyl);

(11) phenyl;

(12) substituted phenyl (*i.e.*, phenyl substituted with from 1 to 3 substituents, preferably one) wherein the substituents are selected from the group consisting of: halo (*e.g.*, Br, Cl, or I, with Br being preferred); NO_2; -OH; $-OCH_3$; $-NH_2$; $-NHR^{22}$; $-N(R^{22})_2$; alkyl (e.g., alkyl having from 1 to 3 carbons with methyl being preferred); -O(CH_2)$_t$phenyl (wherein t is from 1 to 3 with 1 being preferred); and -O(CH_2)$_t$substituted phenyl (wherein t is from 1 to 3 with 1 being preferred); examples of substituted phenyls include, but are not limited to, p-bromophenyl, m-nitrophenyl, o-nitrophenyl, m-hydroxy-phenyl, o-hydroxyphenyl, methoxyphenyl, p-methylphenyl, m-methyl-phenyl, and $-OCH_2C_6H_5$;

(13) naphthyl;

(14) substituted naphthyl, wherein the substituents are as defined for substituted phenyl above;

(15) bridged polycyclic hydrocarbons having from 5 to 10 carbon atoms (*e.g.*, adamantyl and norbornyl);

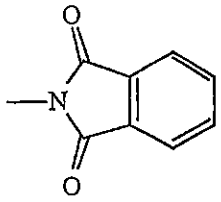
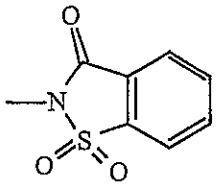
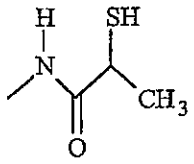
(16) cycloalkyl having from 5 to 7 carbon atoms (*e.g.*, cyclopentyl, and cyclohexyl);

(17) heteroaryl (*e.g.*, pyridyl, and pyridyl N-oxide);

(18) hydroxyalkyl (*e.g.*, -(CH_2)$_v$OH wherein v is 1 to 3, such as, for example, -CH_2OH);

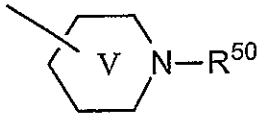
(19) substituted pyridyl or substituted pyridyl N-oxide wherein the substituents are selected from methylpyridyl, morpholinyl, imidazolyl, 1-piperidinyl, 1-(4-methylpiperazinyl), $-S(O)_tR^{11}$, or any of the substituents given above for said substituted phenyl, and said substitutents are bound to a ring carbon by replacement of the hydrogen bound to said carbon;

(20) (21) (22)

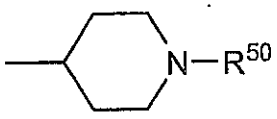
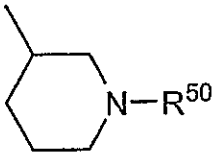
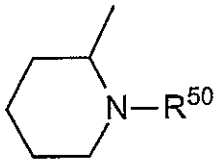

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(23) -NHC(O)-$(CH_2)_k$-phenyl or -NH(O)-$(CH_2)_k$-substitued phenyl, wherein said k is as defined above (*i.e.*, 1-6, usually 1-4 and preferably 1);

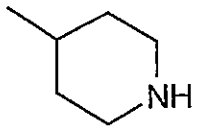
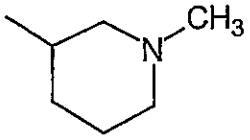
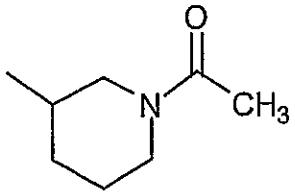
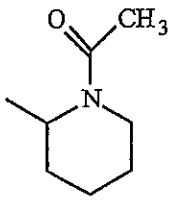
(24) piperidine Ring V:

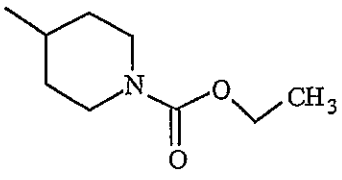
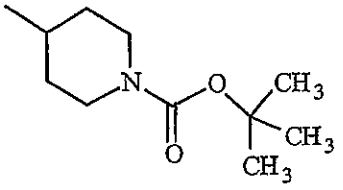

,

wherein R^{50} represents H, alkyl (*e.g.*, methyl), alkylcarbonyl (*e.g.*, $CH_3C(O)$-), alkyloxycarbonyl (*e.g.*, -C(O)O-t-C_4H_9, -$C(O)OC_2H_5$, and -$C(O)OCH_3$), haloalkyl (*e.g.*, trifluromethyl), or --C(O)NH(R^{10}) wherein R^{10} is H or alkyl; Ring V includes


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examples of Ring V include:

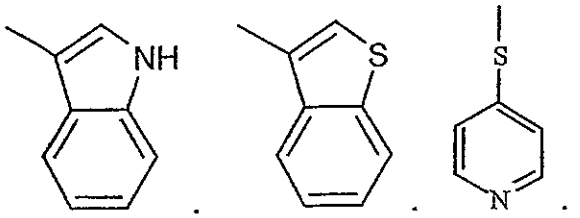

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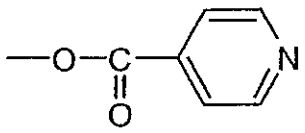
(25) -NHC(O)$CH_2C_6H_5$ or -NHC(O)CH_2-substituted-C_6H_5, for example -NHC(O)CH_2-p-hydroxyphenyl, -NHC(O)CH_2-m-hydroxyphenyl, and -NHC(O)CH_2-o-hydroxyphenyl;

(26) -$NHC(O)OC_6H_5$;

(27) (28) (29)



(30) -OC(O)-heteroaryl, for example

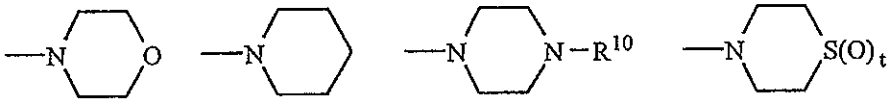


(31) -O-alkyl (*e.g.*, $-OCH_3$);

(32) $-CF_3$;

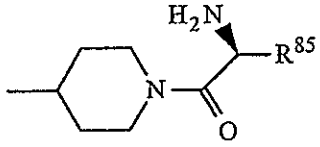
(33) -CN;

(34) a heterocycloalkyl group of the formula



; and

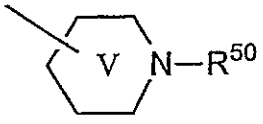
(35) a piperidinyl group of the formula



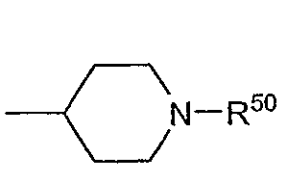
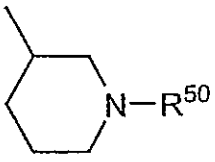
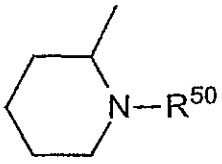
wherein R^{85} is H, alkyl, or alkyl substituted by -OH or $-SCH_3$; or

R^{20} and R^{21} taken together form a =O group and the remaining R^{46} is as defined above; or

Two of R^{20}, R^{21} and R^{46} taken together form piperidine Ring V

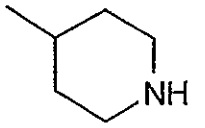
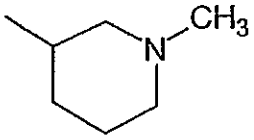
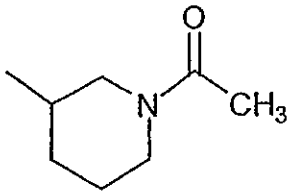
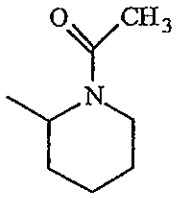


wherein R^{50} represents H, alkyl (e.g., methyl), alkylcarbonyl (e.g., $CH_3C(O)$-), alkyloxycarbonyl (e.g., $-C(O)O$-t-C_4H_9, $-C(O)OC_2H_5$, and $-C(O)OCH_3$), haloalkyl (e.g., trifluro-methyl), or $-C(O)NH(R^{10})$ wherein R^{10} is H or alkyl; Ring V includes

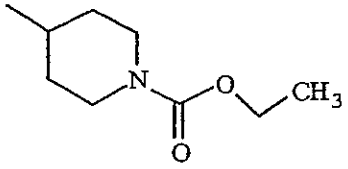
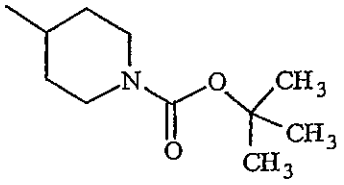




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examples of Ring V include:

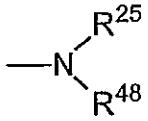





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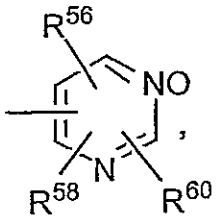
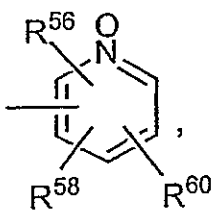
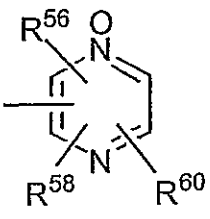
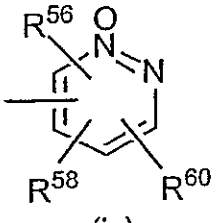
with the proviso R^{46}, R^{20}, and R^{21} are selected such that the carbon atom to which they are bound does not contain more than one heteroatom (i.e., R^{46}, R^{20}, and R^{21} are selected such that the carbon atom to which they are bound contains 0 or 1 heteroatom);

R^{44} represents



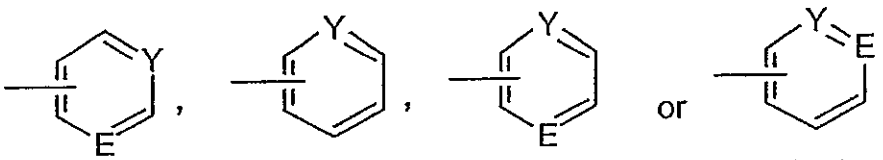
wherein R^{25} represents heteroaryl (e.g., pyridyl or pyridyl N-oxide), N-methylpiperidinyl or aryl (*e.g.*, phenyl and substituted phenyl); and R^{48} represents H or alkyl (*e.g.*, methyl);

R^{54} represents an N-oxide heterocyclic group of the formula (i), (ii), (iii) or (iv):


(i)

(ii)

(iii)
or

(iv)

wherein R^{56}, R^{58}, and R^{60} are the same or different and each is independently selected from H, halo, $-CF_3$, $-OR^{10}$, $-C(O)R^{10}$, $-SR^{10}$, $-S(O)_eR^{11}$ (wherein e is 1 or 2), $-N(R^{10})_2$, $-NO_2$, $-CO_2R^{10}$, $-OCO_2R^{11}$, $-OCOR^{10}$, alkyl, aryl, alkenyl or alkynyl, which alkyl may be substituted with $-OR^{10}$, $-SR^{10}$ or $-N(R^{10})_2$ and which alkenyl may be substituted with OR^{11} or SR^{11}; or

R^{54} represents an N-oxide heterocyclic group of the formula (ia), (iia), (iiia) or (iva):



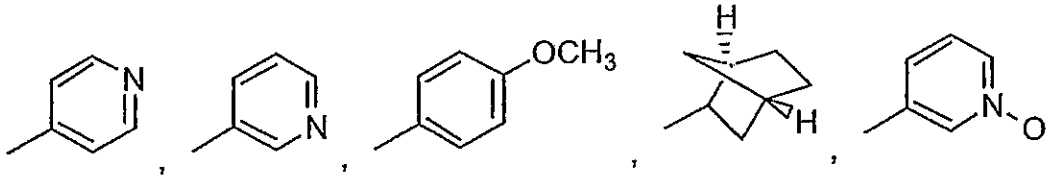
(ia) (iia) (iiia) (iva)

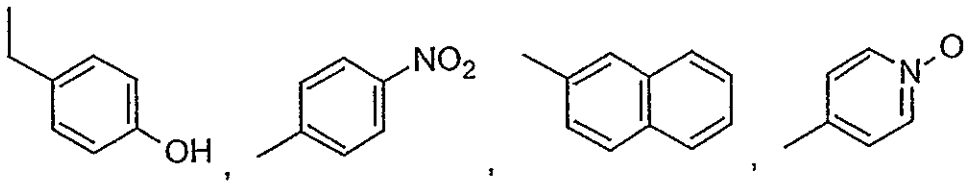
wherein Y represents N^+-O^- and E represents N; or

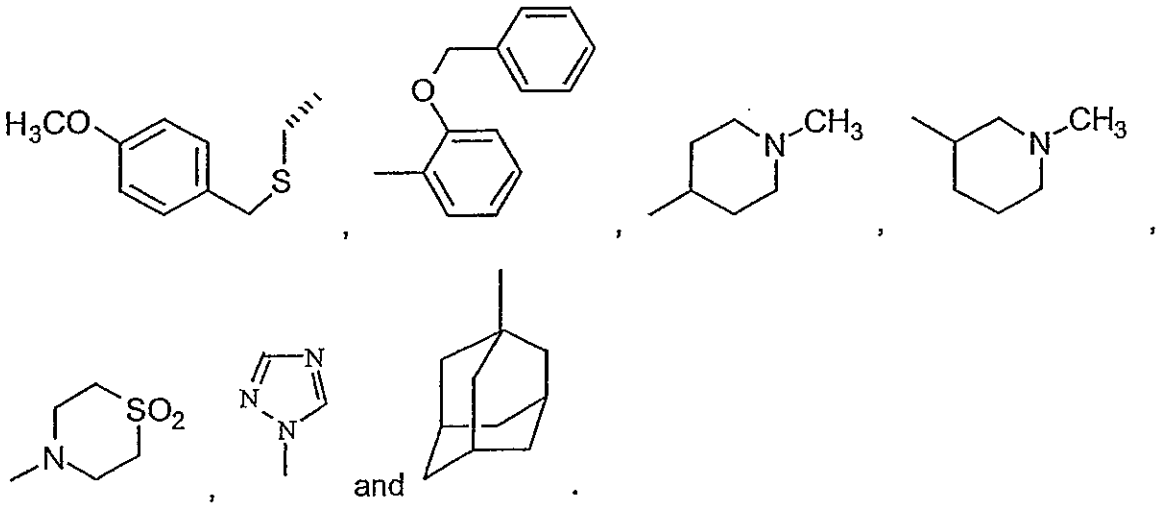
R^{54} represents an alkyl group substituted with one of said N-oxide heterocyclic groups (i), (ii), (iii), (iv), (ia), (iia), (iiia) or (iva);

Z represents O or S such that R can be taken in combination with R^5, R^6, R^7 or R^8 as defined above, or R represents R^{40}, R^{42}, R^{44} or R^{54}.

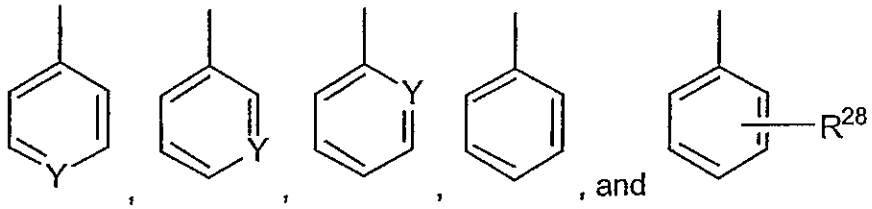
Examples of R^{20}, R^{21}, and R^{46} for the above formulas include:





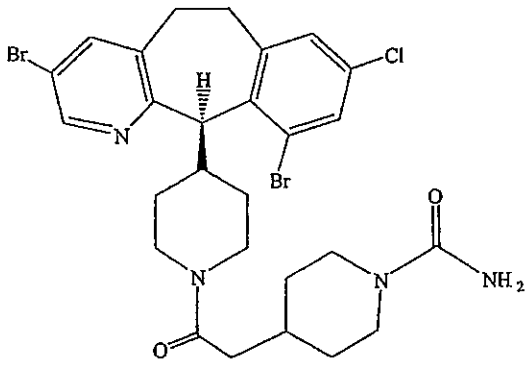


Examples of R^{25} groups include:

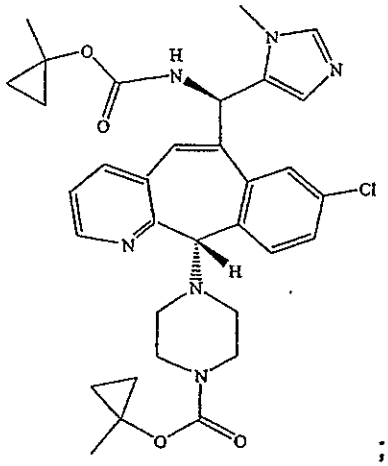


wherein Y represents N or NO, R^{28} is selected from the group consisting of: C_1 to C_4 alkyl, halo, hydroxy, NO_2, amino ($-NH_2$), $-NHR^{30}$, and $-N(R^{30})_2$ wherein R^{30} represents C_1 to C_6 alkyl.

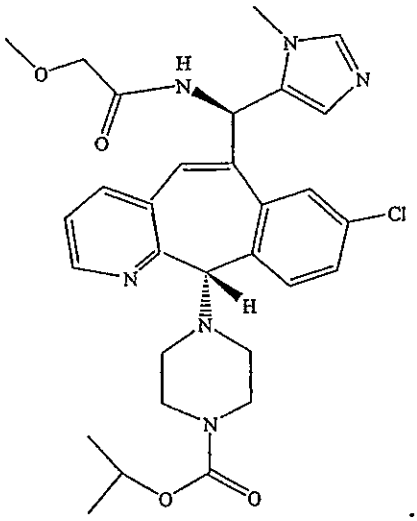
In one embodiment, the following tricyclic amide is included with an anti-IGFR antibody:



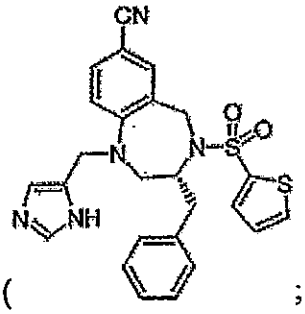
(lonafarnib; Sarasar™; Schering-Plough; Kenilworth, NJ). In another embodiment, one of the following FPT inhibitors is included with an anti-IGFR antibody:



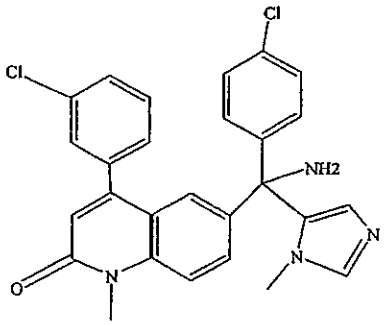
; or



FPT inhibitors, which can be included with an anti-IGFR antibody, include BMS-



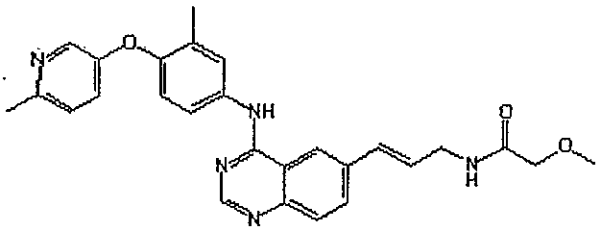
214662 (; Hunt *et al.*, J. Med. Chem. 43(20):3587-95 (2000); Dancey *et al.*, Curr. Pharm. Des. 8:2259-2267 (2002); (R)-7-cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(2-thienylsulfonyl)-1H-1,4-benzodiazepine)) and R155777 (tipifarnib; Garner *et al.*, Drug Metab. Dispos. 30(7):823-30 (2002); Dancey *et al.*, Curr. Pharm. Des. 8:2259-2267 (2002); (B)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)-methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone];

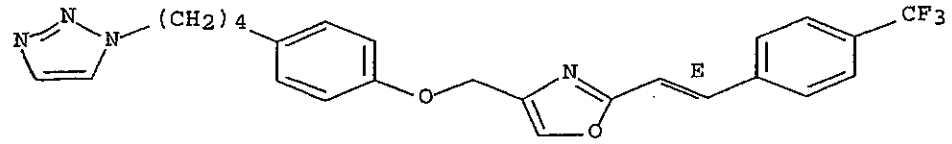


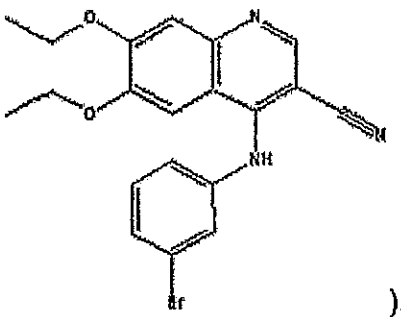
sold as Zarnestra™; Johnson & Johnson; New Brunswick, NJ).

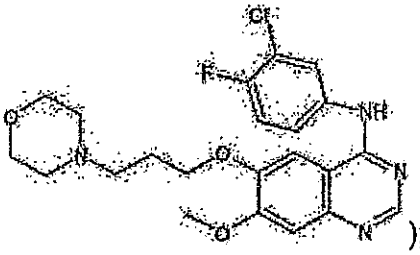
Inhibitors which antagonize the action of the EGF Receptor or HER2, which can be included with an anti-IGFR antibody, include trastuzumab

(sold as Herceptin®; Genentech, Inc.; S. San Francisco, CA) ; CP-724714

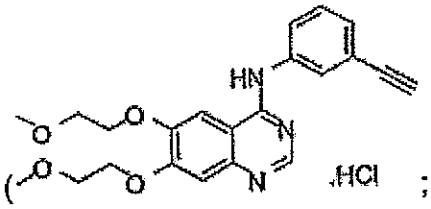
(); TAK-165

(); HKI-272

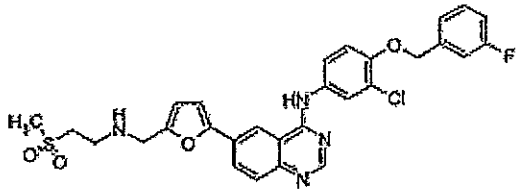
(); gefitinib (Baselga *et al.*, Drugs 60 Suppl 1:33-40 (2000); ZD-1893; 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy) quinazoline;



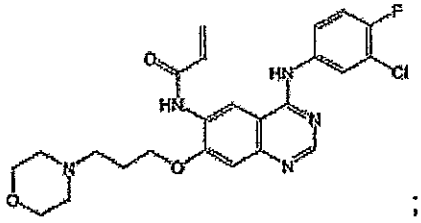
sold as Iressa™; AstraZeneca; Wilmington, DE;); OSI-774



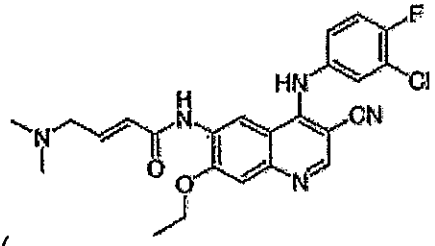
.HCl ; erlotinib, Hidalgo *et al.*, J. Clin. Oncol. 19(13): 3267-3279 (2001)), Lapatanib (



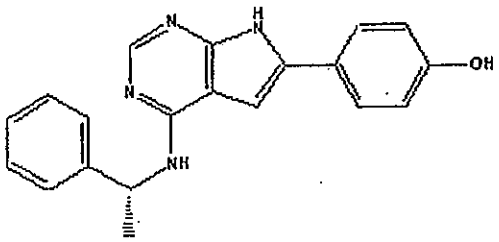
; GW2016; Rusnak *et al.*, Molecular Cancer Therapeutics 1:85-94 (2001); N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine; PCT Application No. WO99/35146), Canertinib (CI-1033;



; Erlichman *et al.*, Cancer Res. 61(2):739-48 (2001); Smaill *et al.*, J. Med. Chem. 43(7):1380-97 (2000)), ABX-EGF antibody (Abgenix, Inc.; Freemont, CA; Yang *et al.*, Cancer Res. 59(6):1236-43 (1999); Yang *et al.*, Crit Rev Oncol Hematol. 38(1):17-23 (2001)), erbitux (U.S. Patent No. 6,217,866; IMC-C225, cetuximab;



Imclone; New York, NY), EKB-569 (; Wissner *et al.*, J. Med. Chem. 46(1): 49-63 (2003)), PKI-166 (



; CGP-75166), GW-572016, any anti-EGFR antibody and any anti-HER2 antibody.

Numerous other small molecules which have been described as being useful to inhibit EGFR can be combined with an anti-IGFR antibody. For example, U.S. Patent 5,656,655, discloses styryl substituted heteroaryl compounds that inhibit EGFR. U.S. Patent 5,646,153 discloses bis mono and/or bicyclic aryl heteroaryl carbocyclic and

heterocarbocyclic compounds that inhibit EGFR and/or PDGFR. U.S. Patent 5,679,683 discloses tricyclic pyrimidine compounds that inhibit the EGFR. U.S. Patent 5,616,582 discloses quinazoline derivatives that have receptor tyrosine kinase inhibitory activity. Fry *et al.*, Science 265 1093-1095 (1994) discloses a compound having a structure that inhibits EGFR (see Figure 1 of Fry *et al.*). U.S. Patent 5,196,446, discloses heteroarylethenediyl or heteroarylethenediylaryl compounds that inhibit EGFR. Panek, *et al.*, Journal of Pharmacology and Experimental Therapeutics 283, 1433-1444 (1997) disclose a compound identified as PD166285 that inhibits the EGFR, PDGFR, and FGFR families of receptors. PD166285 is identified as 6- (2,6- dichlorophenyl)-2-(4-(2-diethylaminoethoxy)phenylarnino)-8-methyl-8H- pyrido(2,3- d)pyrimidin-7-one.

VEGF receptor inhibitors, which can be combined with an anti-IGFR antibody, include PTK787/ZK 222584 (Thomas *et al.*, Semin Oncol. 30(3 Suppl 6):32-8 (2003)) and the humanized anti-VEGF antibody Bevacizumab (sold under the brand name Avastin™; Genentech, Inc.; South San Francisco, CA).

MAP kinase inhibitors, which can be combined with an anti-IGFR antibody, include VX-745 (Haddad, Curr Opin. Investig. Drugs 2(8):1070-6 (2001)).

MAP kinase kinase (MEK) inhibitors, which can be combined with an anti-IGFR antibody, include PD 184352 (Sebolt-Leopold, *et al.* Nature Med. 5: 810-816 (1999)).

mTOR inhibitors, which can be combined with an anti-IGFR antibody, include rapamycin and CCI-779 (Sehgal *et al.*, Med. Res. Rev., 14:1-22 (1994); Elit, Curr. Opin. Investig. Drugs 3(8):1249-53 (2002)).

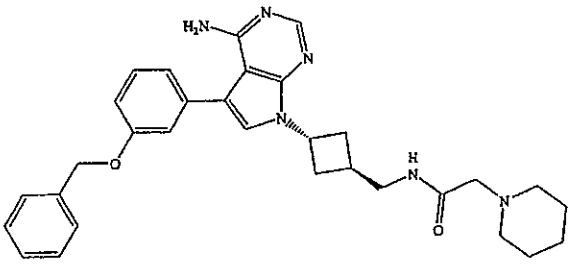
pI3 kinase inhibitors, which can be combined with an anti-IGFR antibody, include LY294002, LY292223, LY292696, LY293684, LY293646 (Vlahos *et al.*, J. Biol. Chem. 269(7): 5241-5248 (1994)) and wortmannin.

Raf inhibitors, which can be combined with an anti-IGFR antibody, include BAY-43-9006, (Wilhelm *et al.*, Curr. Pharm. Des. 8:2255-2257 (2002)), ZM336372, L-779,450 or any other Raf inhibitor disclosed in Lowinger *et al.*, Curr. Pharm Des. 8:2269-2278 (2002).

Cyclin dependent kinase inhibitors, which can be combined with an anti-IGFR antibody, include flavopiridol (L86-8275/HMR 1275; Senderowicz, Oncogene 19(56): 6600-6606 (2000)) and UCN-01 (7-hydroxy staurosporine; Senderowicz, Oncogene 19(56): 6600-6606 (2000)).

IGF/IGFR inhibitors, which can be combined with an anti-IGFR antibody, include IGF inhibitory peptides (U.S. Published Patent Application No. 20030092631 A1; PCT Application Publication NOs. WO 03/27246 A2; WO 02/72780), 4-amino-5-phenyl-7-

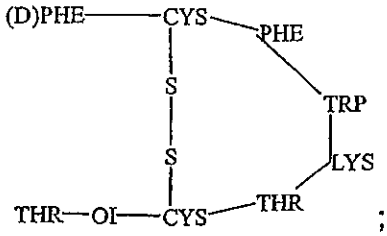
cyclobutyl-pyrrolo[2,3-d] pyrimidine derivatives such as those disclosed in PCT



Application Publication No. WO 02/92599 (*e.g.*,), flavonoid glycones such as quercetin (PCT Application Publication No. WO 03/39538) and anti-IGFR1 antibodies other than those of the present invention.

Other Anti-IGFR1 antibodies, which can be combined with an anti-IGFR antibody of the invention, are disclosed, for example, in Burtrum *et. al* Cancer Research 63:8912-8921(2003); in French Patent Applications FR2834990, FR2834991 and FR2834900 and in PCT Application Publication Nos. WO 03/59951; WO 04/71529; WO 03/106621; WO 04/83248; WO 04/87756 and WO 02/53596.

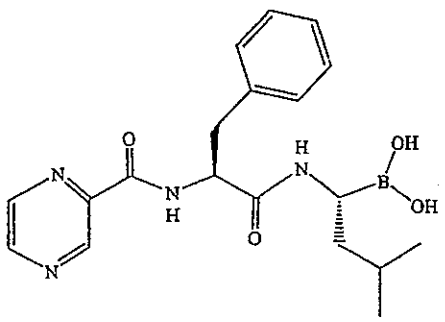
Agents which inhibit IGF production, which can be combined with an anti-IGFR antibody, include octreotide (L-Cysteinamide, D-phenylalanyl- L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl) propyl]-, cyclic (2_7)-disulfide; [R



R*,R*)]; ;

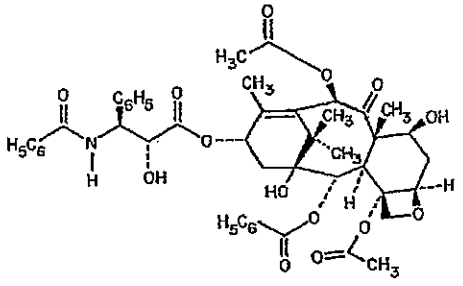
Katz *et al.*, Clin Pharm. 8(4):255-73 (1989); sold as Sandostatin LAR® Depot; Novartis Pharm. Corp; E. Hanover, NJ) .

Proteasome inhibitors, which can be combined with an anti-IGFR antibody, include bortezomib (

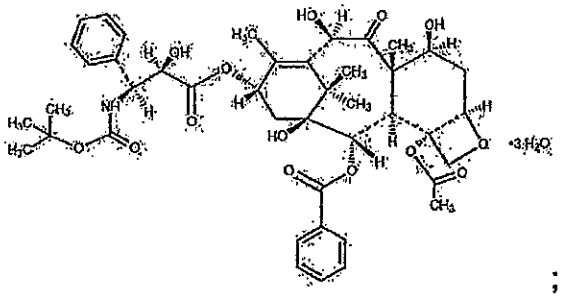


; [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) amino]propyl]amino]butyl] boronic acid; sold as Velcade™; Millennium Pharm., Inc. ; Cambridge, MA).

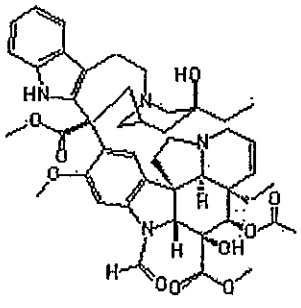
Microtubule stabilizers and microtubule depolymerizers/inhibitors, which can be combined with an anti-IGFR antibody, include paclitaxel



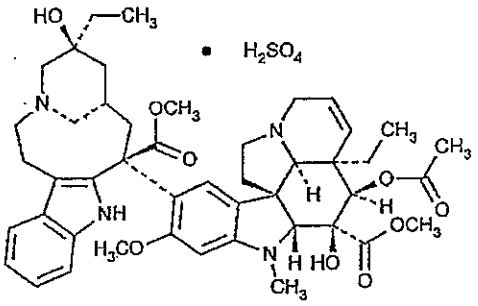
(; sold as Taxol®; Bristol-Myers Squibb; New York, NY) and docetaxel (



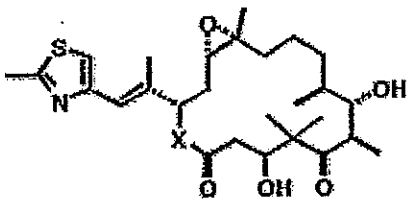
; sold as Taxotere®; Aventis Pharm, Inc.; Bridgewater, NJ); vincristine (



), vinblastine

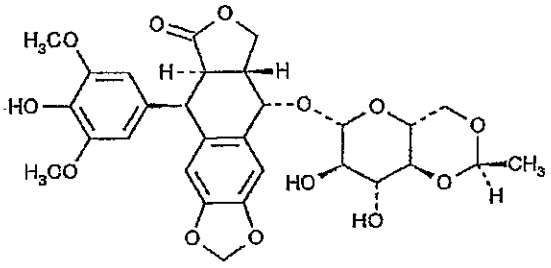


( ), epothilone B and BMS-247550

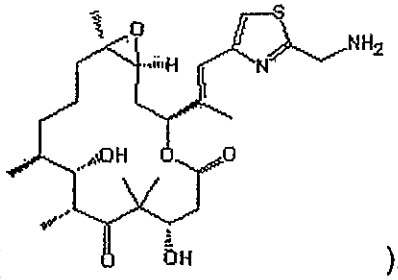


Epothilone B: X=O
BMS-247550: X=NH

(; Lee *et al.*, Clin. Cancer Res. 7(5):1429-37 (2001)), podophyllotoxins and derivatives thereof including Etoposide (VP-16;

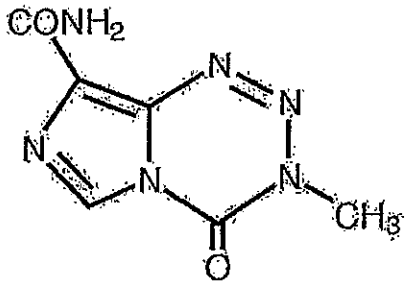


( ) and BMS-310705



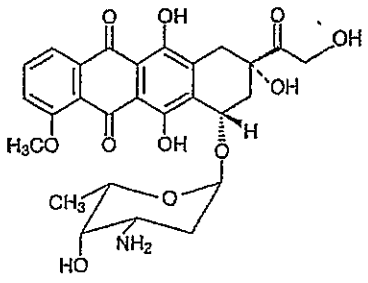
( ).

Temozolomide (

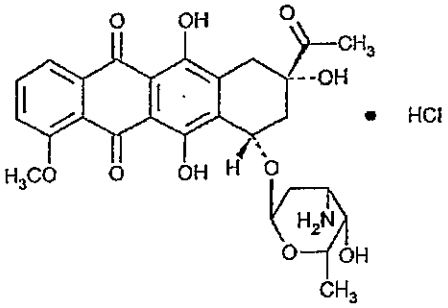


(; sold by Schering Corp.; Kenilworth, NJ as Temodar®) may also be combined with an anti-IGFR antibody of the invention.

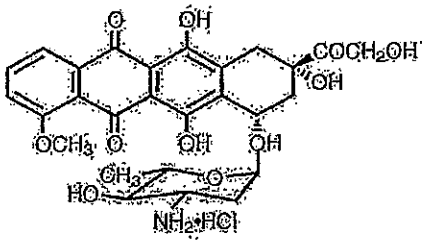
Anthracyclines which may be combined with an anti-IGFR antibody include doxorubicin (



; sold as Doxil®; Ortho Biotech Products L.P.; Raritan, NJ); daunorubicin

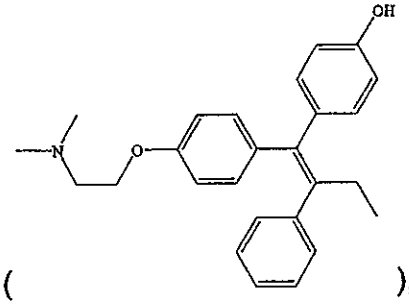


(; sold as Cerubidine®; Ben Venue Laboratories, Inc.;

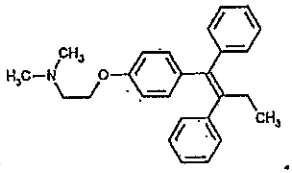


Bedford, OH) and epirubicin (; sold as Ellence®; Pharmacia & Upjohn Co; Kalamazoo, MI).

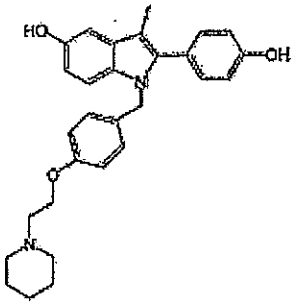
Anti-estrogens and selective estrogen receptor modulators (SERMs), which can be combined with the anti-IGFR antibodies of the invention include droloxifene (3-



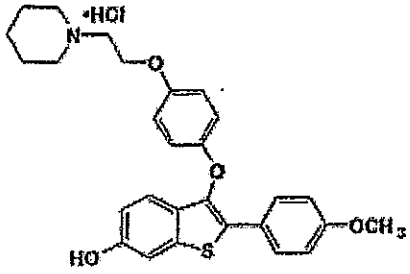
hydroxytamoxifen), 4-hydroxytamoxifen ( ), tamoxifen



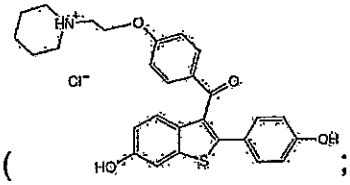
(; sold as Nolvadex®; Astra Zeneca; Wilmington, DE); pipendoxifene



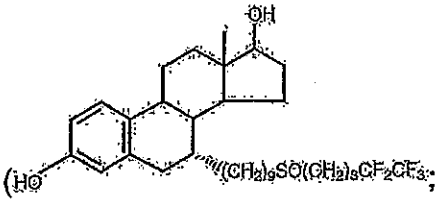
(; ERA-923; Greenberger *et al.*, Clin. Cancer Res. 7(10):3166-77



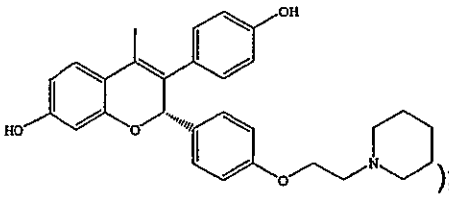
(2001)); arzoxifene (; LY353381; Sato *et al.*, J. Pharmacol.

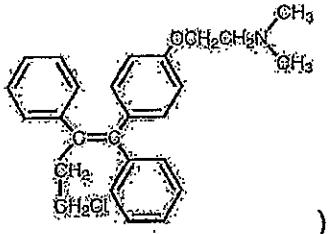


Exp. Ther. 287(1):1-7 (1998)); raloxifene (; sold as Evista®; Eli

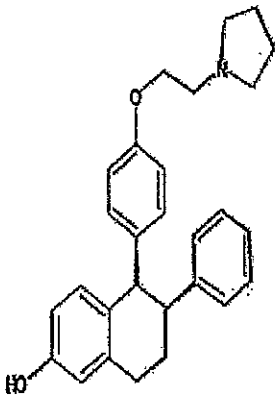


Lilly & Co.; Indianapolis, IN); fulvestrant (; ICI-182780; sold as Faslodex; Astra Zeneca; Wilmington, DE); acolbifene (EM-652;

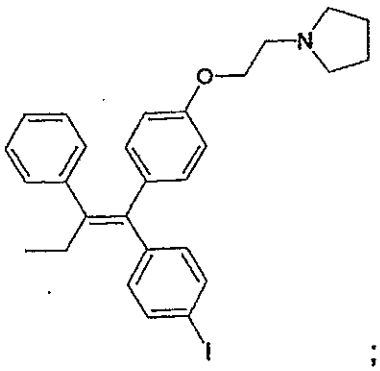




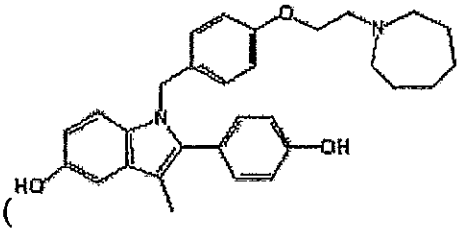
); toremifine ( ); lasofoxifene (CP-



336,156; ; Ke *et al.*, Endocrinology 139(4):2068-76 (1998));

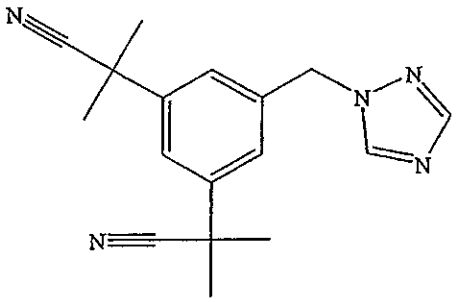


idoxifene (pyrrolidino-4-iodotamoxifen; ; Nuttall *et al.*, Endocrinology 139(12):5224-34 (1998)); TSE-424

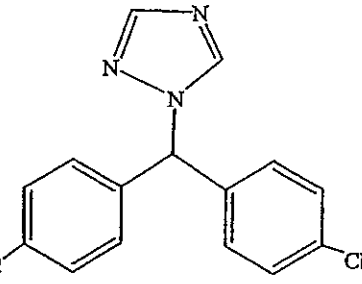


(;Bazedoxifene; WAY-140424); HMR-3339 and ZK-186619.

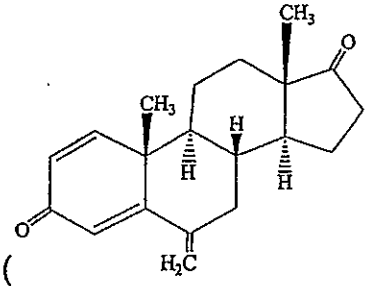
Aromatase inhibitors, which can be included with an anti-IGFR antibody, include



anastrazole (; Dukes *et al.*, J. Steroid. Biochem. Mol. Biol. 58(4):439-45 (1996)), letrozole (

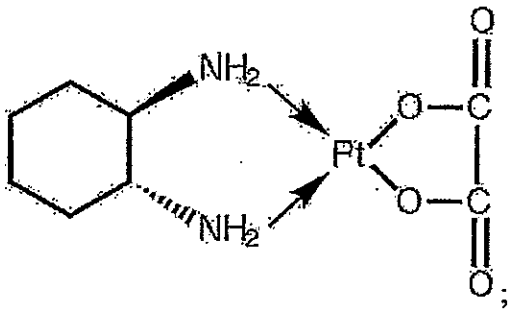


; sold as Femara®; Novartis Pharmaceuticals Corp.; E. Hanover, NJ) and exemestane



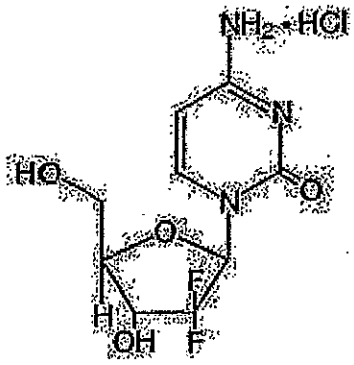
(; sold as Aromasin®; Pharmacia Corp.; Kalamazoo, MI).

Oxaliplatin (

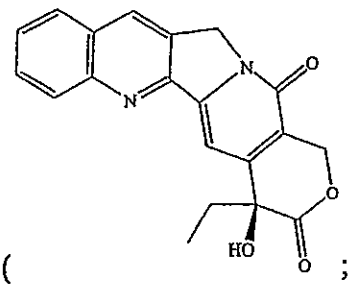


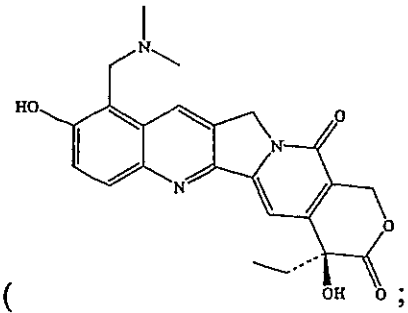
; sold as Eloxatin™ by Sanofi-Synthelabo Inc.; New York, NY) can also be combined with an anti-IGFR antibody of the invention.

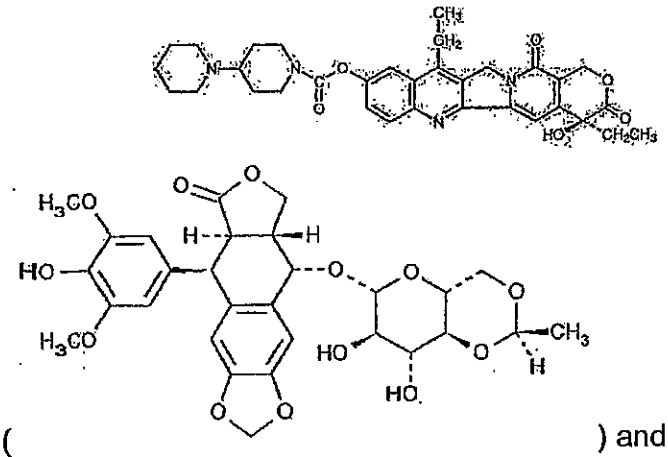
An anti-IGFR antibody can also be combined with gemcitabine HCl



( ) with retinoic acid or with any IGFR inhibitor set forth in any of Mitsiades *et al.*, Cancer Cell 5:221-230 (2004); Garcia-Echeverria *et. al.*,Cancer Cell 5:231-239,2004; WO 2004/030627 or WO 2004/030625.

Topoisomerase inhibitors which may be combined with an anti-IGFR antibody include camptothecin ( ; Stork *et al.*, J. Am. Chem. Soc. 93(16): 4074-4075 (1971); Beisler *et al.*, J. Med. Chem. 14(11): 1116-1117 (1962)), topotecan

( ; sold as Hycamtin®; GlaxoSmithKline, Research Triangle Park, NC; Rowinski *et al.*, J. Clin. Oncol. 10(4): 647-656 (1992)), etoposide

() and irinotecan (

; sold as Camptosar®; Pharmacia & Upjohn Co.; Kalamazoo, MI).

Antisense oligonucleotides can be produced that are complementary to the mRNA of the IGFR1, IGF-1 or IGF-2 gene and can be used to inhibit transcription or translation of the genes. Production of antisense oligonucleotides effective for therapeutic uses is well known in the art. Antisense oligonucleotides are often produced using derivatized or modified nucleotides in order to increase half-life or bioavailability. The primary sequence of the IGFR1, IGF-1 or IGF-2 gene can also be used to design ribozymes. Most synthetic ribozymes are generally hammerhead, tetrahymena and haripin ribozymes. Methods of designing and using ribozymes to cleave specific RNA species are well known in the art.

The chemical structures and other useful information regarding many of the foregoing agents can be found in the Physicians' Desk Reference, 57th ed., 2003; Thompson PDR; Montvale, NJ.

Categorization of a particular agent into a particular class (*e.g.*, FPT inhibitor or microtubule stabilizer) is only done for descriptive purposes and is not meant to limit the invention in any way.

The scope of present invention includes compositions and methods comprising an anti-IGFR antibody along with one or more of the foregoing chemotherapeutic agents or any salt, hydrate, isomer, formulation, solvate or prodrug thereof.

Pharmaceutical Compositions

A combination, or any component thereof, of the invention can be incorporated into a pharmaceutical composition, along with a pharmaceutically acceptable carrier, suitable for administration to a subject *in vivo*. The scope of the present invention includes pharmaceutical compositions which may be administered to a subject by any route, such as a non-parenteral (*e.g.*, oral, ocular, topical or pulmonary (inhalation)) or a parenteral route (*e.g.*, intratumoral injection, intravenous injection, intraarterial injection, subcutaneous injection or intramuscular injection). In one embodiment, the pharmaceutical compositions of the invention comprise an antibody comprising 15H12/19D12 LCF and 15H12/19D12 HCA in association with one or more chemotherapeutic agents and a pharmaceutically acceptable carrier.

As stated above, the combinations of the invention include the binding composition component and chemotherapeutic agent component "in association" with one another. The term "in association" indicates that the components of the combinations of the invention can be formulated into a single composition for simultaneous delivery or formulated separately into two or more compositions (*e.g.*, a kit). For example, the scope of the present invention includes combinations comprising an anti-IGFR1 antibody formulated for parenteral administration (*e.g.*, intravenous) to a subject and a chemotherapeutic agent formulated for oral delivery (*e.g.*, pill, tablet, capsule). Alternatively, both components of the combination can be formulated, separately or together, for parenteral delivery or non-parenteral delivery (*e.g.*, oral).

For general information concerning formulations, see, *e.g.*, Gilman, *et al.*, (eds.) (1990), The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack

Publishing Co., Easton, Pennsylvania.; Avis, *et al.*, (eds.) (1993) Pharmaceutical Dosage Forms: Parenteral Medications Dekker, New York; Lieberman, *et al.*, (eds.) (1990) Pharmaceutical Dosage Forms: Tablets Dekker, New York; and Lieberman, *et al.*, (eds.) (1990), Pharmaceutical Dosage Forms: Disperse Systems Dekker, New York, Kenneth A. Walters (ed.) (2002) Dermatological and Transdermal Formulations (Drugs and the Pharmaceutical Sciences), Vol 119, Marcel Dekker.

Pharmaceutically acceptable carriers are conventional and very well known in the art. Examples include aqueous and nonaqueous carriers, stabilizers, antioxidants, solvents, dispersion media, coatings, antimicrobial agents, buffers, serum proteins, isotonic and absorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for injection into a subject's body.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

Stabilizers, such as α, α-trehalose dihydrate may be included for stabilizing the antibody molecules of the invention from degrading effects of dessication or freeze-drying.

Examples of pharmaceutically-acceptable antioxidants include: water soluble antioxidants such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; and oil-soluble antioxidants such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Prevention of the presence of microorganisms may be ensured both by sterilization procedures, and by the inclusion of various antimicrobial agents such as EDTA, EGTA, paraben, chlorobutanol, phenol sorbic acid, and the like.

Suitable buffers which may be included in the pharmaceutical compositions of the invention include L-histidine based buffers, phosphate based buffers (*e.g.*, phosphate buffered saline, pH ≅ 7), sorbate based buffers or glycine-based buffers.

Serum proteins which may be included in the pharmaceutical compositions of the invention may include human serum albumin.

Isotonic agents, such as sugars, ethanol, polyalcohols (*e.g.*, glycerol, propylene glycol, liquid polyethylene glycol, mannitol or sorbitol), sodium citrate or sodium chloride (*e.g.*, buffered saline) may also be included in the pharmaceutical compositions of the invention.

Prolonged absorption of an injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and/or gelatin.

Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils.

Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. The use of such media and agents for pharmaceutically active substances is well known in the art.

Sterile injectable solutions can be prepared by incorporating a combination of the invention or any component thereof (*e.g.*, binding composition and/or chemotherapeutic agent), in the required amount, in an appropriate solvent, optionally with one or a combination of ingredients enumerated above, as required, followed by sterilization microfiltration. Generally, dispersions are prepared by incorporating the active ingredient (*e.g.*, binding composition and/or chemotherapeutic agent) into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient plus any additional, desired ingredient from a previously sterile-filtered solution thereof.

A combination or the invention or any component thereof (*e.g.*, binding composition and/or chemotherapeutic agent) may also be orally administered. Pharmaceutical compositions for oral administration may include additives and carriers such as starch (*e.g.*, potato, maize or wheat starch or cellulose), starch derivatives (*e.g.*, microcrystalline cellulose or silica), sugars (*e.g.*, lactose), talc, lactose, stearate, magnesium carbonate or calcium phosphate. In order to ensure that oral compositions are well tolerated by the patient's digestive system, mucus formers or resins may be included. It may also be desirable to improve tolerance by formulating in a capsule which

is insoluble in the gastric juices. An exemplary pharmaceutical composition of this invention in the form of a capsule is prepared by filling a standard two-piece hard gelatin capsule with the combination of the invention or any component thereof in powdered form, lactose, talc and magnesium stearate. Oral administration of immunoglobulins has been described (Foster, *et al.*, (2001) Cochrane Database System rev. 3:CD001816)

A combination of the invention or any component thereof (*e.g.*, binding composition and/or chemotherapeutic agent) may also be included in a pharmaceutical composition for topical administration. Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site where treatment is required, such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the combination of the invention or any component thereof (*e.g.*, binding composition and/or chemotherapeutic agent) in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile, aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the combination of the invention or any component thereof in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol or macrogels. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surface active such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as

natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

A combination of the invention or any component thereof (*e.g.*, binding composition and/or chemotherapeutic agent) may also be administered by inhalation. A suitable pharmaceutical composition for inhalation may be an aerosol. An exemplary pharmaceutical composition for inhalation of a combination of the invention or any component thereof may include: an aerosol container with a capacity of 15-20 ml comprising the active ingredient (*e.g.*, binding composition and/or chemotherapeutic agent), a lubricating agent, such as polysorbate 85 or oleic acid, dispersed in a propellant, such as freon, preferably in a combination of 1,2-dichlorotetrafluoroethane and difluorochloromethane. Preferably, the composition is in an appropriate aerosol container adapted for either intranasal or oral inhalation administration.

Dosage

Preferably, a combination of the invention is administered to a subject at a "therapeutically effective dosage" or "therapeutically effective amount" which preferably inhibits a disease or condition (*e.g.*, tumor growth) to any extent-preferably by at least about 20%, more preferably by at least about 40%, even more preferably by at least about 60%, and still more preferably by at least about 80%-100% relative to untreated subjects. The ability of a combination of the invention or any component thereof to inhibit cancer can be evaluated in an animal model system predictive of efficacy in human tumors. Alternatively, this property can be evaluated by examining the ability of a combination of the invention or any component thereof to inhibit tumor cell growth *in vitro* by assays well-known to the skilled practitioner. One of ordinary skill in the art would be able to determine such amounts based on such factors as the subject's size, the severity of the subject's symptoms, and the particular composition or route of administration selected.

Dosage regimens may be adjusted to provide the optimum desired response (*e.g.*, a therapeutic response). For example, a dose may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For

example, the physician or veterinarian could start doses of the antibody or antigen-binding fragment of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. The effectiveness of a given dose or treatment regimen of an antibody or combination of the invention can be determined , for example, by determining whether a tumor being treated in the subject shrinks or ceases to grow. The size of tumor can be easily determined, for example, by X-ray, magnetic resonance imaging (MRI) or visually in a surgical procedure.

In general, a suitable daily dose of a combination of the invention or any component thereof may be that amount which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. It is preferred that administration be by injection, preferably proximal to the site of the target (*e.g.*, tumor). If desired, a therapeutically effective daily dose of an antibody or antibody/chemotherapeutic agent combination of the invention or pharmaceutical composition thereof may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day. In an embodiment, a "therapeutically effective" dosage of any anti-IGFR antibody of the present invention is in the range of about 3 mg/kg (body weight) to about 10 mg/kg (*e.g.*, 3, 4, 5, 6, 7, 8, 9 or 10 mg/kg) per day. In an embodiment, a "therapeutically effective dosage" of a chemotherapeutic agent is as set forth in the Physicians' Desk Reference 2003 (Thomson Healthcare; 57th edition (November 1, 2002)) which is herein incorporated by reference. For example, in an embodiment, the daily dose of gefitinib is 250 mg/day or the daily dose of paclitaxel is about 135 mg/m^2 to about 175 mg/m^2.

Therapeutic Methods and Administration

A combination of the invention or an anti-IGFR antibody or antigen-binding fragment thereof of the invention, alone, can be used to inhibit or reduce the growth or proliferation of any cell, such as a malignant cell, either *in vitro* (*e.g.*, in cell culture) or *in vivo* (*e.g.*, within the body of a subject suffering from a disease mediated by elevated expression or activity of IGFR1 or by elevated expression of its ligand (*e.g.*, IGF-I or IGF-II)). Such inhibition or reduction of growth or proliferation of a cell can be achieved by contacting the cell with the combination.

A combination of the invention or an anti-IGFR antibody or antigen-binding fragment thereof, alone, of the invention can be used for treating or preventing any

disease or condition in a subject in need of such treatment or prevention which is mediated, for example, by elevated expression or activity of IGFR1 or by elevated expression of its ligand (*e.g.*, IGF-I or IGF-II) and which may be treated or prevented by modulation of IGFR1 ligand binding, activity or expression. Preferably, the disease or condition is mediated by an increased level of IGFR1, IGF-I or IGF-II and is treated or prevented by decreasing IGFR1 ligand binding, activity (*e.g.*, autophosphorylation activity) or expression. Preferably, the disease or condition is malignancy, more preferably a malignancy characterized by a tumor which expresses IGFR1, such as, but not limited to, bladder cancer, Wilm's cancer, bone cancer, prostate cancer, lung cancer, colorectal cancer, breast cancer, cervical cancer, synovial sarcoma, ovarian cancer, pancreatic cancer, benign prostatic hyperplasia (BPH), diarrhea associated with metastatic carcinoid and vasoactive intestinal peptide secreting tumors (*e.g.*, VIPoma or Werner-Morrison syndrome). Acromegaly may also be treated with a combination of the invention. Antagonism of IGF-I has been reported for treatment of acromegaly (Drake, *et al.*, (2001) Trends Endocrin. Metab. 12: 408-413). Other non-malignant medical conditions which may also be treated, in a subject, by administering a combination of the invention, include gigantism, psoriasis, atherosclerosis, smooth muscle restenosis of blood vessels or inappropriate microvascular proliferation, such as that found as a complication of diabetes, especially of the eye rheumatoid arthritis, Grave's disease, multiple sclerosis, systemic lupus erythematosus, Hashimoto's Thyroiditis, Myasthenia Gravis, auto-immune thyroiditis and Bechet's disease.

The term "subject" may refer to any organism, preferably an animal, more preferably a mammal (*e.g.*, rat, mouse, dog, cat, rabbit) and most preferably a human.

In an embodiment of the invention, where possible, a composition of the invention is administered to a subject in accordance with the Physicians' Desk Reference 2003 (Thomson Healthcare; 57th edition (November 1, 2002)).

A combination of the invention or any component thereof can be administered by an invasive route such as by injection (see above). Administration by a non-invasive route (*e.g.*, orally; for example, in a pill, capsule or tablet) is also within the scope of the present invention. In an embodiment of the invention, an anti-IGFR antibody of the invention, or pharmaceutical composition thereof, is administered intravenously, subcutaneously, intramuscularly, intraarterially or intratumorally while a chemotherapeutic agent of the invention (*e.g.*, gefitinib (*e.g.*, Iressa™)) is administered orally in tablet form.

In another embodiment, the chemotherapeutic agent is paclitaxel (*e.g.*, Taxol®) which is administered intravenously.

Compositions can be administered with medical devices known in the art. For example, a pharmaceutical composition of the invention can be administered by injection with a hypodermic needle.

The pharmaceutical compositions of the invention may also be administered with a needleless hypodermic injection device; such as the devices disclosed in U.S. Patent Nos. 6,620,135; 6,096,002; 5,399,163; 5,383,851; 5,312,335; 5,064,413; 4,941,880; 4,790,824 or 4,596,556.

Examples of well-known implants and modules form administering pharmaceutical compositions include: U.S. Patent No. 4,487,603, which discloses an implantable micro-infusion pump for dispensing medication at a controlled rate; U.S. Patent No. 4,447,233, which discloses a medication infusion pump for delivering medication at a precise infusion rate; U.S. Patent No. 4,447,224, which discloses a variable flow implantable infusion apparatus for continuous drug delivery; U.S. Patent. No. 4,439,196, which discloses an osmotic drug delivery system having multi-chamber compartments. Many other such implants, delivery systems, and modules are well known to those skilled in the art.

Kits

The present invention also provides kits comprising the components of the combinations of the invention in kit form. A kit of the present invention includes one or more components including, but not limited to, a binding composition, as discussed herein, which specifically binds IGFR1 (*e.g.*, 19D12/15H12 LCF/HCA) in association with one or more additional components including, but not limited to, a chemotherapeutic agent, as discussed herein. The binding composition and/or the chemotherapeutic agent can be formulated as a pure composition or in combination with a pharmaceutically acceptable carrier, in a pharmaceutical composition.

In one embodiment, a kit includes a binding composition of the invention (*e.g.*, 19D12/15H12 LCF/HCA) or a pharmaceutical composition thereof in one container (*e.g.*, in a sterile glass or plastic vial) and a chemotherapeutic agent or a pharmaceutical composition thereof in another container (*e.g.*, in a sterile glass or plastic vial).

In another embodiment of the invention, the kit comprises a combination of the invention, including a binding composition component (*e.g.*, 19D12/15H12 LCF/HCA) along with a chemotherapeutic agent component formulated together, optionally, along

with a pharmaceutically acceptable carrier, in a pharmaceutical composition, in a single, common container.

If the kit includes a pharmaceutical composition for parenteral administration to a subject, the kit can include a device for performing such administration. For example, the kit can include one or more hypodermic needles or other injection devices as discussed above.

The kit can include a package insert including information concerning the pharmaceutical compositions and dosage forms in the kit. Generally, such information aids patients and physicians in using the enclosed pharmaceutical compositions and dosage forms effectively and safely. For example, the following information regarding a combination of the invention may be supplied in the insert: pharmacokinetics, pharmacodynamics, clinical studies, efficacy parameters, indications and usage, contraindications, warnings, precautions, adverse reactions, overdosage, proper dosage and administration, how supplied, proper storage conditions, references, manufacturer/distributor information and patent information.

EXAMPLES

The following examples are provided to further describe the present invention and should not be construed to limit the scope of the invention in any way.

Example 1: Proliferation Assay Using an Anti-IGFR1 Antibody and a Chemotherapeutic Agent.

The ability of cells in culture to proliferate when exposed to varying concentrations of the19D12/15H12 wild-type or 19D12/15H12 LCF/HCA anti-IGFR1 antibody and either paclitaxel, gefitinib, lonafarnib 4-hydroxy tamoxifen or doxorubicin was evaluated in this example.

Cell Preparation. H322 NSCLC cells or MCF7 cells were cultured for several passages no greater than 80% confluency in T-75 TC treated filtered flasks. The cells were trypsinized, counted and resuspended at a concentration of 25000 cells/ml in 10% HI-FBS (heat-inactivated fetal bovine serum) RPMI medium containing NEAA (non-essential amino acids), L-Glu, MEM Vitamins and PS. 100ul of cell suspension (2500 cells) was added to each well of a BD Falcon 96 well black, clear bottom TC treated plate. The cells were allowed to attach and spread overnight at 37°C. The 10% RPMI solution

was replaced with 100µl RPMI containing 2% HI-FBS containing NEAA, L-Glu, MEM Vitamins and PS.

Solution Preparation. All assay reagents were prepared in RPMI containing 2% HI-FBS at 20X concentration and serial diluted for a total of 10 test concentrations per treatment. Every test point was prepared in triplicate on separate assay plates. Each plate included experimental wells containing either (i) antibody 19D12/15H12 and paclitaxel, (ii) antibody 19D12/15H12 and gefitinib; (iii) antibody 19D12/15H12 LCF/HCA and lonafarnib; (iv) antibody 19D12/15H12 and 4-hydroxy tamoxifen; or (v) antibody 19D12/15H12 and doxorubicin along with internal controls of containing either (a) no treatment, (b) reagent1 (paclitaxel, gefitinib, lonafarnib, 4-hydroxy tamoxifen or doxorubicin) alone, and (c) antibody 19D12/15H12 or 19D12/15H12 LCF/HCA alone.

Reagent 1 and 19D12/15H12 or 19D12/15H12 LCF/HCA were set up individually as dose responses as well as in combination with each other. Cell proliferation was measured on Day4.

Assay. Cell proliferation was measured using the Promega Cell Titer-Glo Luminescent Cell Viability Assay (Promega Corp.; Madison, WI). This assay provided a method for determining the number of viable cells in culture based on quantitation of ATP in the culture, which indicates the presence of metabolically active cells.

The assay reagents and assay plates were equilibrated to room temperature and prepared immediately before addition to the assay plates. One volume of assay reagent was added to each well of the assay plate and shaken on an orbital platform for at least ten minutes to allow for equilibration of the ATP reaction and to ensure total lysis of all cells in the assay plate. The reaction had a half-life of five hours but in no case was reading done later than 30 minutes after addition of reagent. Luminescence was detected on Wallac 420 Plate Reader with stacker.

The results from these experiments are shown below in Tables 2-6. The units in the tables (proliferation index) are arbitrary and are proportional to the number of viable cells observed in the culture under each respective condition. The data from the "no treatment" experiments indicate the proliferation index observed in the absence of any drug (*i.e.*, antibody or chemotherapeutic composition).

In Tables 2-6, "ug" indicates micrograms and "uM" indicates micromolar.

Table 2. Proliferation of H322 NSCLC cells in the presence of anti-IGFR1 antibody 19D12/15H12 and paclitaxel ("Taxol").

Antibody 19D12/15H12 LCF/HCA (nM) / Taxol (ng/mL)

	1000	200	40	8	1.6	0.32	0.064	0.0128	0.00256	0.000512
20	14882	14938	16272	23968	47176	54106	52266	50238	48568	52820
4	15794	16310	15258	21956	41402	48226	51580	49332	48232	48314
0.8	17792	16948	14676	23486	41636	52140	51214	49554	53974	52252
0.16	18754	16032	16674	23634	46632	49704	54068	53728	55428	54010
0.032	17468	16782	14752	29406	51924	59734	53824	58734	58048	60032
0.0064	19056	19060	18210	27712	53038	60690	70632	63172	60880	68962
0.00128	19952	20250	20094	34790	61030	68190	71192	69036	62998	71744
0.000256	20876	20890	20222	35418	58662	66950	64984	68864	71162	72908
5.12E-05	22304	21462	23232	46896	80714	77044	79658	73562	80006	84546
1.02E-05	25400	23894	22898	44032	74545	77406	75958	78316	79680	82924

Antibody 19D12/15H12 LCF/HCA (nM) / Taxol (ng/mL)

	1000	200	40	8	1.6	0.32	0.064	0.0128	0.00256	0.000512
20	14870	15094	15452	25194	40292	46498	49024	50218	51442	53750
4	16516	15038	15492	22660	39962	45616	46408	44896	50612	50264
0.8	14796	14110	14022	21984	44652	47520	47290	46948	47332	50984
0.16	16538	14428	14312	22256	41856	52060	52938	54362	51564	49982
0.032	17974	17616	16878	27580	51068	55700	53276	56798	58766	64396
0.0064	21998	18662	18658	30754	58400	66974	72674	70878	72164	70396
0.00128	23030	20980	20906	32318	61380	75388	73794	72076	72602	74058
0.000256	22758	19894	21232	34232	61652	76538	71674	72876	76362	80456
5.12E-05	21702	22424	22344	39384	67068	66364	74268	72709	73390	77974
1.02E-05	23622	22234	21764	38960	68346	70906	71034	74208	73766	75186

Antibody 19D12/15H12 LCF/HCA (nM) / Taxol (ng/mL)

	1000	200	40	8	1.6	0.32	0.064	0.0128	0.00256	0.000512
20	15934	14704	13960	23694	41142	44472	48242	48976	46244	48044
4	15416	15464	15508	21644	37994	45112	43838	48690	49494	51944
0.8	14844	14994	15916	21136	37026	48134	46824	47710	48656	48484
0.16	16782	16786	15532	23878	43976	49102	49568	51606	52426	51598
0.032	19140	18150	17670	27458	55260	61668	66654	65422	60994	59536
0.0064	22696	20462	20124	29964	57072	76988	71298	74152	69218	68814
0.00128	23930	21922	23648	33882	62218	73942	76080	79882	76866	78952
0.000256	24970	21794	22122	33882	62980	83316	80888	86064	77932	75714
5.12E-05	21220	19870	20890	36634	66106	74250	79392	72524	68150	69686
1.02E-05	21408	21356	20574	37962	68052	67564	73422	72328	74388	72110

Antibody 19D12/15H12 LCF/HCA (nM) / Taxol (ng/mL)

20	55106	50680	49038	56114	52446	51826	52490	48302	44120
4	48884	49992	50508	47256	56998	54966	51436	44700	42312
0.8	47470	52010	49636	55228	53706	56984	49396	47080	40944
0.16	59594	52620	53196	55122	53138	58778	50902	49702	51550
0.032	67110	60794	60018	59422	59506	65230	63764	61432	59276
0.0064	79014	72998	69060	64818	74962	76374	68206	70226	61654
0.00128	77870	76502	70644	72430	75326	82604	84158	72520	77014
0.000256	74154	83338	74108	84234	83206	80694	82674	71784	73420
5.12E-05	87030	83636	79810	79650	90294	88940	86782	74996	74408

Antibody 19D12/15H12 LCF/HCA (nM) / Taxol (ng/mL)

1000	26982	24582	23884	23712	25890	24522	24842	20306	20932
200	23650	23668	23164	23482	24314	25752	23960	21420	19372
40	25204	22624	22020	22956	24152	23908	24834	22462	22160
8	33654	34598	31558	36038	35906	34498	33256	41416	38354
1.6	61430	55962	58780	65954	61946	65024	72552	65054	65508
0.32	73668	75506	79986	73002	77072	76356	87640	68504	72500
0.064	63082	74926	73584	75710	75356	87602	75690	76350	75374
0.0128	78312	80172	71110	68078	73092	81374	80916	76870	75698
0.00256	78070	89290	71662	72122	77618	81720	80172	76744	72498

No treatment: 71974; 81788; 75410; 75124; 75558; 79618; 77860; 83468; 78992; 79840; 85414; 87962; 84304; 88926; 77074; 86696; 74354; 77454.

Table 3. Proliferation of H322 NSCLC cells in the presence of anti-IGFR1 antibody 19D12/15H12 and gefitinib ("Iressa").

Antibody 19D12/15H12 LCF/HCA (nM)	Iressa (nM) 20000	4000	800	160	32	6.4	1.28	0.256	0.0512	0.01024
20	9558	15828	19268	21734	31862	41596	47762	52134	59984	61128
4	10376	16138	20236	24352	33156	41640	49994	54620	54206	62870
0.8	10116	16046	19810	23668	35062	46258	50218	49612	53604	60098
0.16	8992	15922	22342	26574	35768	51788	56192	58236	59784	69564
0.032	10384	20756	22894	26754	34428	41682	47362	49520	46866	60414
0.0064	9272	23412	27042	29930	41026	46906	52394	58162	55702	65872
0.00128	11306	26538	31304	33650	46588	55014	56990	56936	59854	74452
0.000256	11030	25926	31676	33960	41866	55438	55030	55860	55694	76588
5.12E-05	11312	25776	32168	34046	50366	59746	61846	56170	61912	77856
1.02E-05	11468	25536	31772	33518	43818	59198	56520	60394	62178	75492

Antibody 19D12/15H12 LCF/HCA (nM)	Iressa (nM) 20000	4000	800	160	32	6.4	1.28	0.256	0.0512	0.01024
20	10256	14646	19414	20748	26104	29688	36636	34068	38386	44984
4	7434	13982	18762	20558	23708	31514	33878	38178	38814	43776
0.8	9450	15536	17874	20264	26930	37782	35146	37854	39790	46940
0.16	8216	16648	20096	21762	27672	35574	37692	39746	43660	50204
0.032	10600	20332	24214	26092	37170	43970	45010	47656	50738	58834
0.0064	9472	23840	27740	31758	43494	49736	52676	53360	56270	69508
0.00128	10994	25884	30786	35254	46102	51656	57484	53240	59572	74556
0.000256	11074	25614	30444	34546	44880	53284	57562	56742	59694	70748
5.12E-05	10856	26726	32516	33914	45230	53468	59308	59268	61842	74782
1.02E-05	12316	27228	32274	35732	44376	55024	57706	58968	69576	77220

Antibody 19D12/15H12 LCF/HCA (nM)	Iressa (nM) 20000	4000	800	160	32	6.4	1.28	0.256	0.0512	0.01024
20	8794	15734	18284	20542	27156	36040	36982	36560	40968	48488
4	7278	14032	18810	20758	23414	32396	33706	33882	35690	46774
0.8	10144	15324	18636	21026	27062	33876	37008	37674	40920	45608
0.16	8448	15310	19562	22450	26956	34532	37372	39046	40020	49212
0.032	9564	19962	23658	26014	31138	45406	46994	50526	48256	60600
0.0064	9654	22866	26700	30792	39610	46272	55464	53168	55588	67954
0.00128	10748	26120	28034	32110	42170	50768	59264	56428	60524	70960
0.000256	11152	26246	29536	34822	42410	51262	59646	56492	67308	74614
5.12E-05	13086	26320	29186	35546	40932	56044	61442	57668	60428	69352
1.02E-05	10894	27054	32100	34678	44726	52768	62750	60398	65932	73544

Antibody 19D12/15H12 LCF/HCA (nM)	Iressa (nM)
20	58598 48444 49166 51020 48730 49684 45064 52120 51960
4	63472 47736 49492 49964 49606 52660 49972 50764 49330
0.8	65622 50708 49752 49306 49694 52460 50044 48780 49206
0.16	67002 51304 53266 49398 50474 53774 52510 48004 49650
0.032	82944 58364 59636 64806 60990 58984 56958 60178 53730
0.0064	100862 69246 72446 68396 66834 73768 73208 70772 66560
0.00128	102034 76940 72448 73608 73492 75502 69358 79496 77492
0.000256	107462 77972 76152 76908 80874 79674 69232 80170 78292
5.12E-05	102770 79660 81936 84040 79398 83148 81960 78368 81372

Iressa (nM)	
20000	10618 11294 10994 11770 11460 9734 12088 11650 12396
4000	27810 24546 24376 26742 28156 24528 28442 27026 27738
800	40002 31290 30954 31800 31390 30998 32232 31366 32328
160	43932 32072 32728 33532 35078 34964 36144 34946 35044
32	58272 41264 40992 44162 42054 43124 45062 41426 45712
6.4	71582 52692 49154 50752 50888 52698 52362 59304 63484
1.28	79748 57670 51772 58016 57048 62268 57264 57770 60032
0.256	73246 58760 59474 57314 58384 59448 66806 64854 56752
0.0512	76032 61018 59690 63252 63688 60730 74464 65802 59448

No treatment: 107584; 107042; 73770; 80360; 80730; 83682; 82196; 81768; 76594; 74958; 78190; 83348; 81032; 78026; 81010; 81632; 72058; 74778.

Table 4. Proliferation of H322 NSCLC cells in the presence of anti-IGFR1 antibody 19D12 (LCF/HCA) and lonafarnib.

lonafarnib (uM)

Antibody 19D12/15H12 LCF/HCA (nM)	10	2	0.4	0.08	0.016	0.0032	0.00064	0.000128	2.56E-05	5.12E-06
20	22887	65425	80588	83638	90851	93313	88977	84231	86387	94181
4	16249	64289	74003	87732	90544	93698	86567	83618	89257	94255
0.8	16422	65033	81211	88566	93368	94731	90121	85926	89908	93068
0.16	19691	74212	79370	95207	94682	92386	95905	89859	87593	92957
0.032	32664	95526	106781	109768	119933	124460	124138	119869	119709	112287
0.0064	36016	117821	125523	136608	134282	142279	138637	132253	134387	131094
0.00128	18089	117945	129629	143264	148075	146870	144201	144368	146985	141886
0.000256	47214	122431	126667	142050	145968	147044	145114	148567	139090	140391
5.12E-05	37457	126574	125493	146377	141190	143914	145795	146753	141184	147030
1.02E-05	33216	127909	123776	134604	140889	142610	142138	147417	145893	143802

lonafarnib (uM)

Antibody 19D12/15H12 LCF/HCA (nM)	10	2	0.4	0.08	0.016	0.0032	0.00064	0.000128	2.56E-05	5.12E-06
20	25599	81353	94441	102269	105276	104847	101476	101812	95178	106063
4	20764	77690	90928	106880	107326	99982	107648	101840	100814	103761
0.8	20754	82864	94954	99767	103085	105548	104157	105083	102191	105169
0.16	31796	83859	99944	102713	114195	115366	102845	109980	105072	108221
0.032	21337	96495	106094	121189	125248	129724	125146	116621	122758	118644
0.0064	36668	111937	118924	136466	140637	139477	139912	144443	138247	144052
0.00128	21924	123895	132128	143031	141540	143420	151166	150090	144396	144645
0.000256	48311	125873	132897	145890	151220	144128	142869	149502	143318	136823
5.12E-05	48664	119468	129321	133949	136336	139465	141690	140419	144102	144108
1.02E-05	43562	118319	121877	131702	143683	141602	138419	169559	135173	144663

lonafarnib (uM)

Antibody 19D12/15H12 LCF/HCA (nM)	10	2	0.4	0.08	0.016	0.0032	0.00064	0.000128	2.56E-05	5.12E-06
20	25332	79142	87710	99399	105519	104613	95139	98673	102026	107719
4	18060	75938	90974	93891	102015	108253	99835	98861	98297	100571
0.8	19703	82941	88791	105006	101589	107751	104522	98935	97246	104178
0.16	23130	80072	91005	103752	112789	106256	105474	102482	101809	99297
0.032	31869	101343	104850	116040	118774	124757	128139	123353	119392	120241
0.0064	28099	117822	116943	134107	139079	142540	142884	131445	140203	134047
0.00128	26945	122121	127278	138720	139301	143652	146461	141979	146123	148973
0.000256	35651	135020	125671	138311	137575	151958	143929	145060	144944	142950
5.12E-05	71640	116076	126056	138805	150323	149387	141235	142107	148337	135959
1.02E-05	23393	121266	126158	139946	146882	142668	155099	151232	153079	145366

lonafarnib (uM)

Antibody 19D12/15H12 LCF/HCA (nM)	10	2	0.4	0.08	0.016	0.0032	0.00064	0.000128	2.56E-05
20	87222	99589	92548	112756	116485	112681	111436	116765	115599
4	86973	95263	99359	113069	111989	115427	116657	111269	111380
0.8	87686	108909	106820	117584	116744	115624	122158	109225	107476
0.16	88076	100801	103264	113402	119792	114893	111254	109486	119384
0.032	101173	112575	111087	121525	126829	119236	120476	119619	127491
0.0064	103393	122551	126487	135788	130783	132775	133999	136391	130520
0.00128	111788	124573	128587	141883	148061	133429	135943	136842	134429
0.000256	109876	126163	120456	139750	141149	139314	143089	138327	140445
5.12E-05	110351	127605	122680	139271	142088	141457	143808	138240	138655

lonafarnib (uM)

Antibody 19D12/15H12 LCF/HCA (nM)	10	2	0.4	0.08	0.016	0.0032	0.00064	0.000128	2.56E-05
10	19478	10458	23206	21356	20500	30885	22728	33558	37475
2	96039	114766	108395	126290	125120	125480	128736	125728	117942
0.4	96566	116350	110889	126539	129131	132824	129715	123707	122379
0.08	111539	122519	121571	140084	136507	138641	141354	139918	139542
0.016	111904	129612	122694	138400	138169	143620	139541	145629	143004
0.0032	111185	124204	122392	141986	141129	142694	141727	141690	141938
0.00064	107175	127792	118530	144611	147139	146830	142720	138984	149101
0.000128	111619	118044	128736	146048	143127	143930	139172	142366	142624
2.56E-05	108451	129321	121819	140423	140297	145549	137649	138705	139746

No treatment: 114280;118325; 135058; 129246; 125513; 119709; 134363; 129286; 138048; 132272; 138562; 134026; 135510; 138660; 132918; 131451; 140071; 135689.

Table 5. Proliferation of MCF7 cells in the presence of anti-IGFR1 antibody

4-hydroxy tamoxifen (ng/mL)

Antibody 19D12/15H12 (nM)	20000	4000	800	160	32	6.4	1.28	0.256	0.0512	0.01024
20	37	3971	11406	10724	13431	12577	15154	17939	15882	17897
4	40	5820	12508	11400	13105	12500	15784	15310	19683	16670
0.8	90	3445	10614	11280	13370	12744	12770	13406	15035	14492
0.16	51	6002	12536	12269	13555	13668	17314	19078	17106	20470
0.032	104	6110	15449	18373	17595	19182	22139	22556	24439	19180
0.0064	72	7757	16479	17958	19548	21212	24601	23112	22358	22710
0.00128	87	9202	21565	23021	22216	24256	26412	27233	26660	23187
0.000256	47	7471	22532	23278	23323	20944	23987	23894	25353	22543
5.12E-05	127	13158	23026	24274	24764	27845	28599	30546	35993	27680
1.02E-05	88	13436	22449	21505	26558	27224	29026	27441	31739	31126

4-hydroxy tamoxifen (ng/mL)

Antibody 19D12/15H12 (nM)	20000	4000	800	160	32	6.4	1.28	0.256	0.0512	0.01024
20	69	4768	12296	11697	12617	12755	14998	17332	16589	18942
4	49	4595	11159	12899	11551	12734	14254	15878	16453	20904
0.8	49	4017	12152	12777	12363	12382	15072	15739	16814	16040
0.16	62	3822	13820	12807	14116	13295	16653	17297	17190	18994
0.032	49	8312	13771	15161	15330	15502	20027	20729	24916	24574
0.0064	58	4944	16301	16891	19000	18186	24664	21450	26585	25930
0.00128	67	7995	18252	20001	20433	22047	24749	26553	24061	28200
0.000256	44	6257	18603	20299	20694	19361	22858	29561	23383	23704
5.12E-05	155	12478	21685	24086	21627	26539	28497	28032	31389	28292
1.02E-05	71	10442	21337	18711	24075	28872	25823	27243	25855	26935

4-hydroxy tamoxifen (ng/mL)

Antibody 19D12/15H12 (nM)	20000	4000	800	160	32	6.4	1.28	0.256	0.0512	0.01024
20	44	6281	12450	12452	13478	13461	15254	16050	14565	16484
4	32	5475	10949	11943	12893	11816	11994	13359	13330	14821
0.8	38	6446	11217	13440	11887	11298	13401	13307	14435	15783
0.16	48	7402	12566	12977	14859	12918	14487	13272	13248	12716
0.032	44	7046	13296	16558	16698	14963	17395	19170	21511	21430
0.0064	38	9971	17183	18826	18601	20504	19703	21629	22131	25221
0.00128	57	6826	18767	18169	21005	19872	20956	25626	26582	24174
0.000256	47	10322	19159	20185	21625	22398	23918	24209	24674	25993
5.12E-05	48	10014	21261	22537	24130	22183	28348	33891	30651	36185
1.02E-05	42	8701	18262	20578	22339	24187	24942	26658	30301	24115

Antibody 19D12/15H12 (nM)										
20	23174	26202	29141	21364	18868	16137	21415	20969	20629	
4	23012	25311	22812	20994	20654	17723	21558	20516	22986	
0.8	22225	27911	24915	19444	18812	19569	23960	18932	24136	
0.16	28829	28863	24086	20817	16735	20162	20953	14080	19403	
0.032	31483	33506	32253	30553	21667	22447	23620	20087	29483	
0.0064	32335	38153	34750	28815	23405	29131	26092	21985	30515	
0.00128	39949	35834	38745	36522	31998	25787	29872	28453	38665	
0.000256	39149	38337	35944	38816	30209	28243	36082	34273	38595	
5.12E-05	42680	42952	41634	39082	35487	31795	33137	30620	28960	

4-hydroxy tamoxifen (ng/mL)										
20000	72	87	71	61	67	80	70	92	80	
4000	10306	14180	10772	10390	8819	8866	10856	7892	17190	
800	21328	22054	21091	21755	19455	16634	23295	18307	19893	
160	22497	24665	25001	19325	17700	21339	23979	17326	21462	
32	25519	27289	25493	19637	16366	23373	21391	15610	21213	
6.4	25230	30579	27858	23336	18722	23597	21593	16646	22699	
1.28	37809	36047	29501	36072	28249	30905	34689	24575	30878	
0.256	44922	43317	40504	41227	32889	40176	46899	40723	45399	
0.0512	45433	40809	35380	37799	32441	35438	40686	31466	36389	

19D12/15H12 and 4-hydroxy tamoxifen.

No treatment: 38094; 32799; 43225; 30131; 35545; 28400; 35256; 18441; 34641; 24138; 28849; 21562; 36446; 25365; 34561; 21852; 40120; 23587.

Table 6. Proliferation of MCF7 cells in the presence of anti-IGFR1 antibody 19D12/15H12 and doxorubicin.

No treatment: 126997; 128567; 116244; 117342; 112806; 114636; 122023; 117403;

Doxorubicin (ug/mL)

Antibody 19D12/15H12 (nM)	20	4	0.8	0.16	0.032	0.0064	0.00128	0.000256	0.0000512	0.00001024
20	9432	11571	4327	14770	28330	61105	67190	68057	63435	67065
4	8464	11472	4480	15979	29169	52900	65198	60868	70110	61696
0.8	7693	11778	4916	14649	25910	56538	55991	60055	64429	70307
0.16	11139	13368	3876	17603	33070	57990	62871	57889	61711	72432
0.032	8212	11386	4339	14678	24337	54110	65887	60368	61919	60165
0.0064	7057	10648	4702	12467	25304	53583	59554	61820	60524	60936
0.00128	9333	11985	4511	16285	30634	62212	65741	69427	68773	71351
0.000256	6667	13174	5698	15544	30696	70725	78623	74312	76193	86861
0.0000512	6793	11124	5649	17621	41883	93794	104241	107406	106322	111388
0.00001024	7789	12606	5132	19799	41284	95276	94958	100293	102670	101144

Doxorubicin (ug/mL)

Antibody 19D12/15H12 (nM)	20	4	0.8	0.16	0.032	0.0064	0.00128	0.000256	0.0000512	0.00001024
20	7489	10465	5202	12812	27202	54983	61586	62242	60307	59288
4	8097	12760	4259	13518	26907	53567	65049	58980	57611	61992
0.8	7962	11444	4620	14232	25870	52978	55162	60064	55903	60959
0.16	7156	11664	4656	14434	23880	51792	56145	62662	54446	63224
0.032	7273	11715	3808	11653	25820	58726	58052	64869	67509	67042
0.0064	9514	11880	4717	13751	26901	55417	69739	59483	61862	70864
0.00128	7624	11335	5168	13974	30690	65877	78141	76721	72500	74819
0.000256	6795	13841	5192	15665	34596	72686	87772	83443	87727	96162
0.0000512	4987	10651	6383	16114	41787	87535	109774	95142	102950	101410
0.00001024	7453	10964	5341	17070	36535	95801	102505	104135	98770	97354

Doxorubicin (ug/mL)

Antibody 19D12/15H12 (nM)	20	4	0.8	0.16	0.032	0.0064	0.00128	0.000256	0.0000512	0.00001024
20	6894	12254	4561	14187	28448	53574	60910	58429	57910	65793
4	7759	12733	4690	13346	27239	48782	54506	56615	58519	58411
0.8	8279	11409	5204	13692	27136	53208	57034	63312	56274	59071
0.16	9293	11582	4477	13437	28068	52677	57275	56349	64286	63113
0.032	7732	12239	4457	13470	26358	56485	67349	64682	63108	60620
0.0064	7083	12668	4685	15548	25719	55245	67424	65321	61740	70000
0.00128	7242	12016	5038	15836	32028	73071	75306	74244	81846	82028
0.000256	7667	11912	4588	17698	33634	81304	90050	86458	82101	96123
0.0000512	5540	13000	4993	16930	35578	81956	97435	90081	89891	90199
0.00001024	8651	11441	5456	18082	41428	84266	104631	94107	88781	103628

Antibody 19D12/15H12 (nM)									
20	68587	64953	54120	63607	61240	60441	72524	63214	56014
4	61918	62606	57447	59014	60339	64229	63861	58382	56115
0.8	65828	68830	59382	63472	59922	63861	68302	59377	60874
0.16	61026	60105	56597	61731	58445	62557	61735	60171	59635
0.032	65968	65014	53068	64005	60882	61339	67666	59746	55775
0.0064	70386	72436	59947	61008	59983	73428	86004	63957	66125
0.00128	87998	85396	72430	77794	70644	74742	85341	70972	75666
0.000256	98787	96373	87642	92406	91506	94941	96941	92043	98687
0.0000512	108894	108108	95976	101359	97684	96453	106595	104255	100190

Doxorubicin (ug/mL)									
20	9006	7776	9201	8561	9331	5986	11238	7007	8551
4	13508	13215	14467	14798	15140	13720	14371	12706	13581
0.8	7826	6924	6188	7517	6873	7476	7217	7509	7035
0.16	18882	17682	19304	21187	20726	17219	24438	17565	17961
0.032	42219	41877	43752	46250	44311	42710	47630	41075	42613
0.0064	94502	95453	92157	94356	108010	99650	104886	96671	97741
0.00128	118478	99555	109394	106089	117727	103222	107569	101631	101676
0.000256	110655	99580	106279	113634	104912	108830	115394	102385	111217
0.0000512	114729	100997	103267	109090	109582	120733	112898	108905	101765

121666; 112160; 123333; 118499; 117737; 120728; 115823; 128693; 124935; 126222.

Example 2: *In vivo* tumor inhibition assay of anti-IGFR and paclitaxel using a NSCLC xenograft model H322.

In this example, the effectiveness of an anti-IGFR/paclitaxel combination of the invention for tumor growth inhibition was demonstrated *in vivo*.

Five million H322 human NSCLC cells in Matrigel were inoculated subcutaneously into nude mice. Anti-IGFR antibody 19D12 and/or paclitaxel treatment was initiated when the tumor size reached ~105-115 mm^3 at day 0. Both 19D12 and paclitaxel were dosed twice per week. Anti-IGFR antibody 19D12 was dosed at 0.5 mg per mouse. Paclitaxel was at 15 mpk. Ten animals per group. Tumor volumes were measured by Labcat.

Table 7. Tumor growth inhibition in mice.

		Day 0	31
Vehicle control	volume (mm3)	112.68	383.70
	SEM	3.09	72.75
	SD	9.28	218.25
	Growth		271.02
0.5 mg 19D12	volume (mm3)	106.57	173.02
	SEM	1.96	38.63
	SD	5.87	115.89
	Growth		66.45
	% inhibition		75.50%
15 mpk Taxol	volume (mm3)	109.54	214.25
	SEM	2.9	27.94
	SD	8.7	83.81
	Growth		104.71
	% inhibition		52%
0.5 mg 19D12+15 mpk Taxol	volume (mm3)	109.79	121.92
	SEM	4.21	22.17
	SD	12.63	66.52
	Growth		12.13
	% inhibition		95.50%

****

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

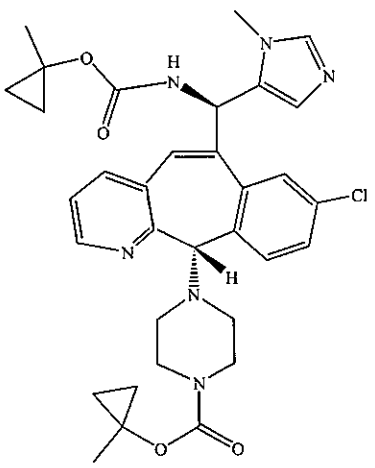
Patents, patent applications, Genbank Accession Numbers and publications are cited throughout this application, the disclosures of which, particularly, including all disclosed chemical structures and antibody amino acid sequences therein, are incorporated herein by reference.

CLAIMS:

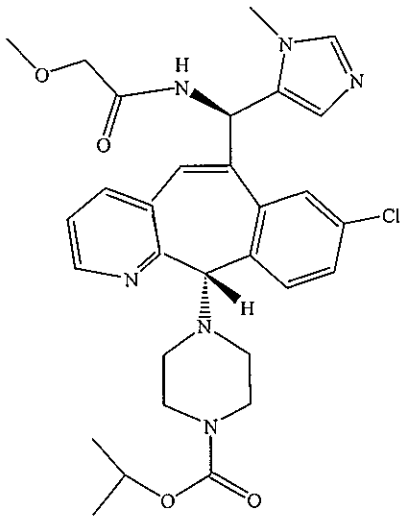
1. A combination comprising:

(a) a recombinant anti-insulin-like growth factor-1 antibody produced by a method comprising introducing a polynucleotide encoding a light chain immunoglobulin variable region amino acid sequence which comprises CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO: 5, CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO: 6 and CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO: 7 into a host cell under conditions suitable for expression of said immunoglobulin and introducing a polynucleotide encoding a heavy chain immunoglobulin variable region amino acid sequence which comprises CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO: 8 or 12 , CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO: 9 and CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO: 10 into a host cell under conditions suitable for expression of said immunoglobulin; and

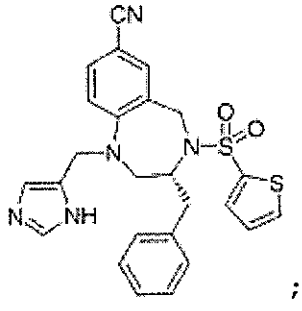
(b) one or more chemotherapeutic agents selected from the group consisting of: lonafarnib;



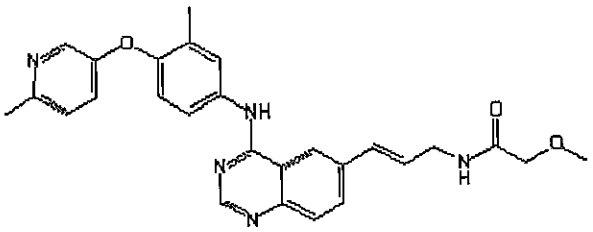
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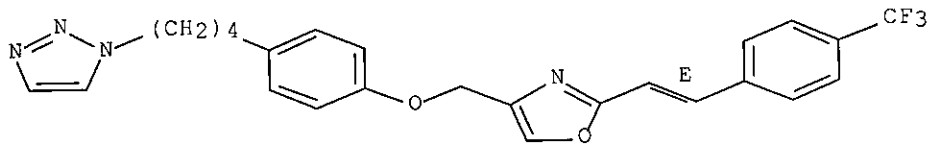
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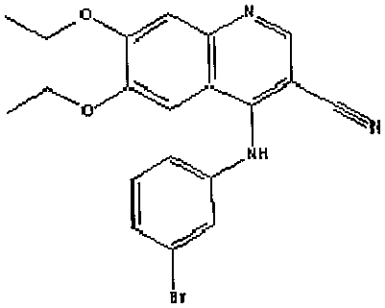


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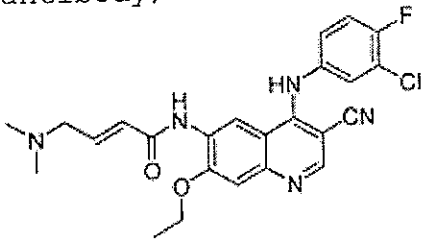


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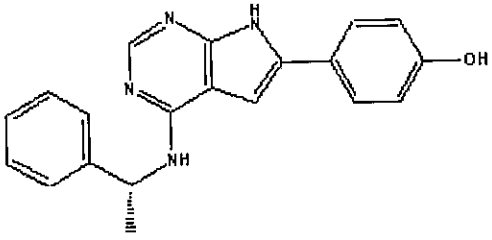




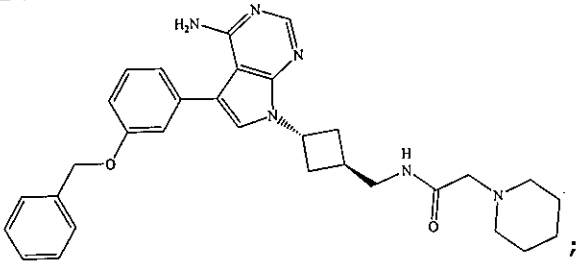
; ; gefitinib; erlotinib; lapatinib; canertinib; ABX-EGF antibody; cetuximab;



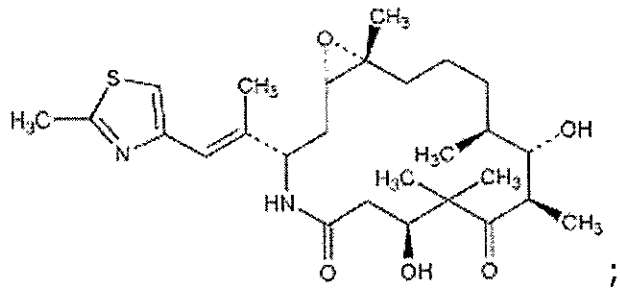
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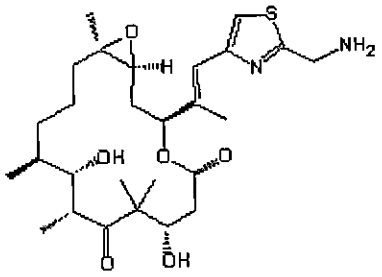
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; L-779,450; quercetin; octreotide; bortezomib; epithilone B;



; etoposide;



; temozolomide; epirubicin; 4-hydroxytamoxifen; pipendoxifene; arzoxifene; fulvestrant; acolbifene; lasofoxifene; idoxifene; bazedoxifene; oxaliplatin; retinoic acid; and camptothecin.

2. The combination of claim 2 wherein the host cell is a Chinese hamster ovary cell.

3. The combination of claim 1 wherein (a) comprises a recombinant antibody comprising a light chain immunoglobulin variable region comprising amino acids 20-128 of SEQ ID NO: 2 and a heavy chain immunoglobulin variable region comprising amino acids of 20-137 of SEQ ID NO: 4.

4. The combination of claim 3 wherein the light chain immunoglobulin variable region is linked to a kappa immunoglobulin constant domain and wherein the heavy chain immunoglobulin variable region is linked to a gamma-1 immunoglobulin constant domain.

5. The combination of claim 4 wherein the therapeutic agent is
lonafarnib;
cetuximab;
bevacizumab;
erlotinib;

rapamycin;
temsirolimus;
sorafenib;
gefitinib;
fulvestrant;
octreotide;
temozolomide; or
4-hydroxytamoxifen.

6. The combination of claim 1 wherein a chemotherapeutic agent is lonafarnib.

7. The combination of claim 1 wherein a chemotherapeutic agent is cetuximab.

8. The combination of claim 1 wherein a chemotherapeutic agent is bevacizumab.

9. The combination of claim 1 wherein a chemotherapeutic agent is sorafenib.

10. The combination of claim 1 wherein a chemotherapeutic agent is gefitinib.

11. The combination of claim 1 wherein a chemotherapeutic agent is fulvestrant.

12. The combination of claim 1 wherein a chemotherapeutic agent is octreotide.

13. The combination of claim 1 wherein a chemotherapeutic agent is temozolomide.

14. The combination of claim 1 wherein a chemotherapeutic agent is 4-hydroxytamoxifen.

15. A pharmaceutical composition comprising the combination of claim 1 along with one or more pharmaceutically acceptable carriers.

16. The combination of claim 1, wherein said recombinant antibody is in a pharmaceutical composition comprising water, buffer and a sugar.

17. Use of a therapeutically effective amount of a combination of claim 1 for preparing a pharmaceutical composition for treating or preventing a medical condition in a mammalian subject in need of such treatment or prevention, which medical condition is selected from the group consisting of acromegaly, bladder cancer, Wilm's cancer, ovarian cancer, pancreatic cancer, benign prostatic hyperplasia, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer, cervical cancer, synovial sarcoma, diarrhea associated with metastatic carcinoid, vasoactive intestinal peptide secreting tumors, gigantism, psoriasis, atherosclerosis, smooth muscle restenosis of blood vessels, inappropriate microvascular proliferation, rheumatoid arthritis, Grave's disease, multiple sclerosis, systemic lupus erythematosus, Hashimoto's Thyroiditis, Myasthenia Gravis, autoimmune thyroiditis and Bechet's disease.

18. The use of claim 17 wherein the chemotherapeutic agent is a member selected from the group consisting of:
lonafarnib;
cetuximab;
bevacizumab;
erlotinib;
rapamycin;
temsirolimus;
sorafenib;
gefitinib;
fulvestrant;
octreotide;
temozolomide; and
4-hydroxytamoxifen.

19. The use of claim 17 wherein the medical condition is selected from the group consisting of bladder cancer, Wilm's cancer, ovarian cancer, pancreatic cancer, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer and cervical cancer.

20. The use of claim 17 wherein one or more components of the combination are suitable to be administered to the subject by a parenteral route.

21. The use of claim 17 wherein the subject is a human.

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Val Gln Cys Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys
            20                  25                  30

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        35                  40                  45

agt agc ttt gct atg cac tgg gtt cgc cag gct cca gga aaa ggt ctg  192
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    50                  55                  60

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65                  70                  75                  80

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                85                  90                  95

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Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
            100                 105                 110

tac tgt gca aga ctg ggg aac ttc tac tac ggt atg gac gtc tgg ggc  384
Tyr Cys Ala Arg Leu Gly Asn Phe Tyr Tyr Gly Met Asp Val Trp Gly
        115                 120                 125

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Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser
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Leu Glu Asn Cys Thr Val Ile Glu Gly Tyr Leu His Ile Leu Leu Ile
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Leu Asp Ala Val Ser Asn Asn Tyr Ile Val Gly Asn Lys Pro Pro Lys
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Glu Cys Gly Asp Leu Cys Pro Gly Thr Met Glu Glu Lys Pro Met Cys
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Glu Lys Thr Thr Ile Asn Asn Glu Tyr Asn Tyr Arg Cys Trp Thr Thr
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35 40 45

Ser Ser Phe Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Ile Ser Val Ile Asp Thr Arg Gly Ala Thr Tyr Tyr Ala Asp
65 70 75 80

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser
85 90 95

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Met Ala Val Tyr
100 105 110

Tyr Cys Ala Arg Leu Gly Asn Phe Tyr Tyr Gly Met Asp Val Trp Gly
115 120 125

Gln Gly Thr Thr Val Thr Val Ser Ser
130 135