activity of other receptors. Preferably, such methods and compositions would employ agonists suitable for modification for the delivery of cytotoxic payloads to target cells, but also suitable for non-cytotoxic uses. Preferably, such methods and compositions would employ antibodies modified to limit their antigenicity when administered to a subject in need thereof.

BRIEF DESCRIPTION OF THE DRAWING

[0006] Figure 1 shows the synergistic effect of combined treatment with DTA-1 (specific for mGITR; see, e.g., Shimizu, et al. (2002) *Nature Immunol.* 3:135-142) and local irradiation. "CR" means complete regression.

[0007] Figure 2 shows the modules of GITR as determined by the method described in Naismith and Sprang (1998) *Trends Biochem. Sci.* 23:74-79. Bold residues indicate the conformational DTA-1-like epitope as determined below.

SUMMARY ~~OF THE INVENTION~~

[0008] The present ~~invention~~disclosure meets these needs in the art and more by providing agonists of GITR, e.g. humanized anti-GITR antibodies.

[0009] T~~In one aspect the~~ ~~invention~~disclosure provides binding compounds, such as an antibodies or fragment thereof, including humanized or chimeric recombinant antibodies, that binds human GITR, comprising an antibody light chain variable domain, or antigen binding fragment thereof, having at least one or more CDRs selected from the group consisting of SEQ ID NOs: 56-88 and a heavy chain variable domain, having at least one or more CDRs selected from the group consisting of SEQ ID NOs: 23-55.

[0009a] In one aspect, there is provided an isolated antibody or antigen-binding fragment thereof that specifically binds to human GITR comprising:

a CDR-L1 that comprises the amino acid sequence set forth in SEQ ID NO: 56 or a variant thereof, wherein the variant comprises one conservative amino acid substitution relative to SEQ ID NO:56;

A CDR-L2 that comprises the amino acid sequence set forth in SEQ ID NO: 67 or variant thereof, wherein the variant comprises one conservative amino acid substitution relative to SEQ ID NO: 67;

a CDR-L3 that comprises the amino acid sequence set forth in SEQ ID NO: 78 or a variant thereof, wherein the variant comprises one conservative amino acid substitution relative to SEQ ID NO: 78;

a CDR-H1 that comprises the amino acid sequence set forth in SEQ ID NO: 23 or a variant thereof, wherein the variant comprises one conservative amino acid substitution relative to SEQ ID NO: 23;

CDR-H2 that comprises the amino acid sequence set forth in SEQ ID NO: 34 or a variant thereof, wherein the variant comprises one conservative amino acid substitution relative to SEQ ID NO: 34; and

CDR-H3 that comprises the amino acid sequence set forth in SEQ ID NO: 45 or a variant thereof, wherein the variant comprises one conservative amino acid substitution relative to SEQ ID NO:45.

[0010] In other embodiments the binding compound of the present ~~invention~~disclosure comprises a light chain variable domain and a heavy chain variable domain, or the antigen binding fragments thereof, described in the preceding two paragraphs.

[0011] In some embodiments, the binding compound comprises a framework region, wherein the amino acid sequence of the framework region is all or substantially all of a human immunoglobulin amino acid sequence.

[0012] In some embodiments the light chain variable domain comprises a sequence selected from the group consisting of SEQ ID NOs: 12-22 or a variant thereof. In some embodiments the heavy chain variable domain comprises a sequence selected from the group consisting of SEQ ID NOs: 1-11. In yet a further embodiment, the binding compound

comprises a light chain variable domain and a heavy chain variable domain, or the antigen binding fragments thereof, described in this paragraph.

[0013] In other embodiments the binding compound of the present ~~invention~~disclosure comprises a light chain variable domain, or an antigen binding fragment thereof, consisting essentially of a sequence selected from the group consisting of SEQ ID NOs: 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, and/or a heavy chain variable domain, or an antigen binding fragment thereof, consisting essentially of a sequence selected from the group consisting of SEQ ID NOs: 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110.

[0013a] In another aspect, there is provided an isolated antibody or antigen-binding fragment thereof that specifically binds to human GITR protein comprising:
CDR-L1, CDR-L2 and CDR-L3 of the light immunoglobulin chain comprising the amino acid sequence set forth in SEQ ID NO: 105; and
CDR-H1, CDR-H2 and CDR-H3 of the heavy immunoglobulin chain comprising the amino acid sequence set forth in SEQ ID NO: 104.

[0013b] In another aspect, there is provided an isolated antibody or antigen-binding fragment thereof that binds specifically to human GITR protein comprising a light chain immunoglobulin variable domain comprising an amino acid sequence which is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 105; and a heavy chain immunoglobulin variable domain comprising an amino acid sequence which is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 104.

[0013c] In another aspect, there is provided an isolated antibody or antigen-binding fragment thereof that specifically binds to human GITR protein comprising:
CDR-L1, CDR-L2 and CDR-L3 of the light immunoglobulin chain comprising the amino acid sequence set forth in SEQ ID NO: 105; wherein residue 31 is Q and residue 57 is Q; and
CDR-H1, CDR-H2 and CDR-H3 of the heavy immunoglobulin chain comprising the amino acid sequence set forth in SEQ ID NO: 104.

[0013d] In another aspect, there is provided an isolated immunoglobulin polypeptide comprising:
CDR-H1 that comprises the amino acid sequence set forth in SEQ ID NO: 23;
CDR-H2 that comprises the amino acid sequence set forth in SEQ ID NO: 34; and
CDR-H3 that comprises the amino acid sequence set forth in SEQ ID NO: 45;
fused to a γ1 human immunoglobulin constant domain.

[0014] In one embodiment, the ~~invention~~disclosure relates to antibodies that are able to block the binding of a binding compound of the present ~~invention~~disclosure to human GITR in a cross-blocking assay. In another aspect, there is provided an isolated antibody or antigen-binding fragment thereof that is able to block binding of the antibody or antigen-binding fragment as defined herein to human GITR protein. In various embodiments the antibody is able to block binding of human GITR to an antibody comprising the CDR sequences of antibodies 36E5, 3D6, 61G6, 6H6, 61F6, 1D8, 17F10, 35D8, 49A1, 9E5, or 31H6 as disclosed herein. In another embodiment, the ~~invention~~disclosure relates to binding compounds that are able to block GITR-mediated activity, such activities including but not limited to, co-stimulation of naïve CD4+ T cell proliferation assay.

[0015] In some embodiments, the binding compound of the present ~~invention~~disclosure further comprises a heavy chain constant region, wherein the heavy chain constant region comprises a γ1, γ2, γ3, or γ4 human heavy chain constant region or a variant thereof. In various embodiments the light chain constant region comprises a lambda or a kappa human light chain constant region.

[0016] In various embodiments the binding compounds of the present ~~invention~~disclosure are polyclonal, monoclonal, chimeric, humanized or fully human antibodies or fragments thereof. The present ~~invention~~disclosure also contemplates that the antigen binding fragment is an antibody fragment selected from the group consisting of Fab, Fab', Fab'-SH, Fv, scFv, $F(ab')_2$, and a diabody.

[0017] The present ~~invention~~disclosure encompasses a method of enhancing an immune response in a human subject comprising administering to a subject in need thereof an antibody (or a antigen binding fragment thereof) specific for GITR in an amount effective to stimulate GITR signaling. In another aspect, there is provided the use of an antibody or antigen-binding fragment as defined herein in the manufacture of a medicament for enhancing an immune response in a human subject. In some embodiments, the antibody specific for GITR is the humanized or chimeric antibody. In further embodiments, the immune response is an anti-infective or anti-viral response. In certain embodiments, the GITR antibody or antigen binding fragment thereof is co-administered with a TGFβ antibody or local radiation.

[0018] The present ~~invention~~disclosure encompasses an isolated nucleic acid encoding the polypeptide sequence of an antibody embodiment of the binding compound of the present ~~invention~~disclosure. In another aspect, there is provided an isolated nucleic acid encoding at least one of the light immunoglobulin chain or the heavy immunoglobulin chain of the antibody or antigen-binding fragment or polypeptide as defined herein. The nucleic acid can be in an expression vector operably linked to control sequences recognized by a host cell transfected with the vector. In another aspect, there is provided an expression vector comprising the nucleic acid as defined herein operably linked to an expression control sequence that is recognized by a host cell when the host cell is transformed with the vector. Also encompassed is a host cell comprising the vector, and a method of producing a polypeptide comprising culturing the host cell under conditions wherein the nucleic acid sequence is expressed, thereby producing the polypeptide, and recovering the polypeptide from the host cell or medium. In another aspect, there is provided an isolated host cell comprising the expression vector as defined herein. In another aspect, there is provided a method of producing a polypeptide comprising: culturing the host cell as defined herein in culture medium under conditions wherein the nucleic acid sequence is expressed; and recovering the polypeptides from the host cell or culture medium or both.

[0019] The present ~~invention~~disclosure provides an antibody or antigen binding fragment thereof, produced by a hybridoma deposited at the American Type Culture Collection (ATCC), wherein the hybridoma is selected from the group consisting of PTA-9889, PTA-9890, PTA-9891, PTA-9892, PTA-9893, PTA-10286, PTA-10287, PTA-10288, PTA-10289, PTA- 10290, and PTA- 10291. In another aspect, there is provided an isolated antibody or antigen-binding fragment thereof, produced by a hybridoma deposited at the American Type Culture Collection (ATCC), wherein the hybridoma is PTA-9890.

[0020] The present ~~invention~~disclosure encompasses an antibody or antigen binding fragment that binds to human GITR protein, wherein the antibody or antigen binging fragment recognizes an epitope spanning module 3 and module 4 of human GITR protein (SEQ ID NO: 89). In another aspect, there is provided an isolated antibody or antigen-binding thereof that binds to human GITR protein, wherein the antibody or antigen-binding fragment recognizes an epitope spanning module 3 and module 4 of human GITR protein (SEQ ID NO: 89). In certain embodiments, the epitope comprises Gly^{57}, Arg^{65}, His^{67}, Lys^{80}, Phe^{81}, Ser^{82}, and Gin^{86}. In yet other embodiments the antibody cross-blocks at least one of the antibodies or antibody fragments produced by the hybridomas selected from group consisting of PTA-9889, PTA-9890, PTA-9891, PTA-9892, PTA-9893, PTA-10286, PTA-10287, PTA-10288, PTA-10289, PTA- 10290, and PTA- 10291.

[0020a] In another aspect, there is provided a pharmaceutical composition comprising the antibody or antigen-binding as defined herein and a pharmaceutically acceptable carrier.

[0020b] In another aspect, there is provided a composition comprising the antibody or antigen-binding fragment as defined herein and a second therapeutic agent.

[0020c] In another aspect, there is provided a composition comprising the antibody or antigen-binding fragment as defined herein and a member selected from the group consisting of thiotepa, busulfan, improsulfan, piposulfan, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine, bullatacin, bullatacinone, camptothecin, topotecan, bryostatin, callystatin, CC-1065, cryptophycin 1, cryptophycin 8, dolastatin, duocarmycin, KW-2189, CB 1-TM1, eleutherobin, pancratistatin, sarcodictyin, spongistatin, chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimnustine, calicheamicin, calicheamicin gamma II, calicheamicin omega II, dynemicin, dynemicin A, clodronate, neocarzinostatin chromophore, aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, deoxydoxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, 5-fluorouracil (5-FU), denopterin, methotrexate, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone, aminoglutethimide, mitotane, trilostane, frolinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, eniluracil, amsacrine, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elformithine, elliptinium acetate, epothilone, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidainine, maytansine, ansamitocins, mitoguazone, mitoxantrone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, rhizoxin, sizofuran, spirogermanium, tenuazonic acid, triaziquone, 2,2',2''-trichlorotriethylamine, T-2 toxin, verracurin A, roridin A, anguidine, urethane, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside, cyclophosphamide, paclitaxel, a cremophor-free, albumin-

engineered nanoparticle formulation of paclitaxel, docetaxel, chloranbucil, gemcitabine, 6-thioguanine, mercaptopurine, methotrexate, cisplatin, carboplatin, vinblastine, platinum, etoposide, ifosfamide, mitoxantrone, vincristine, vinorelbine, novantrone, teniposide, edatrexate, daunomycin, aminopterin, capecitabine, ibandronate, CPT-11, RFS2000, difluoromethylornithine (DMFO), retinoic acid, tamoxifen, raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, toremifene, 4(5)-imidazoles, aminoglutethimide, megestrol acetate, exemestane, formestanie, fadrozole, vorozole, letrozole, anastrozole, flutamide, nilutamide, bicalutamide, leuprolide, goserelin, troxacitabine, angiozyme, allovectin, leuvectin, vaxid, recombinant IL-2, lurtotecan and abarelix.

[0020d] In another aspect, there is provided a composition comprising the antibody or antigen-binding fragment as defined herein and a member selected from the group consisting of an alkylating agent, an ethylenimine, a methylamelamine, an acetogenin, a camptothecin, a cryptophycin, a sarcodictyin, an antibiotic, a bisphosphonate, a mitomycin, an anti-metabolite, a folic acid analogue, a purine analog, an androgen, an anti-adrenal, a folic acid replenisher, an epothilone, a trichothecene, a taxoid, a retinoid, an anti-hormonal agent, an aromatase inhibitor, an anti-androgen, an antisense oligonucleotide, a ribozyme, a HER2 expression inhibitor and a vaccine.

DETAILED DESCRIPTION

[0021] As used herein, including the appended claims, the singular forms of words such as "a," "an," and "the," include their corresponding plural references unless the context clearly dictates otherwise. Table 15 below provides a listing of sequence identifiers used in this application. All references cited herein are incorporated by reference to the same extent as if each individual publication, database entry (e.g. Genbank sequences or GeneID entries), patent application, or patent, was specifically and individually indicated to be incorporated by reference. Citation of the references herein is not intended as an admission that any of the foregoing is pertinent prior art, nor does it constitute any admission as to the contents or date of these publications or documents.

9. An isolated antibody or antigen-binding thereof that binds to human GITR protein, wherein the antibody or antigen-binding fragment recognizes an epitope spanning module 3 and module 4 of human GITR protein (SEQ ID NO: 89).

10. The antibody or antigen-binding fragment of claim 9, wherein the epitope comprises Gly57, Arg65, His67, Lys80, Phe81, Ser82, and Gln86.

11. An isolated antibody or antigen-binding fragment thereof that is able to block binding of the antibody or antigen-binding fragment of any one of claims 1-10 to human GITR protein.

12. An isolated antibody or antigen-binding fragment thereof that specifically binds to human GITR protein comprising:
CDR-L1, CDR-L2 and CDR-L3 of the light immunoglobulin chain comprising the amino acid sequence set forth in SEQ ID NO: 105; wherein residue 31 is Q and residue 57 is Q; and
CDR-H1, CDR-H2 and CDR-H3 of the heavy immunoglobulin chain comprising the amino acid sequence set forth in SEQ ID NO: 104.

~~12~~13. The antibody or antigen-binding fragment of any one of claims 1-~~11~~12 which is an antibody.

~~13~~14. The antibody or antigen-binding fragment of any one of claims 1-~~11~~12 which is a monoclonal antibody.

~~14~~15. The antibody or antigen-binding fragment of any one of claims 1-~~11~~12 which is a humanized antibody.

~~15~~16. The antibody or antigen-binding fragment of any one of claims 1-~~14~~15 wherein the heavy immunoglobulin chain is fused to a γ1 human immunoglobulin constant domain.

~~16~~17. The antibody or antigen-binding fragment of any one of claims 1-~~14~~15, comprising a γ1 human heavy chain constant region or a variant thereof, wherein the constant region variant comprises up to 20 conservatively modified amino acid substitutions.

~~17~~18. The antibody or antigen-binding fragment of any one of claims 1-~~14~~15, comprising a γ4 human heavy chain constant region or a variant thereof, wherein the constant region variant comprises up to 20 conservatively modified amino acid substitutions.

~~18~~19. A pharmaceutical composition comprising the antibody or antigen-binding of any one of claims 1-~~17~~18 and a pharmaceutically acceptable carrier.

~~19~~20. An isolated immunoglobulin polypeptide comprising:
CDR-H1 that comprises the amino acid sequence set forth in SEQ ID NO: 23;
CDR-H2 that comprises the amino acid sequence set forth in SEQ ID NO: 34; and
CDR-H3 that comprises the amino acid sequence set forth in SEQ ID NO: 45;
fused to a γ1 human immunoglobulin constant domain.

~~20~~21. An isolated nucleic acid encoding at least one of the light immunoglobulin chain or the heavy immunoglobulin chain of the antibody or antigen-binding fragment or polypeptide of any one of claims 1-~~19~~20.

~~21~~22. An expression vector comprising the nucleic acid of claim ~~20~~21 operably linked to an expression control sequence that is recognized by a host cell when the host cell is transformed with the vector.

~~22~~23. An isolated host cell comprising the expression vector of claim ~~21~~22.

~~23~~24. The host cell of claim ~~22~~23 which is a Chinese Hamster Ovary cell or a *Pichia pastoris* cell.

~~24~~25. A composition comprising the antibody or antigen-binding fragment of any one of claims 1-~~17~~18 and a second therapeutic agent.

~~25~~26. The composition of claim ~~24~~25 wherein the second therapeutic agent is an antibody.

~~26~~27. A composition comprising the antibody or antigen-binding fragment of any one of claims 1-~~17~~18 and a member selected from the group consisting of thiotepa, busulfan, improsulfan, piposulfan, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine, bullatacin, bullatacinone, camptothecin, topotecan, bryostatin, callystatin, CC-1065, cryptophycin 1, cryptophycin 8, dolastatin, duocarmycin, KW-2189, CB 1-TM1, eleutherobin, pancratistatin, sarcodictyin, spongistatin, chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimnustine, calicheamicin, calicheamicin gamma II, calicheamicin omega II, dynemicin, dynemicin A, clodronate, neocarzinostatin chromophore, aclacinomysins, actinomycin,

authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, deoxydoxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, 5-fluorouracil (5-FU), denopterin, methotrexate, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone, aminoglutethimide, mitotane, trilostane, frolinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, eniluracil, amsacrine, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elformithine, elliptinium acetate, epothilone, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidainine, maytansine, ansamitocins, mitoguazone, mitoxantrone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, rhizoxin, sizofuran, spirogermanium, tenuazonic acid, triaziquone, 2,2',2"-trichlorotriethylamine, T-2 toxin, verracurin A, roridin A, anguidine, urethane, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside, cyclophosphamide, paclitaxel, a cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel, docetaxel, chloranbucil, gemcitabine, 6-thioguanine, mercaptopurine, methotrexate, cisplatin, carboplatin, vinblastine, platinum, etoposide, ifosfamide, mitoxantrone, vincristine, vinorelbine, novantrone, teniposide, edatrexate, daunomycin, aminopterin, capecitabine, ibandronate, CPT-11, RFS2000, difluoromethylornithine (DMFO), retinoic acid, tamoxifen, raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, toremifene, 4(5)-imidazoles, aminoglutethimide, megestrol acetate, exemestane, formestanie, fadrozole, vorozole, letrozole, anastrozole, flutamide, nilutamide, bicalutamide, leuprolide, goserelin, troxacitabine, angiozyme, allovectin, leuvectin, vaxid, recombinant IL-2, lurtotecan and abarelix.

~~27~~28. A composition comprising the antibody or antigen-binding fragment of any one of claims 1-~~17~~ 18 and a member selected from the group consisting of an alkylating agent, an ethylenimine, a methylamelamine, an acetogenin, a camptothecin, a cryptophycin, a sarcodictyin, an antibiotic, a bisphosphonate, a mitomycin, an anti-metabolite, a folic acid analogue, a purine analog, an androgen, an anti-adrenal, a folic acid replenisher, an epothilone, a trichothecene, a taxoid, a retinoid, an anti-

hormonal agent, an aromatase inhibitor, an anti-androgen, an antisense oligonucleotide, a ribozyme, a HER2 expression inhibitor and a vaccine.

2829. A method of producing a polypeptide comprising: culturing the host cell of claim 22-23 in culture medium under conditions wherein the nucleic acid sequence is expressed; and recovering the polypeptides from the host cell or culture medium or both.

2930. Use of an antibody or antigen-binding fragment of any one of claims 1-17-18 in the manufacture of a medicament for enhancing an immune response in a human subject.

3031. The use of claim 2930, wherein the antibody or antigen-binding fragment is co-administered with a second therapeutic agent.

3132. The use of claim 30-31 wherein the second therapeutic agent is an antibody.

3233. The use of claim 2930, wherein the antibody or antigen-binding fragment is co-administered with an anti-TGFβ antibody.

3233. The use of claim 2930, wherein the antibody or antigen-binding fragment is co-administered with local radiation.

3334. The use of claim 2930, wherein the antibody or antigen-binding fragment is co-administered with a member selected from the group consisting of thiotepa, busulfan, improsulfan, piposulfan, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide, trimethylolomelamine, bullatacin, bullatacinone, camptothecin, topotecan, bryostatin, callystatin, CC-1065, cryptophycin 1, cryptophycin 8, dolastatin, duocarmycin, KW-2189, CB 1-TM1, eleutherobin, pancratistatin, sarcodictyin, spongistatin, chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimnustine, calicheamicin, calicheamicin gamma II, calicheamicin omega II, dynemicin, dynemicin A, clodronate, neocarzinostatin chromophore, aclacinomysins, actinomycin,

authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, deoxydoxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, 5-fluorouracil (5-FU), denopterin, methotrexate, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone, aminoglutethimide, mitotane, trilostane, frolinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, eniluracil, amsacrine, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elformithine, elliptinium acetate, epothilone, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidainine, maytansine, ansamitocins, mitoguazone, mitoxantrone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, rhizoxin, sizofuran, spirogermanium, tenuazonic acid, triaziquone, 2,2',2''-trichlorotriethylamine, T-2 toxin, verracurin A, roridin A, anguidine, urethane, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside, cyclophosphamide, paclitaxel, a cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel, docetaxel, chloranbucil, gemcitabine, 6-thioguanine, mercaptopurine, methotrexate, cisplatin, carboplatin, vinblastine, platinum, etoposide, ifosfamide, mitoxantrone, vincristine, vinorelbine, novantrone, teniposide, edatrexate, daunomycin, aminopterin, capecitabine, ibandronate, CPT-11, RFS2000, difluoromethylornithine (DMFO), retinoic acid, tamoxifen, raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, toremifene, 4(5)-imidazoles, aminoglutethimide, megestrol acetate, exemestane, formestanie, fadrozole, vorozole, letrozole, anastrozole, flutamide, nilutamide, bicalutamide, leuprolide, goserelin, troxacitabine, angiozyme, allovectin, leuvectin, vaxid, recombinant IL-2, lurtotecan and abarelix.

~~34~~35. The use of claim ~~29~~30, wherein the antibody or antigen-binding fragment is co-administered with a member selected from the group consisting of an alkylating agent, an ethylenimine, a methylamelamine, an acetogenin, a camptothecin, a cryptophycin, a sarcodictyin, an antibiotic, a bisphosphonate, a mitomycin, an anti-metabolite, a folic acid analogue, a purine analog, an androgen, an anti-adrenal, a folic acid replenisher, an epothilone, a trichothecene, a taxoid, a retinoid, an anti-

hormonal agent, an aromatase inhibitor, an anti-androgen, an antisense oligonucleotide, a ribozyme, a HER2 expression inhibitor and a vaccine.

~~35~~36. The use of claim ~~29~~30, wherein the immune response is against a proliferative disorder.

~~36~~37. The use of claim ~~29-~~30 wherein the immune response is against cancer.

~~37~~38. The use of claim ~~36-~~37 wherein the cancer is a member selected from the group consisting of adenocarcinoma, lymphoma, blastoma, sarcoma, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, pancreatic cancer, glioblastoma, glioma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, myeloma, salivary gland carcinoma, kidney cancer, basal cell carcinoma, melanoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, esophageal cancer, and head and neck cancer.

~~38~~39. The use of claim ~~29~~30, wherein the immune response is against a viral infection.

~~39~~40. The use of claim ~~38-~~39 wherein viral infection is caused by a virus which is a member selected from the group consisting of human papilloma viruses (HPV), herpes simplex virus, hepatitis B virus, hepatitis C virus, measles virus, human immunodeficiency virus (HIV) and Epstein Barr virus (EBV).