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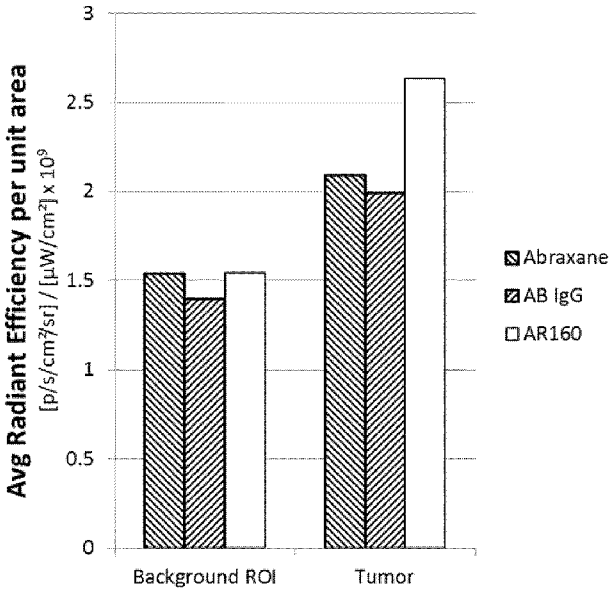
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(54) Title: METHODS FOR IMPROVING THE THERAPEUTIC INDEX FOR A CHEMOTHERAPEUTIC DRUG

(57) Abstract: This disclosure relates to methods for improving the therapeutic index of a chemotherapeutic drug in the treatment of patients afflicted with cancer, including, for example, reducing chemotherapy-related toxicity (e.g., liver toxicity).

FIGURE 1




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# METHODS FOR IMPROVING THE THERAPEUTIC INDEX FOR A CHEMOTHERAPEUTIC DRUG

## BACKGROUND

**[0001]** Chemotherapy remains a mainstay for systemic therapy for many types of cancer, including pancreatic cancer and melanoma. Most chemotherapeutic drugs are only slightly selective to tumor cells, and toxicity to healthy proliferating cells can be high (Allen TM. (2002) Cancer 2:750-763), often requiring dose reduction and even discontinuation of treatment. In theory, one way to overcome chemotherapy toxicity issues as well as improve drug efficacy is to target the chemotherapy drug to the tumor using antibodies that are specific for proteins selectively expressed (or overexpressed) by tumors cells to attract targeted drugs to the tumor. The desired result is altered bio-distribution of the chemotherapy, with more drug going to the tumor and less affecting healthy tissue. Despite 30 years of research, however, specific targeting rarely succeeds in the therapeutic context.

**[0002]** Currently, a combination of paclitaxel with human serum albumin may be administered to a cancer patient to enhance the solubility and therapeutic index of the paclitaxel. Such a combination is sold by Celgene Corporation as ABRAXANE® anti-cancer formulation. In addition, antibodies can be coupled with the paclitaxel and human serum albumin combination to provide for antibody-associated albumin. AVASTIN® (bevacizumab) bound albumin nanoparticles based on this approach are currently undergoing human clinical trials in stage 4 metastatic melanoma with promising results. However, simply because a particular therapeutic elicits a better result is not, in fact, necessarily indicative of a better therapeutic index.

**[0003]** This disclosure provides methods for improving the therapeutic index of chemotherapeutic drugs.

## SUMMARY OF THE INVENTION

**[0004]** The risks of irreversible toxicities, such as direct chemotherapy-induced hepatotoxicity or potentiation of preexisting liver disease, continue to exist for many currently available therapeutics, including ABRAXANE®. There remains a need for anti-

cancer therapeutics with decreased toxicities that can efficiently target tumor cells in order to treat cancer in a patient. Embodiments herein generally relate to compositions and methods that result in improved therapy for cancer therapies.

**[0005]** The instant technology generally relates to methods for increasing the therapeutic index of a chemotherapeutic drug (e.g., lowering toxicity, increasing tumor up-take of the drug, increasing efficacy, etc.) by combining the drug with a protein carrier and an antibody or other molecule (e.g., aptamer) that targets the resulting complex to an aberrant cell (e.g., tumor cell).

**[0006]** In particular, the present disclosure relates to compositions for increasing the therapeutic index of a chemotherapy drug, using antibody therapy with nanoparticles comprising a protein core, such as albumin, or other biocompatible and preferably human carrier protein and, associated with the surface of that core, antibodies, aptamers, or other proteins (e.g. fusion protein) having a carrier protein- (e.g., albumin-)binding portion which associates with the protein core while retaining the binding function of the antibody, aptamer or other binding agents (e.g., protein) to the target ligand on the surface of the particle (e.g., the binding region of the antibody, aptamer or other binding agent is exposed outside of the particle or available, notwithstanding the other internal region).

**[0007]** Without being limited to any theory, it is believed that this invention increases the therapeutic index by rendering the drug less toxic. The lower toxicity allows more drug to be delivered while maintaining acceptable side effects. It is also contemplated that the drug is more efficacious, and as such less drug can be used to get the same results provided by previous compositions. This combination allows for an increase in the therapeutic index by raising the ceiling and lowering the floor. Such a combination is surprising and typically not known.

**[0008]** In one aspect is provided a method for increasing the *in vivo* therapeutic index of a chemotherapeutic drug targeting aberrant mammalian cells, comprising:

a) combining a therapeutically effective amount of the drug with a biocompatible protein carrier;

b) forming a complex with the carrier and an effective amount of an antibody or aptamer which has specificity to an antigen on the aberrant cells, wherein the antibodies or aptamers populate the surface of the complex and retain binding specificity; and

c) administering the complex to a patient, wherein administration enhances delivery of the drug to the cells and reduces one or more side effects of the drug, thereby increasing the therapeutic index of the drug.

**[0009]** In one aspect is provided a method for increasing the *in vivo* therapeutic index of a chemotherapeutic drug targeting aberrant cells in a human patient, comprising:

a) combining a therapeutically effective amount of the drug with a biocompatible protein carrier;

b) forming a complex with the carrier and an effective amount of an antibody or aptamer which has specificity to an antigen on the aberrant cells, wherein the antibodies or aptamers populate the surface of the complex and retain binding specificity; and

c) administering the complex to a patient, wherein administration enhances delivery of the drug to the cells and reduces one or more side effects of the drug, thereby increasing the therapeutic index of the drug.

**[0010]** In a preferred embodiment, the antibody is selected from antibodies directed to a blood-borne tumor or a solid tumor. In one embodiment, the antibody is not directed to melanoma.

**[0011]** In one embodiment, the aberrant mammalian cells are cancer cells, virus-infected cells, or bacteria-infected cells.

**[0012]** In one embodiment, the protein carrier is selected from the group consisting of albumin, gelatin, elastin, gliadin, legumin, zein, soy protein, milk protein, or whey protein. Preferably, the protein carrier is albumin.

**[0013]** In one embodiment, the complex comprises an effective amount of paclitaxel to provide stability to the complex. In one embodiment, the amount of paclitaxel is less than the therapeutically effective amount of paclitaxel.

**[0014]** In one aspect, this disclosure relates to a method for increasing the *in vivo* therapeutic index of a chemotherapeutic drug targeting tumor cells, which method comprises:

a) combining a therapeutically effective amount of the drug with an albumin carrier; and

b) forming a complex with the carrier and an effective amount of antibody or aptamer which has specificity to an antigen on the tumor cells, wherein the antibodies or aptamers populate the surface of the complex and retain antibody binding specificity; and

c) administering the complex to a patient wherein administration enhances delivery of the drug to the tumor cells and reduces one or more side effects of the drug, thereby increasing the therapeutic index of the drug.

**[0015]** In one embodiment, the complex is less than 1 micron in diameter. In one embodiment, the complex has a diameter of between 0.1 and 0.9 microns.

**[0016]** In one embodiment, drug-related toxicity is reduced.

**[0017]** In one aspect, this disclosure relates to a method for increasing the *in vivo* therapeutic index of a chemotherapeutic drug targeting aberrant mammalian cells, which method comprises:

a) combining a therapeutically effective amount of the drug with a biocompatible protein carrier;

b) forming a complex with the carrier and an effective amount of binding agents having specificity to the aberrant cells, wherein the binding agents populate the surface of the complex and retain specificity; and

c) administering said complex to a patient, wherein the administration enhances delivery of the drug to said cells and reduces one or more side effects of the drug, thereby increasing the therapeutic index of the drug.

**[0018]** In one embodiment, the binding agents are aptamers, antibodies, fusion proteins, or Fc receptors. Preferably, the binding agent includes a carrier protein- (e.g., albumin-) binding portion, e.g. at an end opposite the binding moiety. It is contemplated that surface complexation of the antibody occurs through the carrier protein-binding portion of the

binding agent, which results in all or part of the carrier protein-binding portion being associated with (e.g., integrated into) the protein core, while the binding portions (regions) (e.g., Fa and Fb portions, nucleic acid, etc.) of the binding agent remain outside of the protein core, thereby retaining their target-specific binding capabilities. Most preferably, the binding agents are antibodies.

**[0019]** In one embodiment, the aberrant mammalian cells are cancer cells, cells involved in an auto-immune disease, cells involved in an inflammatory disease, virus-infected cells, or bacteria-infected cells.

**[0020]** In one embodiment, the protein carrier is albumin, gelatin, elastin, gliadin, legumin, zein, soy protein, milk protein, or whey protein. Preferably, the protein carrier is albumin.

**[0021]** In one aspect, this disclosure relates to a method of reducing chemotherapy drug-related toxicity in a patient having cancer and at risk of such toxicity, which method comprises treating said patient with a complex comprising a therapeutically effective amount of said drug with an albumin carrier, and an effective amount of antibody or aptamer which has specificity to an antigen on said cancer, wherein said antibodies populate the surface of said complex and retain binding specificity, such that said patient has reduced risk of chemotherapy drug-related toxicity.

**[0022]** In one embodiment, the chemotherapy drug-related toxicity is cardiotoxicity, nephrotoxicity, hepatotoxicity, pulmonary toxicity, dermatologic toxicity, or gastrointestinal toxicity.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0023]** FIG. 1 is a graph indicating the average radiant efficiency per unit area of background or tumors in mice injected with alexaflor 750-labeled ABRAXANE, ABRAXANE coated with non-specific antibody (AB IgG) or ABRAXANE coated with Rituximab (AR160).

## DETAILED DESCRIPTION

**[0024]** After reading this description it will become apparent to one skilled in the art how to implement the invention in various alternative embodiments and alternative applications. However, all the various embodiments of the present invention will not be described herein. It will be understood that the embodiments presented here are presented by way of an example only, and not limitation. As such, this detailed description of various alternative embodiments should not be construed to limit the scope or breadth of the present invention as set forth below.

**[0025]** Before the present invention is disclosed and described, it is to be understood that the aspects described below are not limited to specific compositions, methods of preparing such compositions, or uses thereof as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting.

**[0026]** The detailed description of the invention is divided into various sections only for the reader's convenience and disclosure found in any section may be combined with that in another section. Titles or subtitles may be used in the specification for the convenience of a reader, which are not intended to influence the scope of the present invention.

***Definitions***

**[0027]** Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In this specification and in the claims that follow, reference will be made to a number of terms that shall be defined to have the following meanings:

**[0028]** The terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. As used herein, the singular forms "a", "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise.

**[0029]** "Optional" or "optionally" means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where the event or circumstance occurs and instances where it does not.

**[0030]** The term "about" when used before a numerical designation, *e.g.*, temperature, time, amount, concentration, and such other, including a range, indicates approximations which may vary by ( + ) or ( - ) 10%, 5%,1%, or any subrange or subvalue there between. Preferably, the term "about" when used with regard to a dose amount means that the dose may vary by +/- 10%.

**[0031]** "Comprising" or "comprises" is intended to mean that the compositions and methods include the recited elements, but not excluding others. "Consisting essentially of" when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination for the stated purpose. Thus, a composition consisting essentially of the elements as defined herein would not exclude other materials or steps that do not materially affect the basic and novel characteristic(s) of the claimed invention. "Consisting of" shall mean excluding more than trace elements of other ingredients and substantial method steps. Embodiments defined by each of these transition terms are within the scope of this invention.

**[0032]** The term "antibody" or "antibodies" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules (i.e., molecules that contain an antigen binding site that immuno-specifically bind an antigen). The term also refers to antibodies comprised of two immunoglobulin heavy chains and two immunoglobulin light chains as well as a variety of forms including full length antibodies and portions thereof; including, for example, an immunoglobulin molecule, a monoclonal antibody, a chimeric antibody, a CDR-grafted antibody, a humanized antibody, a Fab, a Fab′, a F(ab′)2, a Fv, a disulfide linked Fv, a scFv, a single domain antibody (dAb), a diabody, a multispecific antibody, a dual specific antibody, an anti-idiotypic antibody, a bispecific antibody, a functionally active epitope-binding fragment thereof, bifunctional hybrid antibodies (e.g., Lanzavecchia et al., *Eur. J. Immunol.* 17, 105 (1987)) and single chains (e.g., Huston et al., *Proc. Natl. Acad. Sci. U.S.A.*, 85, 5879-5883 (1988) and Bird et al., *Science* 242, 423-426 (1988), which are incorporated herein by reference). (See, generally, Hood et

al., *Immunology*, Benjamin, N.Y., 2ND ed. (1984); Harlow and Lane, *Antibodies. A Laboratory Manual*, Cold Spring Harbor Laboratory (1988); Hunkapiller and Hood, *Nature*, 323, 15-16 (1986), which are incorporated herein by reference). The antibody may be of any type (e.g., IgG, IgA, IgM, IgE or IgD). Preferably, the antibody is IgG. More preferably, the antibody contains a Fc domain. An antibody may be non-human (e.g., from mouse, goat, or any other animal), fully human, humanized, or chimeric. Where a particular antibody (e.g., bevacizumab) is recited herein as the antibody, it is contemplated that a different antibody can be substituted.

**[0033]** The term "antigen" is well understood in the art and includes substances which are immunogenic. As used herein, the term "antigen" may also refer to a substance to which a binding agent other than an antibody (e.g., an aptamer) can bind.

**[0034]** The term "aptamer" as used herein relates to a single-stranded DNA or RNA molecule or peptide that binds to a target, for example, small molecules, toxins, peptides, proteins, viruses, bacteria, and even whole cells. Aptamers can be engineered and then selected from large random sequence pools. To increase stability and binding affinity, nucleic acid aptamers may include unnatural or modified bases and/or a mini hairpin structure.

**[0035]** The term "binding agent" is generic to antibodies, aptamers modified to contain a carrier protein-binding portion, fusion proteins, and the like.

**[0036]** The term "biosimilar" as used herein refers to a biopharmaceutical which is deemed to be comparable in quality, safety, and efficacy to a reference product marketed by an innovator company.

**[0037]** The terms "carrier protein" and "protein carrier" are used interchangeably herein and refer to proteins that function to transport therapeutic agents, antibodies, or both. Examples of carrier proteins are discussed in more detail below. Where albumin is recited herein as the carrier protein, it is contemplated that a different carrier protein can be substituted.

**[0038]** The term "dose" and "dosage" refer to an amount of binding agent (e.g., antibody or aptamer) or chemotherapeutic drug (agent) given to a patient in need thereof. The

attending clinician will select an appropriate dose from the range based on the patient's weight, age, health, stage of cancer, level of circulating antigen, and other relevant factors, all of which are well within the skill of the art. The term "unit dose" refers to a dose of the binding agent or chemotherapeutic drug that is given to the patient to provide a desired result. In some instances, the unit dose is sold in a sub-therapeutic formulation (e.g., 10% of the therapeutic dose). The unit dose may be administered as a single dose or a series of subdoses. Additionally, some terms used in this specification are more specifically defined below.

**[0039]** An "effective amount" intends to indicate the amount of a compound or agent (e.g., a chemotherapeutic drug) administered or delivered to the patient which is most likely to result in the desired treatment outcome. The amount is empirically determined by the patient's clinical parameters including, but not limited to the stage of disease, age, gender, histology, and likelihood for recurrence. In addition, the level of circulating antigen can be used to empirically determine the effective amount of the chemotherapeutic drug and/or binding agent to administer to a patient.

**[0040]** An effective amount or a therapeutically effective amount or dose of an agent, e.g., a compound of the invention, refers to that amount of the agent or compound that results in amelioration of symptoms or a prolongation of survival in a subject. Toxicity and therapeutic efficacy of such molecules can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., by determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the ratio LD50/ED50. Agents that exhibit high therapeutic indices are preferred.

**[0041]** A "therapeutically effective amount of paclitaxel" is an amount of paclitaxel which is generally used to treat cancer in a patient. For example, the recommended dose for adults, depending on the cancer to be treated, is 50 milligrams per square meter of patient surface area ($mg/m^2$) to 175 $mg/m^2$. *See, e.g.*, www.drugs.com/dosage/paclitaxel.html. Thus, "less than a therapeutically effective amount" or "sub-therapeutic amount" of paclitaxel refers to an amount of paclitaxel that is less than the therapeutic amount, e.g., 0.1 $mg/m^2$ to

100 mg/m$^2$, or 0.1 mg/m$^2$ to 50 mg/m$^2$, or 1 mg/m$^2$ to 50 mg/m$^2$, or 1 mg/m$^2$ to 40 mg/m$^2$. The amount may be or any subrange or value between any ranges provided.

**[0042]** A "stable" formulation is one in which the protein therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage. For example, various analytical techniques for measuring protein stability are available in the art and are reviewed in Peptide and Protein Drug Delivery, 247-301, Vincent Lee Ed., Marcel Dekker, Inc., New York, N.Y., Pubs. (1991) and Jones, A. Adv. Drug Delivery Rev. 10:29-90 (1993). Stability can be measured at a selected temperature for a selected time period.

**[0043]** The term "express" as applied to an antigen, refers to the amount of the antigen produced by a cancer. In one aspect, the amount is determined by measuring the expression level of an antigen of interest (e.g., VEGF) for a given patient population or control population (e.g. population without cancer), determining the median expression level of that antigen for the population, and comparing the expression level of the same antigen for a patient to the median expression level for the given patient population. For example, if the expression level of an antigen of interest for the patient is determined to be above the median expression level of the patient population or the control population, that patient is determined to have high expression of the antigen of interest. "Overexpression" of an antigen in a sample collected from a patient refers to an increase (i.e., high) of the antigen in the sample. For example, overexpression can be about 1.5 times, or alternatively, about 2.0 times, or alternatively, about 2.5 times, or alternatively, about 3.0 times, or alternatively, about 5 times, or alternatively, about 10 times, or alternatively about 50 times, or yet further alternatively more than about 100 times higher than the expression level detected in a control sample collected from a person not having cancer. Alternatively, if the expression level of an antigen of interest for the patient is determined to be below the median expression level of the patient population, that patient is determined to have low expression of the antigen of interest.

**[0044]** The term "hepatic impairment" refers to any liver damage that reduces liver function. Diseases (e.g. hepatitis) or traumatic injury (e.g., chemical, drugs, alcohol) are non-limiting examples that may reduce normal liver activities.

**[0045]** The terms "lyophilized," "lyophilization" and the like as used herein refer to a process by which the material (e.g., nanoparticles) to be dried is first frozen and then the ice or frozen solvent is removed by sublimation in a vacuum environment. An excipient may be included in pre-lyophilized formulations to enhance stability of the lyophilized product upon storage. In some embodiments, the carrier protein, therapeutic agent, binding agent, or any combination thereof is lyophilized separately. In other embodiments, the carrier protein, therapeutic agent, binding agent, or any combination thereof is first combined and then lyophilized. The lyophilized sample may further contain additional excipients.

**[0046]** The term "nanoparticle" as used herein refers to particles with at least one dimension less than 5 microns. In some embodiments, the nanoparticle is less than 1 micron. For direct administration, the nanoparticle may be larger. Even larger particles are expressly contemplated by the invention. The terms "conjugate" and "complex" as used herein are synonymous with "nanoparticle." The term "nanoparticle" may also encompass discrete multimers of smaller unit nanoparticles. For example, a 320 nm particle comprises a dimer of a unit 160 nm nanoparticle. For 160 nm nanoparticles, multimers would therefore be approximately 320 nm, 480 nm, 640 nm, 800 nm, 960 nm, 1120 nm, and so on as determined by a Mastersizer 2000 (available from Malvern Instruments Ltd, Wocestershire, UK) as described in PCT/US15/54295.

**[0047]** In a population of particles, the size of individual particles is distributed about a mean. Particle sizes for the population can therefore be represented by an average, and also by percentiles. D50 is the particle size below which 50% of the particles fall. 10% of particles are smaller than the D10 value and 90% of particles are smaller than D90. Where unclear, the "average" size is equivalent to D50.

**[0048]** As used herein, the term "therapeutic index" with regard to a chemotherapeutic drug indicates safety of the chemotherapeutic drug. In some aspects, the therapeutic index can include a comparison of the amount of a therapeutic agent that causes the therapeutic effect (e.g., killing cancer cells) to the amount of the therapeutic agent that causes toxicity (e.g., liver toxicity). It is contemplated that according to certain embodiments an improved therapeutic index can occur using the compositions and/or methods described herein, including without limitation when: (1) the dosage of chemotherapeutic drug is

increased above the current therapeutic dosages; (2) the dosage of chemotherapeutic drug remains the same as the current therapeutic dosages; or (3) the dosage of chemotherapeutic drug is decreased below the current therapeutic dosages. In some embodiments, the compositions and methods, including the specifically numbered scenarios in this paragraph can elicit improved or similar therapeutic effect as seen with the current therapeutic dosages with no worse, fewer, or no toxicities.

**[0049]** As used herein, the term "therapeutic effect" refers to achievement of the desired and/or beneficial consequences of a medical treatment. A non-limiting example of a therapeutic effect of the present disclosure is the shrinkage and/or eradication of a tumor and/or killing of cancer cells in a patient.

**[0050]** The term "treating" or "treatment" covers the treatment of a disease or disorder (e.g., cancer), in a subject, such as a human, and includes: (i) inhibiting a disease or disorder, i.e., arresting its development; (ii) relieving a disease or disorder, i.e., causing regression of the disorder; (iii) slowing progression of the disorder; and/or (iv) inhibiting, relieving, or slowing progression of one or more symptoms of the disease or disorder. In some embodiments "treating" or "treatment" refers to the killing of cancer cells. In some embodiments "treating" or "treatment" refers to increasing progression-free survival of the patient(s). In some embodiments "treating" or "treatment" refers to increasing survival rates.

***Methods***

**[0051]** As will be apparent to the skilled artisan upon reading this disclosure, the present disclosure relates to methods for improving the therapeutic index of a chemotherapeutic drug in the treatment of a patient having aberrant cells. In a preferred embodiment, the patient is afflicted with cancer.

**[0052]** The risks of irreversible toxicities, such as direct chemotherapy-induced hepatotoxicity or potentiation of preexisting liver disease, continue to exist for many currently available therapeutics, including ABRAXANE®. There remains a need for anti-cancer therapeutics with decreased toxicities that can efficiently target tumor cells in order to treat cancer in a patient. Embodiments herein generally relate to compositions and methods that result in improved therapy for cancer therapies.

**[0053]** In particular, the present disclosure relates to methods for increasing the therapeutic index of a chemotherapeutic drug (e.g., lowering toxicity, increasing tumor uptake of the drug, increasing efficacy, etc.) by combining the drug with a protein carrier and an antibody or other molecule that targets the resulting complex to an aberrant cell (e.g., tumor cell).

**[0054]** In one aspect is provided a method for increasing the *in vivo* therapeutic index of a chemotherapeutic drug targeting aberrant mammalian cells, comprising:

a) combining a therapeutically effective amount of the drug with a biocompatible protein carrier;

b) forming a complex with the carrier and an effective amount of an antibody or aptamer which has specificity to an antigen on the aberrant cells, wherein the antibodies populate the surface of the complex and retain binding specificity; and

c) administering the complex to a patient, wherein administration enhances delivery of the drug to the cells and reduces one or more side effects of the drug, thereby increasing the therapeutic index of the drug.

**[0055]** In one embodiment, the aberrant mammalian cells are cancer cells, virus-infected cells, or bacteria-infected cells.

**[0056]** In one aspect is provided a method for increasing the *in vivo* therapeutic index of a chemotherapeutic drug targeting aberrant mammalian cells, comprising:

a) combining a therapeutically effective amount of the drug with albumin;

b) forming a complex with the carrier and an effective amount of an antibody which has specificity to an antigen on the aberrant cells, wherein the antibodies populate the surface of the complex and retain binding specificity; and

c) administering the complex to a patient, wherein administration enhances delivery of the drug to the cells and reduces one or more side effects of the drug, thereby increasing the therapeutic index of the drug.

**[0057]** In one aspect, this disclosure relates to a method for increasing the *in vivo* therapeutic index of a chemotherapeutic drug targeting tumor cells, which method comprises:

a) combining a therapeutically effective amount of the drug with an albumin carrier; and

b) forming a complex with the carrier and an effective amount of antibody or aptamer which has specificity to an antigen on the tumor cells, wherein the antibodies or aptamers populate the surface of the complex and retain binding specificity; and

c) administering the complex to a patient wherein administration enhances delivery of the drug to the tumor cells and reduces one or more side effects of the drug, thereby increasing the therapeutic index of the drug.

**[0058]** In one embodiment, the complex is less than 1 micron in diameter.

**[0059]** In one embodiment, drug-related toxicity is reduced.

**[0060]** In one aspect, this disclosure relates to a method for increasing the *in vivo* therapeutic index of a chemotherapeutic drug targeting aberrant mammalian cells, which method comprises:

a) combining a therapeutically effective amount of the drug with a biocompatible protein carrier;

b) forming a complex with the carrier and an effective amount of binding agents having specificity to the aberrant cells, wherein the binding agents populate the surface of the complex and retain specificity; and

c) administering said complex to a patient, wherein the administration enhances delivery of the drug to said cells and reduces one or more side effects of the drug, thereby increasing the therapeutic index of the drug.

**[0061]** In one embodiment, the binding agents are aptamers, antibodies, fusion proteins, or Fc receptors. Preferably, the binding agent has a carrier protein-binding portion, e.g. an albumin-binding portion, that does not bind the target. Any amino acid sequence or other moiety that allows complexation with the albumin is contemplated by this invention. In one embodiment, the albumin-binding domain comprises an amino acid sequence from the Fab region of an antibody, e.g. rituximab or bevacizumab, which mediates binding between the antibody and the albumin.

**[0062]** In one embodiment, the aberrant mammalian cells are cancer cells, virus-infected cells, or bacteria-infected cells. Preferably, the mammal is a human.

**[0063]** In one aspect, this disclosure relates to a method of reducing chemotherapy drug-related toxicity in a patient having cancer and at risk of such toxicity, which method comprises treating said patient with a complex comprising a therapeutically effective amount of said drug with an albumin carrier, and an effective amount of binding agent which has specificity to an antigen on said cancer, wherein said antibodies populate the surface of said complex and retain binding specificity (e.g., antibody binding specificity), such that said patient has reduced risk of chemotherapy drug-related toxicity.

**[0064]** In one embodiment, the chemotherapy drug-related toxicity is cardiotoxicity, nephrotoxicity, hepatotoxicity, pulmonary toxicity, dermatologic toxicity, or gastrointestinal toxicity.

**[0065]** Therapeutic index is a comparison of the amount of a therapeutic agent that causes the therapeutic effect (e.g., killing cancer cells) to the amount of the therapeutic agent that causes toxicity (e.g., liver toxicity). Toxicities of current formulations of chemotherapeutic drugs, in particular ABRAXANE ®, are known include increased hepatic impairment. As the liver is the site of metabolism for most chemotherapeutic drugs, many agents are hepatotoxic (directly or indirectly). Administration of such therapeutics to patients with hepatic impairments is known to include increased myelosuppression such that these patients must be monitored closely. In addition, some high-risk patients are recommended to not receive chemotherapeutic drugs at all.

**[0066]** Other known toxicities that may result from chemotherapy treatment include, but are not limited to, cardiotoxicity, nephrotoxicity, pulmonary toxicity, dermatologic toxicity, and gastrointestinal toxicity. For example, some chemotherapeutic drugs may cause direct injury to the heart (either acute or chronic), including anthrcyclines. Chemotherapy drugs, including cisplatin, cyclophosphamide, and ifosfamide, produce urinary tract/kidney toxicity. Drugs with pulmonary toxicity, including bleomycin, can cause severe pulmonary effects. Dermatologic toxicity is also common with chemotherapeutic drugs, and include transient rash (carmustine, cytarabine, gemcitabine, asparaginase, and procarbazine),

photosensitivity (Mitomycin, 5-FU, methotrexate, vinblastine, and dacarbazine), dermatitis, hyperpigmentation, urticaria, nail changes, alopecia, and radiation recall. Gastrointestinal toxicity, including stomatitis or diarrhea, is also common.

**[0067]** In particular, it is contemplated that patients at higher risk of toxicity, e.g., hepatotoxicity, will benefit from administration of chemotherapeutic drugs in combination with nanoparticles, as described herein.

**[0068]** Determination of patients with hepatic impairment or at risk of hepatic impairment can be determined by any method known to those of skill in the art. Non-limiting examples of ways to determine severity of hepatic impairment include The Child-Pugh classification. This classification system groups patients on the basis of two clinical features (encephalopathy and ascites) and three laboratory based parameters (S-albumin, S-bilirubin, and prothrombin time). Increased albumin is due, at least in part, to decreased synthesis by the hepatocytes in chronic liver disease. Increased levels of bilirubin may be due to cholestasis, hepatocellular failure or extrahepatic causes such as hemolysis. The use of markers like serum albumin, prothrombin time and bilirubin is encouraged and abnormalities in these parameters may be better related to drug elimination capacity than other components of the Child-Pugh classification, e.g. encephalopathy and ascites. Impaired hepatic metabolic capacity can also be tested by administration of a probe drug (e.g., CYP3A4) and observing altered pharmacokinetics of the probe. Exogenous markers that have been used to assess different hepatic drug elimination mechanisms are antipyrine, MEGX (lidocaine metabolite), ICG (indocyanine green) and galactose. These, and other, methods can be used alone or in combination to determine whether a patient suffers or is at risk of hepatic impairment.

**[0069]** Paclitaxel has been associated with hepatotoxicity including elevation of serum aminotransferase in approximately 7-26% of patients, with levels greater than 5 times the upper limit of normal in approximately 2% of those receiving paclitaxel. It has been suggested that liver injury that arises during therapy is due, at least in part, to a direct effect of paclitaxel in inhibiting microtubular function.

**[0070]** It is contemplated in some embodiments that an improved therapeutic index can occur using the compositions and/or methods described herein, for example, when: (1)

the dosage of chemotherapeutic drug is increased above the current therapeutic dosages; (2) the dosage of chemotherapeutic drug remains the same as the current therapeutic dosages; or (3) the dosage of chemotherapeutic drug is decreased below the current therapeutic dosages. In some embodiments, the compositions and methods, including the specifically numbered scenarios in this paragraph can elicit improved or similar therapeutic effect as seen with the current therapeutic dosages with no worse, fewer or no toxicities.

**[0071]** In some embodiments, the carrier protein can be albumin, gelatin, elastin (including topoelastin) or elastin-derived polypeptides (e.g., α-elastin and elastin-like polypeptides (ELPs)), gliadin, legumin, zein, soy protein (e.g., soy protein isolate (SPI)), milk protein (e.g., β-lactoglobulin (BLG) and casein), or whey protein (e.g., whey protein concentrates (WPC) and whey protein isolates (WPI)). In preferred embodiments, the carrier protein is albumin. In preferred embodiments, the albumin is egg white (ovalbumin), bovine serum albumin (BSA), or the like. In even more preferred embodiments, the carrier protein is human serum albumin (HSA). In some embodiments, the carrier protein is a generally regarded as safe (GRAS) excipient approved by the United States Food and Drug Administration (FDA).

**[0072]** In some embodiments, the antibody or aptamer targets a non-cell membrane bound antigen, for example, VEGF. A commercially available antibody that targets VEGF is AVASTIN®/bevacizumab and biosimilars thereof. In some embodiments, the antibody or aptamer binds to a tumor related antigen, a non-tumor related antigen, or both. A tumor related antigen is an antigenic substance produced in or by tumor cells. It is within the ability of one of skill in the art to determine what is a tumor related antigen.

**[0073]** Table 1 depicts a list of non-limiting list of antibodies for cancer targets.

Table 1: Antibodies for cancer targets

| **Antibodies** | | |
|---|---|---|
| | **Biologic** | **Treatment(s)/Target(s)** |
| Monoclonal antibodies (MAbs) | Rituximab (RITUXAN ®) | Non-Hodgkin lymphoma |
| | Alemtuzumab (CAMPATH®) | Chronic lymphocytic leukemia (CLL) |
| | Ipilimumab (YERVOY®) | Metastatic melanoma |

| Antibodies | | |
|---|---|---|
| | **Biologic** | **Treatment(s)/Target(s)** |
| | Bevacizumab (AVASTIN®) | Colon cancer, lung cancer, renal cancer, ovarian cancer, glioblastoma multiforme |
| | Cetuximab (ERBITUX®) | Colorectal cancer, non-small cell lung cancer, head and neck cancer, cervical cancer, glioblastoma, ovarian epithelia, fallopian tube or primary peritoneal cancer, renal cell cancer |
| | Panitumumab (VECTIBIX®) | Colorectal cancer |
| | Trastuzumab (HERCEPTIN ®) | Breast cancer, Adenocarcinoma |
| | $^{90}$Y-ibritumomab tiuxetan (ZEVALIN ®) | Non-Hodgkin lymphoma |
| | Ado-trastuzumab emtansine (KADYCLA®, also called TDM-1) | Breast cancer |
| | Brentuximab vedotin (ADCETRIS®) | Hodgkin lymphoma, Anaplastic large cell lymphoma |
| | Blinatumomab (BLINCYTO) | Acute lymphocytic leukemia (ALL) |
| | Pembrolizumab (KEYTRUDA®) | PD-1 (melanoma, non-small cell lung cancer) |
| | Nivolumab (OPDIVO®) | PD-1 (melanoma, non-small cell lung cancer) |
| | Ofatumumab (ARZERRA®) | Chronic lymphocytic leukemia (CLL) |
| | Pertuzumab (PERJETA®) | Breast cancer |
| | Obinutuzumab (GAZYVA®) | Lymphoma |
| | Dinutuximab (UNITUXIN®) | Neuroblastoma |
| | Denosumab (PROLIA®) | Bone metastases, multiple myeloma, giant cell tumor of bone |

**[0074]** In some embodiments, the antibody is selected from the group consisting of ado-trastuzumab emtansine, alemtuzumab, bevacizumab, blinatumomab, brentuximab vedotin, cetuximab, denosumab, dinutuximab, ibritumomab tiuxetan, ipilimumab, nivolumab, obinutuzumab, ofatumumab, panitumumab, pembrolizumab, pertuzumab, rituximab, trastuzumab, or any biosimilar thereof.

**[0075]** In one embodiment, the antibody or other binding agent comprises a protein carrier-binding domain. The protein carrier-binding domain may be any region, domain, amino acid sequence, etc. which allows for interaction (e.g., hydrophobic interaction) between the protein carrier (e.g., albumin) and the binding agent (or portion thereof). In one embodiment, the binding agent is covalently bound to the albumin or other carrier protein. In one embodiment, the binding agent is bound to the albumin or other carrier protein via hydrophobic interactions.

**[0076]** In some aspects, the complexes and compositions as described herein target non-cancer diseases. Non-cancer diseases include, without limitation, inflammatory diseases, autoimmune diseases, and infectious diseases. In one embodiment, the antibody or other binding agent is specific for an epitope associated with an infectious disease. In one embodiment, the disease is caused by a pathogen selected from the group consisting of bacteria, fungus, virus, or parasite infection. In one embodiment, the antibody or other binding agent is specific for an epitope associated with the pathogen. In one embodiment, the antibody or other binding agent is specific for an epitope associated with a toxin produced by the pathogen. In one embodiment, the antibody or other binding agent targets one or more symptoms of the infectious disease.

**[0077]** Tables 2 and 3 depict non-limiting lists of antibodies and fusion proteins for infectious disease targets.

Table 2: Antibodies and Fusion Protein for Infectious Disease (approved or in trials)

| **Antibodies** | | | |
|---|---|---|---|
| **Biologic** | **Type** | **Treatment(s)** | **Target(s)** |
| Palivizumab | Humanized antibody | Respiratory syncytial virus | RSV F protein |
| Actoxumab | Human antibody | *Clostridium difficile* colitis | Exotoxin TcdA |
| Bezlotoxumab | Human antibody | *Clostridium difficile* infection | Exotoxin TcdB |
| N/A | Fusion protein: Toll-like receptor 4 with IgG1 Fc | Bacterial sepsis | |

Table 3. Other antibodies for infectious disease uses

| Antibodies | | |
|---|---|---|
| **Antibody** | **Type** | **Proposed Treatment/Target** |
| Bezlotoxumab | human | Clostridium difficile colitis |
| CR6261 | human | infectious disease, influenza A |
| Diridavumab | human | influenza A |
| Edobacomab | mouse | sepsis caused by Gram-negative bacteria |
| Efungumab | human | invasive Candida infection |
| Exbivirumab | human | hepatitis B |
| Felvizumab | humanized | respiratory syncytial virus infection |
| Firivumab | human | influenza |
| Foravirumab | human | rabies |
| Ibalizumab | humanized | HIV infection |
| Libivirumab | human | hepatitis B |
| Motavizumab | humanized | respiratory syncytial virus |
| Obiltoxaximab | chimeric | Bacillus anthracis spores |
| Pagibaximab | chimeric | sepsis (Staphylococcus) |
| Panobacumab | human | Pseudomonas aeruginosa infection |
| Pritoxaximab | chimeric | Anti-Shiga toxin 1 B subunit |
| PRO 140 | humanized | HIV infection |
| VRC01LS | humanized | HIV |
| Rafivirumab | human | rabies |
| Raxibacumab | human | anthrax (prophylaxis and treatment) |
| Regavirumab | human | cytomegalovirus infection |
| Setoxaximab | chimeric | E. coli |
| Sevirumab | human | cytomegalovirus infection |
| Suvizumab | humanized | viral infections |
| Tefibazumab | humanized | Staphylococcus aureus infection |
| Tosatoxumab | human | Anti-S. aureus alpha-toxin |
| Tuvirumab | human | chronic hepatitis B |
| Urtoxazumab | humanized | diarrhoea caused by E. coli |

**[0001]** In one embodiment, the antibody is specific for an epitope associated with a non-cancer disease. In one embodiment, the disease is an autoimmune disease. In one

embodiment, the disease is an allergy. In one embodiment, the disease is asthma. In one embodiment, the disease is associated with inflammation or an inflammatory response. Preferably, the disease is not an infectious disease.

**[0002]** Tables 4-6 depict non-limiting lists of antibodies or fusion proteins for non-oncology targets, e.g., autoimmune disease or inflammatory disease.

Table 4: Antibodies approved or in trials for non-oncology targets, e.g., autoimmune disease or inflammatory disease.

| **Antibodies** | | | |
|---|---|---|---|
| **Biologic** | **Type** | **Treatment(s)** | **Target(s)** |
| abciximab | Chimeric | Cardiovascular disease | inhibition of glycoprotein IIb/IIIa |
| basiliximab | Chimeric | Transplant rejection | CD25 |
| certolizumab | Humanized | Crohn's disease; RA | TNF |
| daclizumab | Humanized | Transplant rejection | CD25 |
| eculizumab | Humanized | Paroxysmal nocturnal hemoglobinuria | C5 complement protein |
| efalizumab | Humanized | Psoriasis | CD11a |
| infliximab | Chimeric | Autoimmune disorders | TNF |
| muromonab-CD3 | Murine | Transplant rejection | T-cell CD3 receptor |
| natalizumab | Humanized | Multiple Sclerosis; Crohn's disease | α4 integrin subunit |
| omalizumab | Humanized | Asthma, eczema, allergy | IgE |
| tocilizumab/atlizumab | Humanized | Rheumatoid arthritis (RA); JIA | IL-6R |
| vedolizumab | Humanized | Crohn's disease; ulcerative colitis | α4β7 integrin |
| abrilumab | Human | inflammatory bowel disease; ulcerative colitis; Crohn's disease | α4β7 integrin |
| adalimumab | Human | RA, JIA, psoriatic arthritis, Crohn's disease, AS and plaque psoriasis | TNF |
| belimumab | Human | Systemic lupus erythematosus | BAFF |

| Antibodies | | | |
|---|---|---|---|
| **Biologic** | **Type** | **Treatment(s)** | **Target(s)** |
| canakinumab | Human | Cryopyrin-associated periodic syndrome (CAPS); arthritis; gout; neonatal-onset multisystem inflammatory disease | IL-1β |
| golimumab | Human | Arthritis; Ankylosing spondylitis (AS) | TNF |
| ustekinumab | Human | Psoriatic Arthritis; Plaque Psoriasis; Crohn's disease | IL-12 and IL-23 |
| otelixizumab | chimeric/humanized | diabetes mellitus type 1 | CD3 |
| teplizumab | humanized | diabetes mellitus type 1 | CD3 |
| ocrelizumab | humanized | rheumatoid arthritis, lupus erythematosus etc. | CD20 |
| Alemtuzumab | humanized | Multiple sclerosis | CD52 |
| Mepolizumab | humanized | asthma and white blood cell diseases; Hyper-eosinophilic syndrome | IL-5 |
| Reslizumab | humanized | inflammations of the airways, skin and gastrointestinal tract; Eosinophilic oesophagitis | IL-5 |
| ranibizumab | Humanized | Macular degeneration | VEGF-A |
| Briakinumab | human | psoriasis, rheumatoid arthritis, inflammatory bowel diseases, multiple sclerosis | IL-12 and IL-23 |

Table 5: Fusion proteins approved or in trials for non-oncology targets, e.g., autoimmune disease or inflammatory disease

| Fusion Proteins | | | |
|---|---|---|---|
| **Biologic** | **Description** | **Treatment(s)** | **Target(s)** |
| Aflibercept | VEGF receptor fragment with IgG1 Fc | Wet macular degeneration; colorectal cancer | VEGF |
| belatacept | CTLA-4 with IgG1 Fc | Organ rejection | T cell activation |
| rilonacept | IL-1R with IgG1 Fc | Cryopyrin-associated periodic syndromes; | IL-1 |
| romiplostim | Thrombopoietin-binding peptide with IgG1 Fc | Thrombocytopenia | Activation of TPO receptor |
| abatacept | Mutated CTLA-4 | Rheumatoid arthritis | CD80 and CD86 |

| Fusion Proteins | | | |
|---|---|---|---|
| **Biologic** | **Description** | **Treatment(s)** | **Target(s)** |
| | with IgG1 Fc | | |
| alefacept | LFA-3 with IgG1 Fc | Psoriasis; transplant rejection | CD2 |
| etanercept | TNFR with IgG1 Fc | Rheumatoid arthritis; juvenile idiopathic arthritis (JIA); psoriasis; ankylosing spondylitis | TNF |
| N/A | glucagon like peptide 1 with IgG2 | Type I diabetes | |
| Atacicept | TACI ECD–Fc (IgG1) fusion protein, modified Fc to eliminate effector functions | Systemic lupus erythematosus; graft vs host disease | BAFF and APRIL |

Table 6. Other antibodies for non-oncology uses

| Antibodies | | |
|---|---|---|
| **Antibody** | **Type** | **Proposed Treatment/Target** |
| Alirocumab | human | hypercholesterolemia |
| Anifrolumab | human | systemic lupus erythematosus |
| Anrukinzumab | humanized | Ulcerative colitis |
| Aselizumab | humanized | severely injured patients |
| Atinumab | human | Anti-reticulon 4 |
| Atlizumab | humanized | rheumatoid arthritis |
| Atorolimumab | human | hemolytic disease of the newborn |
| Begelomab | mouse | graft versus host disease |
| Benralizumab | humanized | asthma |
| Bertilimumab | human | severe allergic disorders |
| Bimagrumab | human | myostatin inhibitor |
| Bimekizumab | humanized | arthritis |
| Blosozumab | humanized | osteoporosis |
| Bococizumab | humanized | dyslipidemia |
| Brodalumab | human | inflammatory diseases |
| Brolucizumab | humanized | psoriatic arthritis |
| Caplacizumab | humanized | thrombotic thrombocytopenic purpura, thrombosis |

| Antibodies | | |
|---|---|---|
| **Antibody** | **Type** | **Proposed Treatment/Target** |
| Cedelizumab | humanized | prevention of organ transplant rejections, treatment of autoimmune diseases |
| Clazakizumab | humanized | rheumatoid arthritis |
| Clenoliximab | chimeric | rheumatoid arthritis |
| Concizumab | humanized | bleeding |
| Dapirolizumab pegol | humanized | lupus |
| Dectrekumab | human | allergic rhinitis (hay fever), allergic asthma, rectal fistula in patients with Crohn's disease, oesophagitis and pulmonary fibrosis |
| Dupilumab | human | atopic diseases |
| Eldelumab | human | Crohn's disease, ulcerative colitis |
| Elsilimomab | mouse | immunosuppression |
| Enlimomab pegol | mouse | Arthritis/transplant rejection |
| Enokizumab | humanized | asthma |
| Etrolizumab | humanized | inflammatory bowel disease |
| Evinacumab | human | dyslipidemia |
| Evolocumab | human | hypercholesterolemia |
| Fanolesomab | mouse | appendicitis (diagnosis) |
| Fasinumab | human | acute sciatic pain |
| Fezakinumab | human | rheumatoid arthritis, psoriasis |
| Fletikumab | human | rheumatoid arthritis |
| Fontolizumab | humanized | Crohn's disease etc. |
| Foralumab | human | Inflammatory diseases |
| Fresolimumab | human | idiopathic pulmonary fibrosis, focal segmental glomerulosclerosis, cancer |
| Fulranumab | human | pain |
| Gavilimomab | mouse | graft versus host disease |
| Gevokizumab | humanized | diabetes etc. |
| Gomiliximab | chimeric | allergic asthma |
| Guselkumab | human | psoriasis |
| Idarucizumab | humanized | reversal of anticoagulant effects of dabigatran |
| Inclacumab | human | inflammation |
| Inolimomab | mouse | graft versus host disease |
| Itolizumab | humanized | psoriasis |

| Antibodies | | |
|---|---|---|
| **Antibody** | **Type** | **Proposed Treatment/Target** |
| Ixekizumab | humanized | autoimmune diseases |
| Keliximab | chimeric | chronic asthma |
| Lambrolizumab | humanized | antineoplastic agent |
| Lampalizumab | humanized | Macular degeneration |
| Lebrikizumab | humanized | asthma |
| Lerdelimumab | human | reduction of scarring after glaucoma surgery |
| Ligelizumab | humanized | severe asthma and chronic spontaneous urticaria |
| Lodelcizumab | humanized | hypercholesterolemia |
| Lulizumab pegol | humanized | autoimmune diseases |
| Maslimomab | mouse | immunosuppression |
| Mavrilimumab | human | rheumatoid arthritis |
| Metelimumab | human | systemic scleroderma |
| Morolimumab | human | Anti-Rhesus factor |
| Namilumab | human | psoriasis |
| Nebacumab | human | sepsis |
| Nemolizumab | humanized | Atopic dermatitis |
| Nerelimomab | mouse | TNF inhibitor |
| Odulimomab | mouse | prevention of organ transplant rejections, immunological diseases |
| Olokizumab | humanized | Inflammatory disease |
| Opicinumab | human | multiple sclerosis |
| Orticumab | human | Inflammatory disease |
| Oxelumab | human | asthma |
| Ozanezumab | humanized | ALS and multiple sclerosis |
| Ozoralizumab | humanized | inflammation |
| Pascolizumab | humanized | asthma |
| Pateclizumab | humanized | TNF |
| Perakizumab | humanized | arthritis |
| Pexelizumab | humanized | reduction of side effects of cardiac surgery |
| Placulumab | human | Inflammatory diseases |
| Priliximab | chimeric | Crohn's disease, multiple sclerosis |
| Quilizumab | humanized | asthma |
| Ralpancizumab | humanized | dyslipidemia |

| Antibodies | | |
|---|---|---|
| **Antibody** | **Type** | **Proposed Treatment/Target** |
| Refanezumab | humanized | recovery of motor function after stroke |
| Rinucumab | human | neovascular age-related macular degeneration |
| Roledumab | human | anti-RhD |
| Romosozumab | humanized | osteoporosis |
| Rontalizumab | humanized | systemic lupus erythematosus |
| Rovelizumab | humanized | haemorrhagic shock etc. |
| Ruplizumab | humanized | rheumatic diseases |
| Sarilumab | human | rheumatoid arthritis, ankylosing spondylitis |
| Secukinumab | human | uveitis, rheumatoid arthritis psoriasis |
| Sifalimumab | humanized | SLE, dermatomyositis, polymyositis |
| Simtuzumab | humanized | fibrosis |
| Siplizumab | humanized | psoriasis, graft-versus-host disease (prevention) |
| Sirukumab | human | rheumatoid arthritis |
| Sonepcizumab | humanized | choroidal and retinal neovascularization |
| Sontuzumab | humanized | non-alcoholic steatohepatitis/primary sclerosing cholangitis |
| Stamulumab | human | muscular dystrophy |
| Tadocizumab | humanized | percutaneous coronary intervention |
| Talizumab | humanized | allergic reaction |
| Tanezumab | humanized | pain |
| Telimomab aritox | mouse | Immunosuppressive (linked to A chain of ricin protein) |
| Teneliximab | chimeric | Anti-CD40 |
| Tesidolumab | human | Choroiditis; Dry age-related macular degeneration; Panuveitis; Paroxysmal nocturnal haemoglobinuria; Wet age-related macular degeneration |
| TGN1412 | humanized | chronic lymphocytic leukemia, rheumatoid arthritis |
| Tildrakizumab | humanized | immunologically mediated inflammatory disorders |
| Toralizumab | humanized | rheumatoid arthritis, lupus nephritis etc. |
| Tralokinumab | human | asthma etc. |
| Tregalizumab | humanized | Anti-CD4 |

| Antibodies | | |
|---|---|---|
| **Antibody** | **Type** | **Proposed Treatment/Target** |
| Trevogrumab | human | muscle atrophy due to orthopedic disuse and sarcopenia |
| Vatelizumab | humanized | Multiple sclerosis |
| Vepalimomab | mouse | inflammation |
| Visilizumab | humanized | Crohn's disease, ulcerative colitis |
| Zanolimumab | human | rheumatoid arthritis, psoriasis, T-cell lymphoma |
| Zolimomab aritox | mouse | systemic lupus erythematosus, graft-versus-host disease |

**[0078]** In some aspects, the nanoparticle composition further comprises a therapeutic agent. In one embodiment, the therapeutic agent is an antibiotic or antimicrobial. In one embodiment, the therapeutic agent is an anti-inflammatory agent. Such therapeutic agents are known in the art. In some aspects, the complex further comprises a sub-therapeutic amount of paclitaxel, which amount is sufficient to allow formation of the complex.

**[0079]** Aptamers are DNA or RNA molecules that can bind to a target molecule (e.g., a protein expressed by the cancer cell or aberrant cell). This disclosure employs aptamers that target aberrant cells, such as cancer cells or virus-infected cells. Aptamers are selected based on their relative binding affinities to the molecule of interest from a library of nucleic acids or peptides. The library can be as large as 1015 members – preferably either single strand DNA or RNA. Methodology to isolate aptamers having strong binding affinities is reported by DeGrasse, *PLoS One*, 2012, 7(3) e33410, which is incorporated herein by reference in its entirety.

**[0080]** Like an antibody, an aptamer can specifically bind to its target with picomolar to nanomolar affinity. Importantly, unlike antibodies, aptamers can be directly amplified by PCR. Aptamers have been widely used in many applications, including target detection, enzyme inhibition, receptor regulation, and drug delivery. Some aptamers (e.g., MACUGEN, for age-related macular degeneration) have been approved by the FDA, and several show promise towards various diseases, including cancer. *See, e.g.*, Wu *et al.*, Theranostics. 2015; 5(4): 322–344, which is incorporated herein by reference in its entirety.

**[0081]** Without being bound by theory, it is contemplated that the combination of unglycosylated or partially glycosylated antibody or fusion protein may alter its binding capability to a protein core. In such cases, the protein will coat or bind to the portion of the antibody, aptamer, or fusion protein that interacts with the protein core (e.g., albumin), thereby reducing the immunogenicity of the binding agent while imparting increased stability and/or efficacy of the antibody, the aptamer or fusion protein *in vivo*.

**[0082]** In some embodiments, the antibody is a non-therapeutic and non-endogenous human antibody. In some embodiments, the antibody is a chimeric antibody, a non-endogenous human antibody, a humanized antibody, or non-human antibody.

**[0083]** In some embodiments, the chemotherapeutic drug is selected from the group consisting of abiraterone, bendamustine, bortezomib, carboplatin, cabazitaxel, cisplatin, chlorambucil, dasatinib, docetaxel, doxorubicin, epirubicin, erlotinib, etoposide, everolimus, gefitinib, idarubicin, imatinib, hydroxyurea, imatinib, lapatinib, leuprorelin, melphalan, methotrexate, mitoxantrone, nedaplatin, nilotinib, oxaliplatin, paclitaxel, pazopanib, pemetrexed, picoplatin, romidepsin, satraplatin, sorafenib, vemurafenib, sunitinib, teniposide, triplatin, vinblastine, vinorelbine, vincristine, and cyclophosphamide.

**[0084]** Both ABRAXANE ® and albumin particles comprising other chemotherapeutic agents are disclosed by U.S. Patent Nos. 7,758,891; 7,820,788; 7,923,536; 8,034,375; 8,138,229; 8,268,348; 8,314,156; 8,853,260; and 9,101,543, each of which is incorporated herein by reference in its entirety. In addition, carrier protein, chemotherapeutic drug, antibody conjugates, or combinations thereof are disclosed by PCT/US2015/054295 and U.S. Publication No. 2014/0178486, each of which is incorporated herein by reference in its entirety.

**[0085]** Table 7 depicts a list of non-limiting list of chemotherapeutic agents. It should be understood, that while targets are limited, the use of the agents is not limited only to the listed targets. It is contemplated that each individually can be used for any type of cancer, including those listed throughout the disclosure.

Table 7: Cancer therapeutic agents

| Cancer Drugs | |
|---|---|
| **Drug** | **Target(s)** |
| Abitrexate (Methotrexate) | Acute lymphoblastic leukemia; breast cancer; gestational trophoblastic disease, head and neck cancer; lung cancer; mycosis fungoides; non-Hodgkin lymphoma; osteosarcoma |
| ABRAXANE (Paclitaxel Albumin-stabilized Nanoparticle Formulation) | Breast cancer; non-small cell lung cancer; pancreatic cancer |
| ABVD (Adriamycin, bleomycin, vinblastine sulfate, dacarbazine) | Hodgkin lymphoma |
| ABVE (Adriamycin, bleomycin, vincristine sulfate, etoposide) | Hodgkin lymphoma (in children) |
| ABVE-PC(Adriamycin, bleomycin, vincristine sulfate, etoposide, prednisone, cyclophosphamide) | Hodgkin lymphoma (in children) |
| AC (Adriamycin cyclophosphamide) | Breast cancer |
| AC-T (Adriamycin, cylclophosphamide, Taxol) | Breast cancer |
| Adcetris (Brentuximab Vedotin) | Anaplastic large cell lymphoma; Hodgkin lymphoma |
| ADE (Cytarabine (Ara-C), Daunorubicin Hydrochloride, Etoposide) | Acute myeloid leukemia (in children) |
| Ado-Trastuzumab Emtansine | Breast cancer |
| Adriamycin (Doxorubicin Hydrochloride) | Acute lymphoblastic leukemia; acute myeloid leukemia; breast cancer, gastric (stomach) cancer; Hodgkin lymphoma; neuroblastoma; non-Hodgkin lymphoma; ovarian cancer; small cell lung cancer; soft tissue and bone sarcomas; thyroid cancer; transitional cell bladder cancer; Wilms tumor |
| Adrucil (Fluorouracil) | Basal cell carcinoma; breast cancer; colorectal cancer; gastric (stomach) adenocarcinoma; pancreatic cancer; squamous cell carcinoma of the head and neck |
| Afatinib Dimaleate | Non-small cell lung cancer |
| Afinitor (Everolimus) | Breast cancer, pancreatic cancer; renal cell carcinoma; subependymal giant cell astrocytoma |
| Alimta (Pemetrexed Disodium) | Malignant pleural mesothelioma; non-small cell lung cancer |
| Ambochlorin (Chlorambucil) | Chronic lymphocytic leukemia; Hodgkin lymphoma; non-Hodgkin lymphoma |
| Anastrozole | Breast cancer |
| Aredia (Pamidronate Disodium) | Breast cancer; multiple myeloma |
| Arimidex (Anastrozole) | Breast cancer |

| | |
|---|---|
| Aromasin (Exemestane) | Advanced breast cancer; early-stage breast cancer and estrogen receptor positive |
| Arranon (Nelarabine) | T-cell acute lymphoblastic leukemia; T-cell lymphoblastic lymphoma |
| Azacitidine | Myelodysplastic syndromes |
| BEACOPP | Hodgkin lymphoma |
| Becenum (Carmustine) | Brain tumors; Hodgkin lymphoma; multiple myeloma; non-Hodgkin lymphoma |
| Beleodaq (Belinostat) | Peripheral T-cell lymphoma |
| BEP | Ovarian germ cell tumors; testicular germ cell tumors |
| Bicalutamide | Prostate cancer |
| BiCNU (Carmustine) | Brain tumors; Hodgkin lymphoma; multiple myeloma; non-Hodgkin lymphoma |
| Bleomycin | Hodgkin lymphoma; non-Hodgkin lymphoma; penile cancer; squamous cell carcinoma of the cervix; squamous cell carcinoma of the head and neck; squamous cell carcinoma of the vulva; testicular cancer |
| Bosulif (Bosutinib) | Chronic myelogenous leukemia |
| Brentuximab Vedotin | Anaplastic large cell lymphoma; Hodgkin lymphoma |
| Busulfan | Chronic myelogenous leukemia |
| Busulfex (Busulfan) | Chronic myelogenous leukemia |
| Cabozantinib-S-Malate | Medullary thyroid cancer |
| CAF | Breast cancer |
| Camptosar (Irinotecan Hydrochloride) | Colorectal cancer |
| CAPOX | Colorectal cancer |
| Carfilzomib | Multiple myeloma |
| Casodex (Bicalutamide) | Prostate cancer |
| CeeNU (Lomustine) | Brain tumors; Hodgkin lymphoma |
| Ceritinib | Non-small cell lung cancer |
| Cerubidine (Daunorubicin Hydrochloride) | Acute lymphoblastic leukemia; acute myeloid leukemia |
| Chlorambucil | Chronic lymphocytic leukemia; Hodgkin lymphoma; non-Hodgkin lymphoma |
| CHLORAMBUCIL-PREDNISONE | Chronic lymphocytic leukemia |
| CHOP | Non-Hodgkin lymphoma |
| Cisplatin | Bladder cancer; cervical cancer; malignant mesothelioma; non-small cell lung cancer; ovarian cancer; squamous cell carcinoma of the head and neck; testicular cancer |
| Clafen (Cyclophosphamide) | Acute lymphoblastic leukemia; acute myeloid leukemia; breast cancer; chronic lymphocytic leukemia; chronic myelogenous leukemia; Hodgkin lymphoma; multiple myeloma; |

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| | mycosis fungoides; neuroblastoma; non-Hodgkin lymphoma; ovarian cancer; retinoblastoma |
| Clofarex (Clofarabine) | Acute lymphoblastic leukemia |
| CMF | Breast cancer |
| Cometriq (Cabozantinib-S-Malate) | Medullary thyroid cancer |
| COPP | Hodgkin lymphoma; non-Hodgkin lymphoma |
| COPP-ABV | Hodgkin lymphoma |
| Cosmegen (Dactinomycin) | Ewing sarcoma; gestational trophoblastic disease; rhabdomyosarcoma; solid tumors; testicular cancer; Wilms tumor |
| CVP | Non-Hodgkin lymphoma; chronic lymphocytic leukemia |
| Cyclophosphamide | Acute lymphoblastic leukemia; acute myeloid leukemia; breast cancer; chronic lymphocytic leukemia; chronic myelogenous leukemia; Hodgkin lymphoma; multiple myeloma; mycosis fungoides; neuroblastoma; non-Hodgkin lymphoma; ovarian cancer; retinoblastoma. |
| Cyfos (Ifosfamide) | Testicular germ cell tumors |
| Cyramza (Ramucirumab) | Adenocarcinoma; colorectal cancer; non-small cell lung cancer |
| Cytarabine | Acute lymphoblastic leukemia; acute myeloid leukemia; chronic myelogenous leukemia; meningeal leukemia |
| Cytosar-U (Cytarabine) | Acute lymphoblastic leukemia; acute myeloid leukemia; chronic myelogenous leukemia; meningeal leukemia |
| Cytoxan (Cyclophosphamide) | Acute lymphoblastic leukemia; acute myeloid leukemia; breast cancer; chronic lymphocytic leukemia; chronic myelogenous leukemia; Hodgkin lymphoma; multiple myeloma; mycosis fungoides; neuroblastoma; non-Hodgkin lymphoma; ovarian cancer; retinoblastoma |
| Dacarbazine | Hodgkin lymphoma; melanoma |
| Dacogen (Decitabine) | Myelodysplastic syndromes |
| Dactinomycin | Ewing sarcoma; gestational trophoblastic disease; rhabdomyosarcoma; solid tumors; testicular cancer; Wilms tumor |
| Daunorubicin Hydrochloride | Acute lymphoblastic leukemia; acute myeloid leukemia |
| Degarelix | Prostate cancer |
| Denileukin Diftitox | Cutaneous T-cell lymphoma |
| Denosumab | Giant cell tumor of the bone; breast cancer, |

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| | prostate cancer |
| DepoCyt (Liposomal Cytarabine) | Lymphomatous meningitis |
| DepoFoam (Liposomal Cytarabine) | Lymphomatous meningitis |
| Docetaxel | Breast cancer; adenocarcinoma of the stomach or gastroesophageal junction; non-small cell lung cancer; prostate cancer; squamous cell carcinoma of the head and neck |
| Doxil (Doxorubicin Hydrochloride Liposome) | AIDS-related Kaposi sarcoma; multiple myeloma; ovarian cancer |
| Doxorubicin Hydrochloride | Acute lymphoblastic leukemia; acute myeloid leukemia; breast cancer; gastric (stomach) cancer; Hodgkin lymphoma; neuroblastoma; non-Hodgkin lymphoma; ovarian cancer; small cell lung cancer; soft tissue and bone sarcomas; thyroid cancer; transitional cell bladder cancer; Wilms tumor. |
| Dox-SL (Doxorubicin Hydrochloride Liposome) | AIDS-related Kaposi sarcoma; multiple myeloma; ovarian cancer |
| DTIC-Dome (Dacarbazine) | Hodgkin lymphoma; melanoma |
| Efudex (Fluorouracil) | Basal cell carcinoma; breast cancer; colorectal cancer; gastric (stomach) adenocarcinoma; pancreatic cancer; squamous cell carcinoma of the head and neck |
| Ellence (Epirubicin Hydrochloride) | Breast cancer |
| Eloxatin (Oxaliplatin) | Colorectal cancer; stage III colon cancer |
| Emend (Aprepitant) | Nausea and vomiting caused by chemotherapy and nausea and vomiting after surgery |
| Enzalutamide | Prostate cancer |
| Epirubicin Hydrochloride | Breast cancer |
| EPOCH | Non-Hodgkin lymphoma |
| Erbitux (Cetuximab) | Colorectal cancer; squamous cell carcinoma of the head and neck |
| Eribulin Mesylate | Breast cancer |
| Erivedge (Vismodegib) | Basal cell carcinoma |
| Erlotinib Hydrochloride | Non-small cell lung cancer; pancreatic cancer |
| Erwinaze (Asparaginase Erwinia chrysanthemi) | Acute lymphoblastic leukemia |
| Etopophos (Etoposide Phosphate) | Small cell lung cancer; testicular cancer |
| Evacet (Doxorubicin Hydrochloride Liposome) | AIDS-related Kaposi sarcoma; multiple myeloma; ovarian cancer |
| Everolimus | Breast cancer; pancreatic cancer; renal cell carcinoma; subependymal giant cell astrocytoma |
| Evista (Raloxifene Hydrochloride) | Breast cancer |

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| Exemestane | Breast cancer |
| Fareston (Toremifene) | Breast cancer |
| Farydak (Panobinostat) | Multiple myeloma |
| Faslodex (Fulvestrant) | Breast cancer |
| FEC | Breast cancer |
| Femara (Letrozole) | Breast cancer |
| Filgrastim | Neutropenia |
| Fludara (Fludarabine Phosphate) | Chronic lymphocytic leukemia |
| Fluoroplex (Fluorouracil) | Basal cell carcinoma; breast cancer; colorectal cancer; gastric (stomach) adenocarcinoma; pancreatic cancer; squamous cell carcinoma of the head and neck |
| Folex (Methotrexate) | Acute lymphoblastic leukemia; breast cancer; gestational trophoblastic disease; head and neck cancer; lung cancer; mycosis fungoides; non-Hodgkin lymphoma; osteosarcoma |
| FOLFIRI | Colorectal cancer |
| FOLFIRI-BEVACIZUMAB | Colorectal cancer |
| FOLFIRI-CETUXIMAB | Colorectal cancer |
| FOLFIRINOX | Pancreatic cancer |
| FOLFOX | Colorectal cancer |
| Folotyn (Pralatrexate) | Peripheral T-cell lymphoma |
| FU-LV | Colorectal cancer; esophageal cancer; gastric cancer |
| Fulvestrant | Breast cancer |
| Gefitinib | Non-small cell lung cancer |
| Gemcitabine Hydrochloride | Breast cancer; non-small cell lung cancer; ovarian cancer; pancreatic cancer |
| GEMCITABINE-CISPLATIN | Biliary tract cancer; bladder cancer; cervical cancer; malignant mesothelioma; non-small cell lung cancer; ovarian cancer; pancreatic cancer |
| GEMCITABINE-OXALIPLATIN | Pancreatic cancer |
| Gemtuzumab Ozogamicin (antibody drug conjugate) | Acute myeloid leukemia |
| Gemzar (Gemcitabine Hydrochloride) | Breast cancer; non-small cell lung cancer; ovarian cancer; pancreatic cancer |
| Gilotrif (Afatinib Dimaleate) | Non-small cell lung cancer |
| Gleevec (Imatinib Mesylate) | Acute lymphoblastic leukemia; chronic eosinophilic leukemia or hypereosinophilic syndrome; chronic myelogenous leukemia; dermatofibrosarcoma protuberans; gastrointestinal stromal tumor; myelodysplastic/myeloproliferative neoplasms; systemic mastocytosis. |
| Gliadel (Carmustine Implant) | Glioblastoma multiforme; malignant glioma |

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| Goserelin Acetate | Breast cancer; prostate cancer |
| Halaven (Eribulin Mesylate) | Breast cancer |
| Hycamtin (Topotecan Hydrochloride) | Cervical cancer; ovarian cancer; small cell lung cancer |
| Hyper-CVAD | Acute lymphoblastic leukemia; non-Hodgkin lymphoma |
| Ibrance (Palbociclib) | Breast cancer |
| Ibrutinib | Chronic lymphocytic leukemia; mantel cell lymphoma; |
| ICE | Hodgkin lymphoma; non-Hodgkin lymphoma |
| Iclusig (Ponatinib Hydrochloride) | Acute lymphoblastic leukemia; Chronic myelogenous leukemia |
| Idamycin (Idarubicin Hydrochloride) | Acute myeloid leukemia |
| Imatinib Mesylate | Acute lymphoblastic leukemia; chronic eosinophilic leukemia or hypereosinophilic syndrome; chronic myelogenous leukemia; dermatofibrosarcoma protuberans; gastrointestinal stromal tumor; myelodysplastic/myeloproliferative neoplasms; systemic mastocytosis. |
| Imbruvica (Ibrutinib) | Chronic lymphocytic leukemia; mantle cell lymphoma; Waldenström macroglobulinemia |
| Inlyta (Axitinib) | Renal cell carcinoma |
| Iressa (Gefitinib) | Non-small cell lung cancer |
| Irinotecan Hydrochloride | Colorectal cancer |
| Istodax (Romidepsin) | Cutaneous T-cell lymphoma |
| Ixempra (Ixabepilone) | Breast cancer |
| Jevtana (Cabazitaxel) | Prostate cancer |
| Keoxifene (Raloxifene Hydrochloride) | Breast cancer |
| Kyprolis (Carfilzomib) | Multiple myeloma |
| Lenvima (Lenvatinib Mesylate) | Thyroid cancer |
| Letrozole | Breast cancer |
| Leucovorin Calcium | Colorectal cancer |
| Leukeran (Chlorambucil) | Chronic lymphocytic leukemia; Hodgkin lymphoma; non-Hodgkin lymphoma |
| Leuprolide Acetate | Prostate cancer |
| Linfolizin (Chlorambucil) | Chronic lymphocytic leukemia; Hodgkin lymphoma; non-Hodgkin lymphoma |
| LipoDox (Doxorubicin Hydrochloride Liposome) | AIDS-related Kaposi sarcoma; multiple myeloma; ovarian cancer |
| Lomustine | Brain tumors; Hodgkin lymphoma |
| Lupron (Leuprolide Acetate) | Prostate cancer |
| Lynparza (Olaparib) | Ovarian cancer |
| Marqibo (Vincristine Sulfate Liposome) | Acute lymphoblastic leukemia |
| Matulane (Procarbazine Hydrochloride) | Hodgkin lymphoma |
| Mechlorethamine Hydrochloride | Bronchogenic carcinoma; chronic |

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| | lymphocytic leukemia; chronic myelogenous leukemia; Hodgkin lymphoma; malignant pleural effusion, malignant pericardial effusion, and malignant peritoneal effusion; mycosis fungoides; non-Hodgkin lymphoma |
| Megace (Megestrol Acetate) | Breast cancer; endometrial cancer |
| Mekinist (Trametinib) | Melanoma |
| Mercaptopurine | Acute lymphoblastic leukemia |
| Mesnex (Mesna) | Hemorrhagic cystitis |
| Methazolastone (Temozolomide) | Anaplastic astrocytoma; glioblastoma multiforme |
| Mexate (Methotrexate) | Acute lymphoblastic leukemia; breast cancer; gestational trophoblastic disease; head and neck cancer; lung cancer; mycosis fungoides; non-Hodgkin lymphoma; osteosarcoma |
| Mexate-AQ (Methotrexate) | Acute lymphoblastic leukemia; breast cancer; gestational trophoblastic disease; head and neck cancer; lung cancer; mycosis fungoides; non-Hodgkin lymphoma; osteosarcoma |
| Mitoxantrone Hydrochloride | Acute myeloid leukemia; prostate cancer |
| Mitozytrex (Mitomycin C) | Gastric (stomach) and pancreatic adenocarcinoma |
| MOPP | Hodgkin lymphoma |
| Mozobil (Plerixafor) | Multiple myeloma; non-Hodgkin lymphoma |
| Mustargen (Mechlorethamine Hydrochloride) | Bronchogenic carcinoma; chronic lymphocytic leukemia; chronic myelogenous leukemia; Hodgkin lymphoma; malignant pleural effusion, malignant pericardial effusion, and malignant peritoneal effusion; mycosis fungoides; non-Hodgkin lymphoma |
| Myleran (Busulfan) | Chronic myelogenous leukemia |
| Mylotarg (Gemtuzumab Ozogamicin) | Acute myeloid leukemia |
| Nanoparticle Paclitaxel (Paclitaxel Albumin-stabilized Nanoparticle Formulation) | Breast cancer; Non-small cell lung cancer; Pancreatic cancer |
| Navelbine (Vinorelbine Tartrate) | Non-small cell lung cancer |
| Nelarabine | T-cell acute lymphoblastic leukemia |
| Neosar (Cyclophosphamide) | Acute lymphoblastic leukemia; Acute myeloid leukemia; Breast cancer; Chronic lymphocytic leukemia; Chronic myelogenous leukemia; Hodgkin lymphoma; Multiple myeloma; Mycosis fungoides; Neuroblastoma; Non-Hodgkin lymphoma; Ovarian cancer; Retinoblastoma |
| Nexavar (Sorafenib Tosylate) | Hepatocellular carcinoma; Renal cell carcinoma; Thyroid cancer |
| Nilotinib | Chronic myelogenous leukemia |

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| Nivolumab | Melanoma; Squamous non-small cell lung cancer |
| Nolvadex (Tamoxifen Citrate) | Breast cancer |
| Odomzo (Sonidegib) | Basal cell carcinoma |
| OEPA | Hodgkin lymphoma |
| OFF | Pancreatic cancer |
| Olaparib | Ovarian cancer |
| Oncaspar (Pegaspargase) | Acute lymphoblastic leukemia |
| OPPA | Hodgkin lymphoma |
| Oxaliplatin | Colorectal cancer; Stage III colon cancer |
| Paclitaxel | AIDS-related Kaposi sarcoma; Breast cancer; Non-small cell lung cancer; Ovarian cancer |
| Paclitaxel Albumin-stabilized Nanoparticle Formulation | Breast cancer; Non-small lung cancer; Pancreatic cancer |
| PAD | Multiple myeloma |
| Palbociclib | Breast cancer |
| Pamidronate Disodium | Breast cancer; Multiple myeloma |
| Panitumumab | Colorectal cancer |
| Panobinostat | Multiple myeloma |
| Paraplat (Carboplatin) | Non-small cell lung cancer; Ovarian cancer |
| Paraplatin (Carboplatin) | Non-small cell lung cancer; Ovarian cancer |
| Pazopanib Hydrochloride | Renal cell carcinoma; Soft tissue sarcoma |
| Pegaspargase | Acute lymphoblastic leukemia |
| Pemetrexed Disodium | Malignant pleural mesothelioma; Non-small cell lung cancer |
| Platinol (Cisplatin) | Bladder cancer; Cervical cancer; Malignant mesothelioma; Non-small cell lung cancer; Ovarian cancer; Squamous cell carcinoma of the head and neck; Testicular cancer |
| Platinal-AQ (Cisplatin) | Bladder cancer; Cervical cancer; Malignant mesothelioma; Non-small cell lung cancer; Ovarian cancer; Squamous cell carcinoma of the head and neck; Testicular cancer |
| Plerixafor | Multiple myeloma; Non-Hodgkin lymphoma |
| Pomalidomide | Multiple myeloma |
| Pomalyst (Pomalidomide) | Multiple myeloma |
| Pontinib Hydrochloride | Acute lymphoblastic leukemia; Chronic myelogenous leukemia |
| Pralatrexate | Peripheral T-cell lymphoma |
| Prednisone | Acute lymphoblastic leukemia; Chronic lymphocytic leukemia; Hodgkin lymphoma; Multiple myeloma; Non-Hodgkin lymphoma; Prostate cancer; Thymoma and thymic carcinoma |
| Procarbazine Hydrochloride | Hodgkin lymphoma |
| Provenge (Sipuleucel-T) | Prostate cancer |

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| Purinethol (Mercaptopurine) | Acute lymphoblastic leukemia |
| Radium 223 Dichloride | Prostate cancer |
| Raloxifene Hydrochloride | Breast cancer |
| R-CHOP | Non-Hodgkin lymphoma |
| R-CVP | Non-Hodgkin lymphoma |
| Regorafenib | Colorectal cancer; Gastrointestinal stromal tumor |
| R-EPOCH | B-cell non-Hodgkin lymphoma |
| Revlimid (Lenalidomide) | Mantle cell lymphoma; Multiple myeloma; Anemia |
| Rheumatrex (Methotrexate) | Acute lymphoblastic leukemia; Breast cancer; Gestational trophoblastic disease; Head and neck cancer; Lung cancer; Non-Hodgkin lymphoma; Osteosarcoma |
| Romidepsin | Cutaneous T-cell lymphoma |
| Rubidomycin (Daunorubicin Hydrochloride) | Acute lymphoblastic leukemia; Acute myeloid leukemia |
| Sipuleucel-T | Prostate cancer |
| Somatuline Depot (Lanreotide Acetate) | Gastroenteropancreatic neuroendocrine tumors |
| Sonidegib | Basal cell carcinoma |
| Sorafenib Tosylate | Hepatocellular carcinoma; Renal cell carcinoma; Thyroid cancer |
| Sprycel (Dasatinib) | Acute lymphoblastic leukemia; Chronic myelogenous leukemia |
| STANFORD V | Hodgkin lymphoma |
| Stivarga (Regorafenib) | Colorectal cancer; Gastrointestinal stromal tumor |
| Sunitnib Malate | Gastronintestinal stromal tumor; Pancreatic cancer; Renal cell carcinoma |
| Sutent (Sunitinib Malate) | Gastronintestinal stromal tumor; Pancreatic cancer; Renal cell carcinoma |
| Synovir (Thalidomide) | Multiple myeloma |
| Synribo (Omacetaxine Mepesuccinate) | Chronic myelogenous leukemia |
| TAC | Breast cancer |
| Tafinlar (Dabrafenib) | Melanoma |
| Tamoxifen Citrate | Breast cancer |
| Tarabine PFS (Cytarabine) | Acute lymphoblastic leukemia; Acute myeloid leukemia; Chronic myelogenous leukemia |
| Tarceva (Erlotinib Hydrochloride) | Non-small cell lung cancer; Pancreatic cancer |
| Targretin (Bexarotene) | Skin problems caused by cutaneous T-cell lymphoma |
| Tasigna (Niltinib) | Chronic myelogenous leukemia |
| Taxol (Paclitaxel) | AIDS-related Kaposi sarcoma; Breast cancer; Non-small cell lung cancer; Ovarian cancer |

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| Taxotere (Docetaxel) | Breast cancer; Adenocarcinoma; Non-small cell lung cancer; Prostate cancer; Squamous cell carcinoma of the head and neck |
| Temodar (Temozolomide) | Anaplastic astrocytoma; Glioblastoma multiforme |
| Temozolomide | Anaplastic astrocytoma; Glioblastoma multiforme |
| Thiotepa | Bladder cancer; Breast cancer; Malignant pleural effusion, malignant pericardial effusion, and malignant peritoneal effusion; Ovarian cancer |
| Toposar (Etoposide) | Small cell lung cancer; Testicular cancer |
| Topotecan Hydrochloride | Cervical cancer; Ovarian cancer; Small cell lung cancer |
| Toremifene | Breast cancer |
| Torisel (Temsirolimus) | Renal cell carcinoma |
| TPF | Squamous cell carcinoma of the head and neck; Gastric (stomach) cancer |
| Trastuzumab | Adenocarcinoma; Breast cancer |
| Treanda (Bendamustine Hydrochloride) | B-cell non-Hodgkin lymphoma; Chronic lymphocytic leukemia |
| Trisenox (Arsenic Trioxide) | Acute promyelocytic leukemia |
| Tykerb (Lapatinib Ditosylate) | Breast cancer |
| Vandetabib | Medullary thyroid cancer |
| VAMP | Hodgkin lymphoma |
| VeIP | Ovarian germ cell; Testicular cancer |
| Velban (Vinblastine Sulfate) | Breast cancer; Choriocarcinoma; Hodgkin lymphoma; Kaposi sarcoma; Mycosid fungoides; Non-Hodgkin lymphoma; Testicular cancer |
| Velcade (Bortezomib) | Mulitple myeloma; Mantle cell lymphoma |
| Velsar (Vinblastine Sulfate) | Breast cancer; Choriocarcinoma; Hodgkin lymphoma; Kaposi sarcoma; Mycosis fungoides; Non-Hodgkin lymphoma; Testicular cancer |
| VePesid (Etoposide) | Small cell lung cancer; Testicular cancer |
| Viadur (Leuprolide Acetate) | Prostate cancer |
| Vidaza (Azacitidine) | Myelodysplastic syndromes |
| Vincasar PFS (Vincristine Sulfate) | Acute leukemia; Hodgkin lymphoma; Neuroblastoma; Non-Hodgkin lymphoma; Rhabdomyosarcoma; Wilms tumor |
| Vincristine Sulfate Liposome | Acute lymphoblastic leukemia |
| Vinorelbine Tartrate | Non-small cell lung cancer |
| VIP | Testicular cancer |
| Visbodegib | Basal cell carcinoma |
| Voraxaze (Glucarpidase) | Toxic blood levels of the anticancer drug |

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| | methotrexate |
| Votrient (Pazopanib Hydrochloride) | Renal cell carcinoma; Soft tissue sarcoma |
| Wellcovorin (Leucovorin Calcium) | Colorectal cancer; Anemia |
| Xalkori (Crizotinib) | Non-small cell lung cancer |
| Xeloda (Capecitabine) | Breast cancer; Colorectal cancer |
| XELIRI | Colorectal cancer; Esophageal cancer; Gastric (stomach) cancer |
| XELOX | Colorectal cancer |
| Xofigo (Radium 223 Dichloride) | Prostate cancer |
| Xtandi (Enzalutamide) | Prostate cancer |
| Zaltrap (Ziv-Aflibercept) | Colorectal cancer |
| Zelboraf (Vemurafenib) | Melanoma |
| Ziv-Aflibercept | Colorectal cancer |
| Zoladex (Goserelin Acetate) | Breast cancer; Prostate cancer |
| Zolinza (Vorinostat) | Cutaneous T-cell lymphoma |
| Zometa (Zoledronic Acid) | Multiple myeloma |
| Zydelig (Idelalisib) | Chronic lymphocytic leukemia; Non-Hodgkin lymphoma (Follicula B-cell non Hodgkin lymphoma and Small lymphocytic lymphoma) |
| Zykadia (Certinib) | Non-small cell lung cancer |
| Zytiga (Abiraterone Acetate) | Prostate cancer |

**[0086]** In some embodiments, the chemotherapeutic agent is associated with a carrier protein. In some embodiments, the complex further comprises a sub-therapeutic amount of paclitaxel.

**[0087]** In some embodiments, the effective amount of the chemotherapeutic agent is selected from an amount consisting of about 100 mg/m$^2$, about 105 mg/m$^2$, about 110 mg/m$^2$, about 115 mg/m$^2$, about 120 mg/m$^2$, about 125 mg/m$^2$, about 130 mg/m$^2$, about 135 mg/m$^2$, about 140 mg/m$^2$, about 145 mg/m$^2$, about 150 mg/m$^2$, about 155 mg/m$^2$, about 160 mg/m$^2$, about 165 mg/m$^2$, about 170 mg/m$^2$, about 175 mg/m$^2$, about 180 mg/m$^2$, about 185 mg/m$^2$, about 190 mg/m$^2$, about 195 mg/m$^2$, or about 200 mg/m$^2$ of the chemotherapeutic drug.

**[0088]** It is to be understood that the therapeutic agent (i.e., chemotherapeutic agent) may be located inside the nanoparticle, on the outside surface of the nanoparticle, or both. The nanoparticle may contain more than one different therapeutic agents, for example, two therapeutic agents, three therapeutic agents, four therapeutic agents, five therapeutic agents,

or more. Furthermore, a nanoparticle may contain the same or different therapeutic agents inside and outside the nanoparticle.

**[0089]** In one aspect, the amount of chemotherapeutic agent, e.g. paclitaxel, in the nanoparticle is sufficient to allow formation of the nanoparticle. The use of sub-therapeutic amounts of paclitaxel for formation of antibody-albumin nanoparticle complexes is described, for example, in U.S. Provisional App. No. 62/384,119, which is incorporated herein by reference in its entirety.

**[0090]** In one embodiment, the amount of paclitaxel present in the nanoparticle composition is greater than or equal to a minimum amount capable of providing stability to the nanoparticles. In one embodiment, the amount of paclitaxel present in the nanoparticle composition is greater than or equal to a minimum amount capable of providing affinity of the at least one therapeutic agent to the protein carrier. In one embodiment, the amount of paclitaxel present in the nanoparticle composition is greater than or equal to a minimum amount capable of facilitating complex-formation of the at least one therapeutic agent and the protein carrier.In one embodiment, the weight ratio of the carrier protein and the paclitaxel of the nanoparticle composition is greater than about 9:1. In one embodiment, the weight ratio is greater than about 10:1, or 11:1, or 12:1, or 13:1, or 14:1, or 15:1, or about 16:1, or about 17:1, or about 18:1, or about 19:1, or about 20:1, or about 21:1, or about 22:1, or about 23:1, or about 24:1, or about 25:1, or about 26:1, or about 27:1, or about 28:1, or about 29:1, or about 30:1. In one embodiment, the amount of paclitaxel is equal to an minimum amount capable of providing stability to the nanoparticles. In one embodiment, the amount of paclitaxel is greater than or equal to a minimum amount capable of providing affinity of the at least one therapeutic agent to the protein carrier. In one embodiment, the amount of paclitaxel is greater than or equal to a minimum amount capable of facilitating complex-formation of the at least one therapeutic agent and the protein carrier. In any of the embodiments, the amount of paclitaxel can be less than a therapeutic amount for paclitaxel. In other words, the amount can be less than what is provided or contemplated for providing a therapeutic benefit, such as for example, a chemotherapeutic amount to effectively treat a cancer.

**[0091]** In one embodiment, the amount of paclitaxel present in the nanoparticle composition is less than about 5 mg/mL upon reconstitution with an aqueous solution. In one embodiment, the amount of paclitaxel present in the nanoparticle composition is less than about 4.54 mg/mL, or about 4.16 mg/mL, or about 3.57 mg/mL, or about 3.33 mg/mL, or about 3.12 mg/mL, or about 2.94 mg/mL, or about 2.78 mg/mL, or about 2.63 mg/mL, or about 2.5 mg/mL, or about 2.38 mg/mL, or about 2.27 mg/mL, or about 2.17 mg/mL, or about 2.08 mg/mL, or about 2 mg/mL, or about 1.92 mg/mL, or about 1.85 mg/mL, or about 1.78 mg/mL, or about 1.72 mg/mL, or about 1.67 mg/mL upon reconstitution with an aqueous solution.

**[0092]** In some embodiments any antibody, aptamer, therapeutic agent, or any combination thereof is expressly excluded.

**[0093]** Cancers or tumors that can be treated by the compositions and methods described herein include, but are not limited to cancers listed in the above tables and: biliary tract cancer; brain cancer, including glioblastomas and medulloblastomas; breast cancer; uterine cancer; tubal cancer; cervical cancer; choriocarcinoma; colon cancer; bladder cancer; endometrial cancer; vaginal cancer; vulvar cancer; esophageal cancer; mouth cancer; gastric cancer; kidney cancer; hematological neoplasms, including acute lymphocytic and myelogenous leukemia; multiple myeloma; AIDS associated leukemias and adult T-cell leukemia lymphoma; intraepithelial neoplasms, including Bowen's disease and Paget's disease; liver cancer (hepatocarcinoma); lung cancer; head or neck cancers or oral cancers (mouth, throat, esophageal, nasopharyngeal, jaw, tonsil, nasal, lip, salivary gland, tongue, etc.); lymphomas, including Hodgkin's disease and lymphocytic lymphomas; neuroblastomas; neuroendocrine tumors; oral cancer, including squamous cell carcinoma; adrenal cancer; anal cancer; angiosarcoma; appendix cancer; bile duct cancer; bone cancer; carcinoid tumors; soft tissue sarcoma; rhabdomyosarcoma; eye cancer; ovarian cancer, including those arising from epithelial cells, stromal cells, germ cells and mesenchymal cells, and fallopian tube cancer; gallbladder cancer; pancreas cancer; prostate cancer; rectal cancer; sarcomas, including leiomyosarcoma, rhabdomyosarcoma, liposarcoma, fibrosarcoma and osteosarcoma; skin cancer, including melanoma, Kaposi's sarcoma, basocellular cancer and squamous cell cancer; testicular cancer, including germinal tumors (seminoma, non-

seminoma[teratomas, choriocarcinomas]), stromal tumors and germ cell tumors; penile cancer; hemangioendothelioma; gastrointestinal cancer; ureteral cancer; urethral cancer; spinal cancer; pituitary gland cancer; primary central nervous system (CNS) lymphoma; thyroid cancer, including thyroid adenocarcinoma and medullar carcinoma; and renal cancer including adenocarcinoma and Wilms tumor. In important embodiments, cancers or tumors include breast cancer, prostate cancer, colorectal cancer, lymphoma, multiple myeloma, and melanoma

**[0094]** In some cases, complexes as described herein can be designed to have an average diameter that is less than 1 μm. For example, appropriate concentrations of carrier protein and antibody (or other binding agent) can be used such that complexes having an average diameter that is less than 1 μm are formed. In some cases, the complexes provided herein can have an average diameter that is between 0.1 μm and 1 μm (e.g., between 0.1 μm and 0.95 μm, between 0.1 μm and 0.9 μm, between 0.1 μm and 0.8 μm, between 0.1 μm and 0.7 μm, between 0.1 μm and 0.6 μm, between 0.1 μm and 0.5 μm, between 0.1 μm and 0.4 μm, between 0.1 μm and 0.3 μm, between 0.1 μm and 0.2 μm, between 0.2 μm and 1 μm, between 0.3 μm and 1 μm, between 0.4 μm and 1 μm, between 0.5 μm and 1 μm, between 0.2 μm and 0.6 μm, between 0.3 μm and 0.6 μm, between 0.2 μm and 0.5 μm, or between 0.3 μm and 0.5 μm). Complexes provided herein having an average diameter that is between 0.1 μm and 0.9 μm can be administered systemically (e.g., intravenously) to treat cancer or other disease located within a mammal's body.

**[0095]** In some cases, a complex as provided herein can have greater than 60 percent (e.g., greater than 65, 70, 75, 80, 90, 95, or 99 percent) of the complexes having a diameter that is between 0.1 μm and 0.9 μm (e.g., between 0.1 μm and 0.95 μm, between 0.1 μm and 0.9 μm, between 0.1 μm and 0.8 μm, between 0.1 μm and 0.7 μm, between 0.1 μm and 0.6 μm, between 0.1 μm and 0.5 μm, between 0.1 μm and 0.4 μm, between 0.1 μm and 0.3 μm, between 0.1 μm and 0.2 μm, between 0.2 μm and 1 μm, between 0.3 μm and 1 μm, between 0.4 μm and 1 μm, between 0.5 μm and 1 μm, between 0.2 μm and 0.6 μm, between 0.3 μm and 0.6 μm, between 0.2 μm and 0.5 μm, or between 0.3 μm and 0.5 μm). Complexes provided herein having greater than 60 percent (e.g., greater than 65, 70, 75, 80, 90, 95, or 99 percent) of the complexes with a diameter that is between 0.1 μm and 0.9 μm can be

administered systemically (e.g., intravenously) to treat cancer or other disease expressing the relevant antigen located within a mammal's body.

**[0096]** In general, any appropriate combination of carrier protein, chemotherapy agent, and binding agent can be used as described herein. For example, an appropriate amount of carrier protein (e.g., with a chemotherapeutic agent), and an appropriate amount of binding agent can be mixed together in the same container. This mixture can be incubated at an appropriate temperature (e.g., room temperature, between 5 °C and 60 °C, between 23 °C and 60 °C, between 15 °C and 30 °C, between 15 °C and 25 °C, between 20 °C and 30 °C, or between 20 °C and 25 °C) for a period of time (e.g., about 30 minutes, or between about 5 minutes and about 60 minutes, between about 5 minutes and about 45 minutes, between about 15 minutes and about 60 minutes, between about 15 minutes and about 45 minutes, between about 20 minutes and about 400 minutes, or between about 25 minutes and about 35 minutes) before being administered to a patient having a cancer.

**[0097]** In some cases, carrier protein nanoparticles comprising a chemotherapy agent can be contacted with a binding agent to form complexes that are stored prior to being administered to a patient. For example, a composition can be formed as described herein and stored for a period of time (e.g., days or weeks) prior to being administered to a patient.

**[0098]** Any appropriate method can be used to obtain complexes as described herein. Any appropriate method can be used to administer a complex as provided herein to a mammal. For example, a composition containing carrier protein/binding agent/chemotherapeutic agent complexes can be administered via injection (e.g., subcutaneous injection, intramuscular injection, intravenous injection, or intrathecal injection).

**[0099]** Before administering a composition containing a complex as provided herein to a mammal, the mammal can be assessed to determine whether or not the mammal has a cancer or disease expressing the relevant antigen. Any appropriate method can be used to determine whether or not a mammal has a cancer or disease expressing the relevant antigen. For example, a mammal (e.g., human) can be identified using standard diagnostic techniques.

In some cases, a tissue biopsy can be collected and analyzed to determine whether or not a mammal has a cancer or disease expressing the antigen.

**[0100]** After identifying a mammal as having the disease or cancer, the mammal can be administered a composition containing a complex as provided herein. For example, a composition containing the complex can be administered prior to or in lieu of surgical resection of a tumor. In some cases, a composition containing a complex as provided herein can be administered following resection of a tumor.

**[0101]** In some cases the nanoparticle complex as described herein may be administered with an effective amount of NK or NK-92 cells. The NK or NK-92 cells may be administered to the subject concurrently with the complexes or may be administered sequentially to the subject. For example, the NK-92 cells may be administered before the complexes are administered to the subject. An effective amount of the NK or NK-92 cells can be any amount that further reduces the progression rate of a cancer or disease expressing the antigen recognized by the binding agent (e.g., antibody or aptamer), increases the progression-free survival rate, or increases the median time to progression as compared using the complexes without the NK or NK-92 cells, and preferably without producing significant toxicity to the mammal.

**[0102]** If a particular mammal fails to respond to a particular amount, then the amount can be increased by, for example, two fold. After receiving this higher concentration, the mammal can be monitored for both responsiveness to the treatment and toxicity symptoms, and adjustments made accordingly. The effective amount can remain constant or can be adjusted as a sliding scale or variable dose depending on the mammal's response to treatment. Various factors can influence the actual effective amount used for a particular application. For example, the frequency of administration, duration of treatment, use of multiple treatment agents, route of administration, and severity of the cancer or disease may require an increase or decrease in the actual effective amount administered.

**[0103]** A composition containing a complex as provided herein can be administered to a mammal in any appropriate amount, at any appropriate frequency, and for any appropriate duration effective to achieve a desired outcome (e.g., to increase progression-free

survival). In some cases, a composition as provided herein can be administered to a mammal having a cancer or disease to reduce the progression rate of the cancer or disease by 5, 10, 25, 50, 75, 100, or more percent. For example, the progression rate can be reduced such that no additional cancer progression is detected.

**[0104]** Any appropriate method can be used to determine whether or not the progression rate of cancer is reduced. For example, the progression rate of a cancer can be assessed by imaging tissue at different time points and determining the amount of cancer cells present. The amounts of cancer cells determined within tissue at different times can be compared to determine the progression rate. After treatment as described herein, the progression rate can be determined again over another time interval. In some cases, the stage of cancer after treatment can be determined and compared to the stage before treatment to determine whether or not the progression rate was reduced.

**[0105]** In some cases, a composition as provided herein can be administered to a mammal having a cancer under conditions where progression-free survival is increased (e.g., by 5, 10, 25, 50, 75, 100, or more percent) as compared to the median progression-free survival of corresponding mammals having untreated cancer or the median progression-free survival of corresponding mammals having cancer treated with the carrier protein, chemotherapy agent, and the binding agent without forming complexes prior to administration. In some cases, a composition as provided herein can be administered to a mammal having a cancer to increase progression-free survival by 5, 10, 25, 50, 75, 100, or more percent as compared to the median progression-free survival of corresponding mammals having a cancer and having received the carrier protein, chemotherapy agent, carrier protein/chemotherapy agent nanoparticle (without a binding agent), or binding agent alone. Progression-free survival can be measured over any length of time (e.g., one month, two months, three months, four months, five months, six months, or longer).

**[0106]** In some cases, a composition containing a complex as provided herein can be administered to a mammal having a under conditions where the 8-week progression-free survival rate for a population of mammals is 65% or greater (e.g., 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80% or greater) than that observed in a population of comparable mammals not receiving a composition containing complexes as

provided herein. In some cases, the composition can be administered to a mammal having a cancer under conditions where the median time to progression for a population of mammals is at least 150 days (e.g., at least 155, 160, 163, 165, or 170 days).

**[0107]** An effective amount of a composition containing complexes as provided herein can be any amount that reduces the progression rate of a cancer or disease expressing the antigen recognized by the binding agent, increases the progression-free survival rate, or increases the median time to progression without producing significant toxicity to the mammal. If a particular mammal fails to respond to a particular amount, then the amount can be increased by, for example, two fold. After receiving this higher concentration, the mammal can be monitored for both responsiveness to the treatment and toxicity symptoms, and adjustments made accordingly. The effective amount can remain constant or can be adjusted as a sliding scale or variable dose depending on the mammal's response to treatment. Various factors can influence the actual effective amount used for a particular application. For example, the frequency of administration, duration of treatment, use of multiple treatment agents, route of administration, and severity of the cancer or disease may require an increase or decrease in the actual effective amount administered.

**[0108]** The frequency of administration can be any frequency that reduces the progression rate of a cancer or disease, increases the progression-free survival rate, or increases the median time to progression without producing significant toxicity to the mammal. For example, the frequency of administration can be from about once a month to about three times a month, or from about twice a month to about six times a month, or from about once every two months to about three times every two months. The frequency of administration can remain constant or can be variable during the duration of treatment. A course of treatment with a composition as provided herein can include rest periods. For example, the composition can be administered over a two week period followed by a two week rest period, and such a regimen can be repeated multiple times. As with the effective amount, various factors can influence the actual frequency of administration used for a particular application. For example, the effective amount, duration of treatment, use of multiple treatment agents, route of administration, and severity of the cancer or disease may require an increase or decrease in administration frequency.

**[0109]** An effective duration for administering a composition provided herein can be any duration that reduces the progression rate of a cancer or disease, increases the progression-free survival rate, or increases the median time to progression without producing significant toxicity to the mammal. Thus, the effective duration can vary from several days to several weeks, months, or years. In general, the effective duration for the treatment of a cancer or disease can range in duration from several weeks to several months. In some cases, an effective duration can be for as long as an individual mammal is alive. Multiple factors can influence the actual effective duration used for a particular treatment. For example, an effective duration can vary with the frequency of administration, effective amount, use of multiple treatment agents, route of administration, and severity of the cancer or disease.

**[0110]** A composition containing carrier protein/chemotherapy agent/ binding agent complexes as provided herein can be in any appropriate form. For example, a composition provided herein can be in the form of a solution or powder with or without a diluent to make an injectable suspension. A composition also can contain additional ingredients including, without limitation, pharmaceutically acceptable vehicles. A pharmaceutically acceptable vehicle can be, for example, saline, water, lactic acid, mannitol, or combinations thereof.

**[0111]** After administering a composition provided herein to a mammal, the mammal can be monitored to determine whether or not the cancer or disease was treated. For example, a mammal can be assessed after treatment to determine whether or not the progression rate of the cancer or disease was reduced (e.g., stopped). As described herein, any method can be used to assess progression and survival rates.

## OTHER EMBODIMENTS

**[0112]** It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

## EXAMPLES

**[0113]** One skilled in the art would understand that descriptions of making and using the particles described herein is for the sole purpose of illustration, and that the present disclosure is not limited by this illustration.

***Example 1. Albumin Nanoparticles Comprising Rituximab (AR160)***

**[0114]** The particles are synthesized by adding between about 5 mg and about 20 mg of rituximab (or non-specific IgG) to 20 mg of ABRAXANE. Saline is then added to a final volume of 2 ml for a final concentration of 10 mg/ml ABRAXANE, and the mixture is allowed to incubate at room temperature for 30 minutes to allow particle formation. Particles average about 160 nm and are termed "AR160" nanoparticles.

**[0115]** Optionally, the composition is divided into aliquots and frozen at -80°C. Once frozen the aliquots are optionally lyophilized overnight with the Virtis 3L benchtop lyophilizer (SP Scientific, Warmister, PA) with the refrigeration on. A lyophilized preparation is generated.

**[0116]** The dried aliquots are stored at room temperature. These samples are reconstituted in saline at room temperature for 30 minutes, followed by centrifugation for 7 minutes at 2000 x g. The resulting sample is then resuspended in the appropriate buffer, as needed.

***Example 2. Evaluation of Tumor Uptake of AR160***

**[0117]** Mice were injected via subcutaneous injection with lymphoma cells and tumors allowed to form. Mice received intravenous (IV) injection of equal amounts of alexaflor 750-labeled ABRAXANE (ABX), ABRAXANE coated with non-specific antibodies (AB IgG), or AR160.

**[0118]** Twenty-four hours after IV injection, tumor accumulation of the respective treatments was determined based on a fluorescence threshold. Background was determined based on a region of the mouse without a tumor. FIG. 1 is a graphical representation of background and tumor fluorescence. Table 8 indicates the numerical values for each,

including tumor-associated fluorescence (average radiant efficiency from the tumor minus background). Addition of rituximab to the ABRAXANE nanoparticle (AR160) results in a nearly 100% increase in tumor uptake of ABRAXANE.

Table 8: Average Radiant Efficiency and Adjusted Tumor-Associated Fluorescence

| | **Background** | **Tumor** | **Tumor-associated Fluorescence** |
|---|---|---|---|
| ABX | 1.541 | 2.09 | 0.549 |
| AB IgG | 1.4005 | 1.99 | 0.5895 |
| AR160 | 1.545 | 2.637 | 1.092 |

**WHAT IS CLAIMED IS:**

1. A method for increasing the *in vivo* therapeutic index of a chemotherapeutic drug targeting aberrant mammalian cells, which method comprises:

a) combining a therapeutically effective amount of said drug with a biocompatible protein carrier;

b) forming a complex with said carrier and an effective amount of an antibody which has specificity to an antigen on said aberrant cells, wherein said antibodies populate the surface of said complex and retain binding specificity; and

c) administering said complex to a patient, wherein said administration enhances delivery of said drug to said cells and reduces one or more side effects of said drug, thereby increasing the therapeutic index of said drug.

2. The method of claim 1, wherein the aberrant mammalian cells are selected from the group consisting of cancer cells, virus-infected cells, and bacteria-infected cells.

3. The method of claim 1 or claim 2, wherein the protein carrier is selected from the group consisting of albumin, gelatin, elastin, gliadin, legumin, zein, soy protein, milk protein, and whey protein.

4. The method of claim 3, wherein the protein carrier is albumin.

5. The method of claim 4, wherein the complex further comprises an effective amount of paclitaxel to form said complex.

6. The method of claim 5, wherein the amount of paclitaxel is between 0.1 $mg/m^2$ and 50 $mg/m^2$.

7. A method for increasing the *in vivo* therapeutic index of a chemotherapeutic drug targeting tumor cells, which method comprises:

a) combining a therapeutically effective amount of said drug with an albumin carrier; and

b) forming a complex with said carrier and an effective amount of antibody which has specificity to an antigen on said tumor cells, wherein said antibodies populate the surface of said complex and retain binding specificity; and

c) administering said complex to a patient wherein said administration enhances delivery of said drug to said tumor cells and reduces one or more side effects of said drug, thereby increasing the therapeutic index of said drug.

8. The method of claim 7, wherein the complex further comprises an effective amount of paclitaxel to form said complex.

9. The method of claim 8, wherein the amount of paclitaxel is between 0.1 $mg/m^2$ and 50 $mg/m^2$.

10. The method of any one of the above claims, wherein said complex is less than 1 micron in diameter.

11. The method of any one of the above claims, wherein drug-related toxicity is reduced.

12. A method of reducing chemotherapy drug-related toxicity in a patient having cancer and at risk of such toxicity, which method comprises treating said patient with a complex comprising a therapeutically effective amount of said drug with an albumin carrier, and an effective amount of antibody which has specificity to an antigen on said cancer, wherein said antibodies populate the surface of said complex and retain binding specificity, such that said patient has reduced risk of chemotherapy drug-related toxicity.

13. The method of claim 12, wherein the chemotherapy drug-related toxicity is selected from the group consisting of cardiotoxicity, nephrotoxicity, hepatotoxicity, pulmonary toxicity, dermatologic toxicity, and gastrointestinal toxicity.

14. A method for increasing the *in vivo* therapeutic index of a chemotherapeutic drug targeting aberrant mammalian cells, which method comprises:

a) combining a therapeutically effective amount of said drug with a biocompatible protein carrier;

b) forming a complex with said carrier and an effective amount of binding agent having specificity to said aberrant cells, wherein said binding agent populates the surface of said complex and retain specificity and further wherein said binding agent has a carrier protein-binding portion; and

c) administering said complex to a patient, wherein said administration enhances delivery of said drug to said cells and reduces one or more side effects of said drug, thereby increasing the therapeutic index of said drug.

15. The method of claim 14, wherein the binding agent is selected from the group consisting of aptamer, antibody, fusion protein, and Fc receptor.

16. The method of claim 14 or claim 15, wherein the aberrant mammalian cells are selected from the group consisting of cancer cells, virus-infected cells, and bacteria-infected cells.

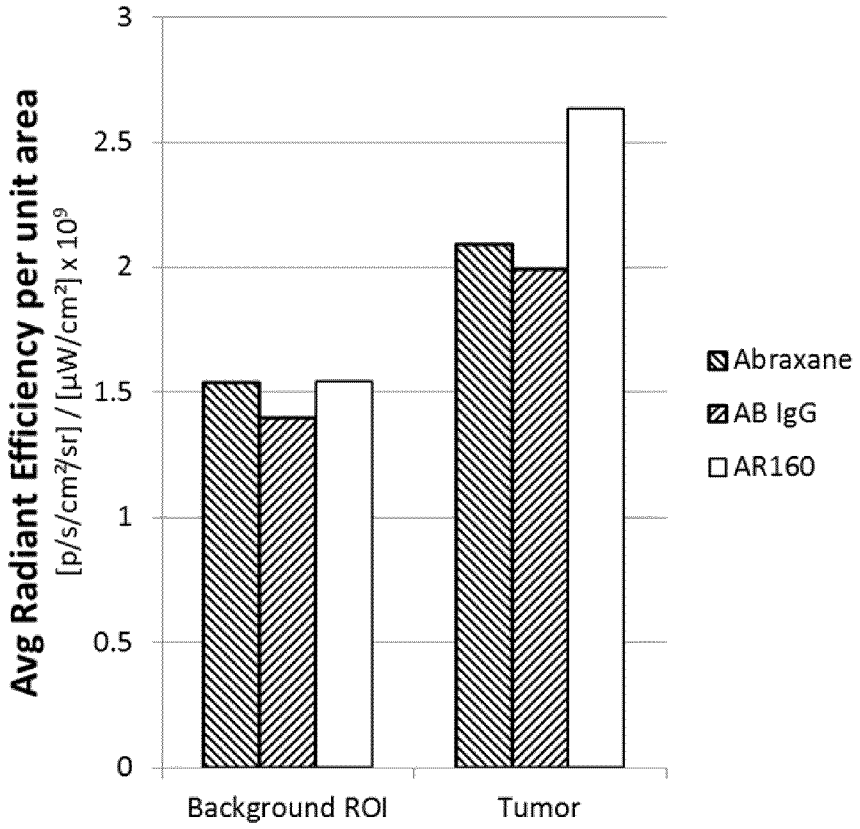
17. The method of any one of claims 14-16, wherein the protein carrier is selected from the group consisting of albumin, gelatin, elastin, gliadin, legumin, zein, soy protein, milk protein, and whey protein.

18. The method of claim 17, wherein the protein carrier is albumin.

19. The method of claim 18, wherein the complex further comprises an effective amount of paclitaxel to form said complex.

20. The method of claim 19, wherein the amount of paclitaxel is between 0.1 $mg/m^2$ and 50 $mg/m^2$.

# FIGURE 1


Avg Radiant Efficiency per unit area
[p/s/cm²/sr] / [µW/cm²] x 10⁹
3
2.5
2
1.5
1
0.5
0
Background ROI
Tumor
Abraxane
AB IgG
AR160

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/23442

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 39/44, 47/50, 47/64, 47/68; A61P 35/00 (2017.01)
CPC - A61K 39/44, 47/48, 47/4813, 47/48907; B82Y 5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>-----<br>Y | US 2012/0263739 A1 (LANGER, K et al.) October 18, 2012; abstract; paragraphs [0017], [0028], [0030], [0032], [0068], [0070], [0072]; claim 7 | 1-2, 3/1-2, 4/3/1-2, 5/4/3/1-2, 7-8, 12, 14-15, 16/14-15<br>---<br>6/5/4/3/1-2, 9, 13 |
| Y | US 2007/0166388 A1 (DESAI, NP et al.) July 19, 2007; paragraph [0037] | 6/5/4/3/1-2, 9 |
| Y | US 2010/0311679 A1 (OLSON, RD et al.) December 9, 2010; paragraphs [0007], [0028] | 13 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 19 May 2017 (19.05.2017) | 16 JUN 2017 |
| Name and mailing address of the ISA/<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | Authorized officer<br>Shane Thomas<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/210 (second sheet) (January 2015)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/23442

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 10-11, 17-20
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.