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(54) Title: TREATMENT OF LUNG ADENOCARCINOMA

(57) Abstract: In certain embodiments the present invention provides methods useful in the treatment of lung cancer, such as lung adenocarcinoma. In some embodiments such methods comprise administering to a subject in need thereof a TNF- α inhibitor, such as the TNF- α inhibitory antibody certolizumab, optionally together with one or more chemotherapeutic agents. In certain embodiments the present invention provides pharmaceutical compositions comprising a TNF- α inhibitor and one or more chemotherapeutic agents. These and other embodiments are described further in the present patent application.



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TREATMENT OF LUNG ADENOCARCINOMA

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of U.S. Provisional Patent Application No. 62/337,813 filed on May 17, 2016, the contents of which are hereby incorporated by reference in their entirety.

INCORPORATION BY REFERENCE

[0002] For countries that permit incorporation by reference, all of the references cited in this disclosure are hereby incorporated by reference in their entireties. In addition, any manufacturers' instructions or catalogues for any products cited or mentioned herein are incorporated by reference. Documents incorporated by reference into this text, or any teachings therein, can be used in the practice of the present invention.

[0003] Numbers in parentheses following text represent the numbered references provided in the Reference List provided at the end of this patent disclosure.

BACKGROUND

[0004] Lung cancer is the most common cause of cancer death worldwide. Despite newer targeted therapy options, lung cancer survival statistics are still discouraging. For example, the cure rate for stage I non-small cell lung cancer (NSCLC) is 60% and for stage IIIA NSCLC is just 20% (1). One hurdle to developing better therapies has been the limited understanding of the mechanisms underlying chemotherapy resistance and metastatic spread in lung cancer.

[0005] Recent studies have identified a tumor necrosis factor alpha (TNF- α) / CXCL1/2 / S100A8/9 paracrine inflammatory loop that enhances cancer cell survival, causes chemotherapy resistance, and promotes the development of metastases in breast cancer (2). Furthermore, these studies demonstrated that downregulation of certain components of this paracrine axis could enhance chemotherapeutic efficacy and block metastatic propagation in breast cancer models (2). Other studies found similar effects in a Lewis lung carcinoma (LLC) mouse model (3). However, prior to the present invention it was not known if downregulation of this paracrine inflammatory loop might provide beneficial effects in other

tumor types. Furthermore, prior to the present invention it was not known if and how these effects might translate to treatment of human patients.

SUMMARY OF THE INVENTION

[0006] The present invention is based, in part, on a series of discoveries relating to the role of TNF- α , CXCL1/2, and/or S100A8/9 in lung adenocarcinoma, and relating to the effects of inhibitors of some of such molecules on lung adenocarcinomas in human subjects - as described in more detail in the Examples section of this patent specification. Building on these discoveries the present invention provides certain new methods and compositions for the treatment of lung adenocarcinoma.

[0007] For example, in some embodiments the present invention provides methods for treating lung adenocarcinoma, such methods comprising administering to subjects in need thereof an effective amount of either: (a) a TNF- α inhibitor, (b) a CXCL1/2 inhibitor, or (c) a S100A8/9 inhibitor, or any combination thereof. In some embodiments the present invention provides methods for treating lung adenocarcinoma, such methods comprising administering to subjects in need thereof an effective amount of a TNF- α inhibitor. In some embodiments such methods further comprise administering to the subject an effective amount of one or more chemotherapeutic agents. For example, in certain embodiments both a platinum-based chemotherapeutic agent and a non-platinum-based chemotherapeutic agent are administered. In one exemplary embodiment the present invention provides methods for treating lung adenocarcinoma, such methods comprising administering to subjects in need thereof an effective amount of a TNF- α inhibitor and an effective amount of one or more chemotherapeutic agents. In another exemplary embodiment the present invention provides methods for treating lung adenocarcinoma, such methods comprising administering to subjects in need thereof an effective amount of a TNF- α inhibitor, an effective amount of a platinum-based chemotherapeutic agent, and an effective amount of a non-platinum-based chemotherapeutic agent.

[0008] In other embodiments present invention provides pharmaceutical compositions comprising an effective amount of (a) a TNF- α inhibitor, a CXCL1/2 inhibitor, or a S100A8/9 inhibitor, and (b) one or more chemotherapeutic agents. In some such embodiments such compositions comprise a TNF- α inhibitor and one or more

chemotherapeutic agents. In some such embodiments such compositions comprise a TNF- α inhibitor, a platinum-based chemotherapeutic agent, and a non-platinum-based chemotherapeutic agent.

[0009] Examples of suitable TNF- α inhibitors that can be used in the methods and compositions of the present invention, including in all of the embodiments described above and elsewhere herein, include, but are not limited to, certolizumab, certolizumab pegol (Cimzia), infliximab (Remicade), etanercept (Enbrel), adalimumab (Humira), golimumab (Simponi), thalidomide (Immunoprin), lenalidomide (Revlimid), xanthine derivatives, pentoxifylline, and bupropion. In some embodiments the TNF- α inhibitor is a TNF- α inhibitory antibody. In some embodiments the TNF- α inhibitor is a TNF- α inhibitory antibody selected from the group consisting of certolizumab, certolizumab pegol (Cimzia), infliximab (Remicade), adalimumab (Humira), and golimumab (Simponi). In some embodiments the TNF- α inhibitor is the TNF- α inhibitory antibody certolizumab (e.g. certolizumab pegol (Cimzia)).

[00010] Examples of suitable platinum-based chemotherapeutic agents that can be used in the methods and compositions of the present invention, including in all of the embodiments described above and elsewhere herein, include, but are not limited to, cisplatin and carboplatin.

[00011] Examples of suitable non-platinum-based chemotherapeutic agents that can be used in the methods and compositions of the present invention, including in all of the embodiments described above and elsewhere herein, include, but are not limited to, paclitaxel, gemcitabine, and pemetrexed.

[00012] These and other embodiments of the present invention are described in more detail elsewhere in this patent application, including in the Figures, Brief Description of the Figures, Detailed Description, and Examples sections of this patent application. Furthermore, it should be understood that variations and combinations of each of the embodiments described throughout this patent application are contemplated and are intended to fall within the scope of the present invention.

BRIEF DESCRIPTION OF THE FIGURES

[00013] **Fig. 1.** Prominent copy number gain of S100A9 gene in lung adenocarcinomas. S100A9 gene copy number was determined by Oncomine analysis from dataset from among 51 different cancer types.

[00014] **Fig. 2.** Paraffin tissue microarray samples were immunostained with an antibody against S100A8/9. Lung cancer subtypes include Muco-epidermoid (Muco-epi), Large Cell, Squamous, Bronchio-alveolar (Bralveo) and lung adenocarcinoma (Adenoca). S100A8/9 expression was highest in Adenoca.

[00015] **Fig. 3A-B.** Gene expression of CXCL1/2 and S100A8/9 in metastatic lung cancer cells. Metastatic derivatives were isolated from three rounds of in-vivo selection of two adenocarcinoma cell lines, H2030 and PC9. Relative gene expression of the indicated genes were tested by qRT-PCR analysis in parental and metastatic H2030 (**Fig. 3A**) and PC9 (**Fig. 3B**) adenocarcinoma cell lines.

[00016] **Fig. 4.** RAGE (S100A8 receptor) knockdown inhibits metastasis formation in PC9 lung adenocarcinoma cells selected for brain metastatic potential. N=3 mice per condition, photon flux was assessed 4 weeks after intracardiac injection of cells. The left panel is a graph showing photon flux after injection of control PC9 cells or cells treated with the RAGE shRNA. The two right-hand panels show photon flux images in from mice injected with control PC9 cells (middle panel) or cells treated with the RAGE shRNA (right-hand panel).

[00017] **Fig. 5.** 18 patients were treated with certolizumab - 3 at a 200mg dose and 15 at a 400mg dose. Treatment was well-tolerated with no DLTs. 16 patients were evaluable for response with 9 PRs (56%), 7 SDs (44%), and 0 PD (0%) as shown in this waterfall plot.

DETAILED DESCRIPTION

[00018] Some of the main embodiments of the present invention are described in the above Summary of the Invention section of this patent application, as well as in the Figures, Brief Description of the Figures, Examples, and Claims sections of this application. This Detailed Description section provides certain additional description relating to the compositions and methods of the present invention, and is intended to be read in conjunction with all other sections of the present patent application. The sub-headings provided below, and throughout this patent disclosure, are not intended to denote limitations of the various aspects or

embodiments of the invention, which are to be understood by reference to the specification as a whole.

Definitions

[00019] As used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents, unless the context clearly dictates otherwise. The terms “a” (or “an”) as well as the terms “one or more” and “at least one” can be used interchangeably

[00020] Furthermore, “and/or” is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term “and/or” as used in a phrase such as “A and/or B” is intended to include A and B, A or B, A (alone), and B (alone). Likewise, the term “and/or” as used in a phrase such as “A, B, and/or C” is intended to include A, B, and C; A, B, or C; A or B; A or C; B or C; A and B; A and C; B and C; A (alone); B (alone); and C (alone).

[00021] Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form unless otherwise stated. Numeric ranges provided herein are inclusive of the numbers defining the range. Where a numeric term is preceded by “about,” the term includes the stated number and values $\pm 10\%$ of the stated number.

[00022] An “active agent” is an agent (e.g. a small molecule, or a protein/peptide - such as an antibody), for example as described and/or claimed herein, that has the recited activity – such as TNF- α inhibitory activity, CXCL1/2- inhibitory activity, S100A8/9- inhibitory activity, or chemotherapeutic activity. “Active agents” include, but are not limited to, the specific inhibitors described in this patent disclosure. It is also contemplated that, in each of the embodiments of the present patent disclosure that involve use of specified active agents, analogues, variants, or derivatives of each of such specified active agents can be used. One of skill in the art can readily determine whether an analogue, variant, or derivative of any of such specified active agent is suitable for use in accordance with the compositions and methods of the present invention, for example based on whether the analogue, variant, or derivative has one or more of the desired activities, such as, for example, TNF- α inhibitory activity, CXCL1/2- inhibitory activity, S100A8/9- inhibitory activity, or chemotherapeutic activity.

[00023] As mentioned above, in some embodiments active agents can be antibodies. The term “antibody,” as used herein, encompasses intact polyclonal antibodies, intact monoclonal antibodies, antibody fragments (such as Fab, Fab', F(ab')₂, and Fv, and single chain Fv (scFv) fragments, single-domain antibodies (sdAb or nanobodies)), fusion proteins comprising an antigen determination portion of an antibody, bispecific antibodies generated from at least two intact antibodies, chimeric antibodies, humanized antibodies, human antibodies, and any other modified immunoglobulin molecule(s) comprising an antigen recognition site - so long as the antibodies have the desired and/or recited biological activity - such as TNF- α inhibitory activity. Various different types of antibody fragments, and methods of making and using such antibody fragments, are known in the art. See, for example, Fridy et al., *Nature Methods*. 2014 Dec;11(12):1253-60 (the contents of which are hereby incorporated by reference) for a description of the production of nanobody repertoires multi-specific antibodies. An antibody can be of any the five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, or subclasses (isotypes) thereof (e.g. IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2), based on the identity of their heavy-chain constant domains referred to as alpha, delta, epsilon, gamma, and mu, respectively. The different classes of immunoglobulins have different and well-known subunit structures and three-dimensional configurations. Antibodies can be naked, or conjugated to other molecules such as toxins, radioisotopes, or any of the other specific molecules recited herein.

[00024] The terms “inhibit,” “block,” “reduce,” and “suppress” are used interchangeably and refer to any statistically significant decrease in biological activity, including – but not limited to - full blocking of the activity.

[00025] “Certolizumab” is the antibody (Fab fragment of a humanized recombinant monoclonal antibody) to TNF α that is the active component of the certolizumab pegol product currently sold in the U.S. under the tradename Cimzia. Unless otherwise stated, or clear from the context, the term “certolizumab” includes certolizumab linked to polyethylene glycol or “certolizumab pegol.” Thus, wherever the term “certolizumab” is used, “certolizumab pegol” is included. Furthermore, one of skill in the art will appreciate that, in those embodiments that refer specifically to “certolizumab pegol,” non-pegylated “certolizumab” may also be used. The certolizumab antibody is well known in the art, and it can be made, formulated, and used as described in the art.

[00026] Various other terms are defined elsewhere in this patent disclosure, where used. Furthermore, terms that are not specifically defined herein may be more fully understood in the context in which the terms are used and/or by reference to the specification in its entirety. Where no explicit definition is provided, all technical and scientific terms used herein have the meanings commonly understood by those of ordinary skill in the art to which this invention pertains.

TNF- α Inhibitors

[00027] In certain embodiments the present invention provides methods for the treatment of lung adenocarcinomas that comprise administration of one or more TNF- α inhibitors. In certain other embodiments the present invention provides compositions comprising one or more TNF- α inhibitors. In some of such embodiments, any suitable TNF- α inhibitor can be used. In some embodiments the suitability of a TNF- α inhibitor for use in accordance with the methods of the present invention may be ascertained from the literature (for example from published studies demonstrating anti-TNF- α activity), or may be ascertained by employing various assays for anti-TNF- α activity or anti-tumor activity, such as those described in the Examples section of the present patent application and/or those known in the art. Several TNF- α inhibitors that are known in the art can be used in conjunction with the present invention. For example, in some embodiments, any one or more of the following TNF- α inhibitors (or classes of inhibitors) may be used: certolizumab, certolizumab pegol (Cimzia), infliximab (Remicade), etanercept (Enbrel), adalimumab (Humira), golimumab (Simponi), thalidomide (Immunoprin), lenalidomide (Revlimid), xanthine derivatives, pentoxifylline, and bupropion. In some embodiments the TNF- α inhibitor may be a small molecule. In some embodiments the TNF- α inhibitor may be an antibody. In some embodiments the TNF- α inhibitor may be other suitable agent that has TNF- α inhibitory activity. In some embodiments, any suitable variant, analogue or derivative of any one of such TNF- α inhibitors may be used. In some embodiments the TNF- α inhibitor may be linked to, or capable or co-delivery with, another agent that can confer upon the TNF- α inhibitor the ability to target a lung tumor, or lung tumor cells.

Additional Active Agents

[00028] In certain embodiments the present invention provides methods for the treatment of

lung adenocarcinomas that comprise administration of a CXCL1/2 inhibitor. In some embodiments an inhibitor of a CXCL1/2 receptor (such as the CXCL1/2 receptor referred to as CXCR2) may be used. In some such embodiments any suitable CXCL1/2 inhibitor or CXCL1/2 receptor inhibitor known in the art may be used.

[00029] In certain embodiments the present invention provides methods for the treatment of lung adenocarcinomas that comprise administration of a S100A8/9 inhibitor. In some embodiments an inhibitor of a S100A8/9 receptor (such as the S100A8/9 receptor referred to as RAGE) may be used. In some such embodiments any suitable S100A8/9 inhibitor or S100A8/9 receptor inhibitor known in the art may be used.

[00030] In certain embodiments the present invention provides methods for the treatment of lung adenocarcinomas that comprise administration to a subject of one or more TNF- α inhibitors, CXCL1/2 inhibitors, and/or S100A8/9 inhibitors, and also administration to the subject of one or more additional active agents useful in the treatment of lung adenocarcinomas, for example chemotherapeutic agents or other active agents. For example, in some embodiments the methods of the present invention may involve administration of one or more chemotherapeutic agents selected from the group consisting of: cisplatin, carboplatin, gemcitabine, paclitaxel, docetaxel, pemetrexed, etoposide and/or vinorelbine. In some such embodiments both one or more platinum-based chemotherapeutic agents (such as cisplatin or carboplatin) and one or more non-platinum-based chemotherapeutic agents (such as gemcitabine, paclitaxel, docetaxel, pemetrexed, etoposide and/or vinorelbine) may be administered to the subject. Similarly, in some embodiments the methods of the present invention may involve administration of one or more non-chemotherapeutic agents, such as, for example, erlotinib (Tarceva), gefitinib, afatinib (Gilotrif), denosumab, bevacizumab (Avastin), ceritinib (Zykadia), crizotinib (Xalkori), nivolumab (Opdivo), and/or ramucirumab (Cyramza). Similarly, in certain embodiments the present invention provides methods for the treatment of lung adenocarcinomas that comprise administration to a subject of one or more TNF- α inhibitors and also administration to the subject of one or more additional active agents selected from the group consisting of: Abitrexate (Methotrexate), Abraxane (Paclitaxel Albumin-stabilized Nanoparticle Formulation), Afatinib Dimaleate, Afinitor (Everolimus), Alecensa (Alectinib), Alectinib, Alimta (Pemetrexed Disodium), Avastin (Bevacizumab), Bevacizumab, Carboplatin, Ceritinib, Crizotinib, Cyramza (Ramucirumab), Docetaxel,

Erlotinib Hydrochloride, Everolimus, Folex (Methotrexate), Folex PFS (Methotrexate), Gefitinib, Gilotrif (Afatinib Dimaleate), Gemcitabine Hydrochloride, Gemzar (Gemcitabine Hydrochloride), Iressa (Gefitinib), Keytruda (Pembrolizumab), Mechlorethamine Hydrochloride, Methotrexate, Methotrexate LPF (Methotrexate), Mexate (Methotrexate), Mexate-AQ (Methotrexate), Mustargen (Mechlorethamine Hydrochloride), Navelbine (Vinorelbine Tartrate), Necitumumab, Nivolumab, Opdivo (Nivolumab), Osimertinib, Paclitaxel, Paclitaxel Albumin-stabilized Nanoparticle Formulation, Paraplat (Carboplatin), Paraplatin (Carboplatin), Pembrolizumab, Pemetrexed Disodium, Portrazza (Necitumumab), Ramucirumab, Tagrisso (Osimertinib), Tarceva (Erlotinib Hydrochloride), Taxol (Paclitaxel), Taxotere (Docetaxel), Vinorelbine Tartrate, Xalkori (Crizotinib), and Zykadia (Ceritinib)

Methods of Treatment & Prevention

[00031] In certain embodiments the present invention provides methods for the treatment and/or prevention of lung adenocarcinoma in subjects in need thereof, such methods comprising administering to the subject an effective amount of certain active agents.

[00032] The term “lung adenocarcinoma” is used herein in accordance with its normal usage in the art and refers to a subtype of non-small cell lung cancers (NSCLCs).

[00033] As used herein, the terms “treat,” “treating,” and “treatment” encompass a variety of activities aimed at achieving a detectable improvement in one or more clinical indicators or symptoms associated with lung adenocarcinoma. For example, such terms include, but are not limited to, reducing the rate of growth of a lung cancer (or of lung cancer cells, or of other cells within a lung tumor), halting the growth of a lung cancer (or of lung cancer cells, or of other cells within a lung tumor), causing regression of a lung cancer (or of lung cancer cells, or of other cells within a lung tumor), reducing the size of a lung tumor (for example as measured in terms of tumor volume or tumor mass), reducing the grade of a lung cancer, eliminating a lung cancer (or lung cancer cells, or other cells within a lung tumor), preventing, delaying, or slowing recurrence (rebound) of a lung cancer, improving symptoms associated with lung cancer, improving survival from lung cancer, inhibiting or reducing spreading of a lung cancer (e.g. metastases), and the like.

[00034] For each of the methods and compositions described herein that are directed to

“treatment” of lung adenocarcinoma, in some embodiments such methods and compositions can be employed for “prevention” of lung adenocarcinoma. As used herein the terms “prevent” and/or “prevention” refer to prophylactic or preventative measures that prevent and/or slow the development of a lung adenocarcinoma. Thus, those in need of prevention include those at risk of, or susceptible to, lung adenocarcinoma. In certain embodiments, a lung adenocarcinoma is successfully prevented according to the methods provided herein if the patient develops, transiently or permanently, e.g., fewer or less severe symptoms associated with the lung adenocarcinoma, or a later onset of symptoms associated with the lung adenocarcinoma, than a patient who has not been subject to the methods and/or compositions of the invention.

[00035] In certain embodiments the methods of treatment and/or prevention provided herein may be employed in conjunction with other lung adenocarcinoma treatment and/or prevention methods, including, but not limited to, surgical methods (e.g. for tumor resection), radiation therapy methods, treatment with chemotherapeutic agents, or treatment with non-chemotherapeutic agents. Similarly, in certain embodiments the methods of treatment and/or prevention provided herein may be employed in conjunction with procedures used to monitor disease status/progression, such as biopsy methods and diagnostic methods (e.g. MRI methods or other imaging methods).

[00036] In some embodiments the present invention provides methods for determining whether a subject is a candidate for prevention or treatment using any of the compositions or methods provided herein. In some of such embodiments the subject is also subsequently treated using the compositions and/or methods provided herein.

[00037] For example, in some embodiments the present invention provides methods for determining whether a subject is a candidate for treatment with a composition or method as described herein, wherein such methods involve performing an assay to determine if a subject has a lung adenocarcinoma having a S100A8/9 gene amplification, and/or if a subject has a lung adenocarcinoma in which S100A8/9 is over-expressed and/or over-produced, and/or if a subject has a lung adenocarcinoma in which TNF- α is over-expressed and/or over-produced, and/or if a subject has a lung adenocarcinoma in which CXCL1/2 is over-expressed and/or over-produced. Suitable assays that can be used are provided in the Examples section of this patent disclosure and/or are known in the art. Each of the embodiments described herein that

involves performing such an assay to determine whether a subject is a candidate for treatment, may, in some embodiments, also comprise a preliminary step of obtaining a sample of lung adenocarcinoma cells from the subject, or obtaining a sample of protein, DNA, or RNA from such cells. Similarly, each of the embodiments described herein that involves performing an assay to determine whether a subject is a candidate for treatment, may, in some embodiments, also comprise a subsequent step of treating the subject using one of the methods or compositions provided herein. For example, in some embodiments the methods of the present invention involve first determining whether a subject has a lung adenocarcinoma having a S100A8/9 gene amplification, and/or has a lung adenocarcinoma in which S100A8/9, TNF- α , and/or CXCL1/2 is over-expressed and/or over-produced, and then, if the subject does have such a S100A8/9 gene amplification, and/or has a lung adenocarcinoma in which S100A8/9, TNF- α , and/or CXCL1/2 is over-expressed and/or over-produced, subsequently treating the subject with one of the methods or compositions described herein.

Subjects

[00038] The terms “subject,” “individual,” and “patient” - which are used interchangeably herein, are intended to refer to any subject. In some embodiments the subject is a mammalian subject. Mammalian subjects include humans, domestic animals, farm animals, sports animals, and zoo animals including, e.g., humans, non-human primates, dogs, cats, mice, rats, guinea pigs, and the like. In some embodiments the subject is a human subject, for example a human subject for whom therapy or prophylaxis desired. In most of the embodiments of the present invention the subject has, or is suspected of having, a non-small cell lung cancer (NSCLC), such as, in particular, an adenocarcinoma of the lung.

[00039] In some embodiments the subject has an adenocarcinoma of the lung that is stage IA or above. In some embodiments the subject has an adenocarcinoma of the lung that is stage IB or above. In some embodiments the subject has an adenocarcinoma of the lung that is stage IIA or above. In some embodiments the subject has an adenocarcinoma of the lung that is stage IIB or above. In some embodiments the subject has an adenocarcinoma of the lung that is stage IIIA or above. In some embodiments the subject has an adenocarcinoma of the lung that is stage IIIB or above. In some embodiments the subject has an adenocarcinoma of the lung that is stage IV or above.

[00040] In some embodiments the subject has an adenocarcinoma of the lung that is metastatic.

[00041] In some embodiments the subject has a lung adenocarcinoma having a S100A8/9 gene amplification. In some embodiments the subject has a lung adenocarcinoma in which S100A8/9 is over-expressed and/or over-produced. In some embodiments the subject has a lung adenocarcinoma in which TNF- α is over-expressed and/or over-produced. In some embodiments the subject has a lung adenocarcinoma in which CXCL1/2 is over-expressed and/or over-produced.

Administration Routes

[00042] In carrying out the treatment and/or prevention methods described herein, any suitable method or route of administration can be used to deliver the active agents.

[00043] In some embodiments systemic administration may be employed. "Systemic administration" means that the active agent is administered such that it enters the circulatory system, for example, via enteral, parenteral, inhalational, or transdermal routes. Enteral routes of administration involve the gastrointestinal tract and include, without limitation, oral, sublingual, buccal, and rectal delivery. Parenteral routes of administration involve routes other than the gastrointestinal tract and include, without limitation, intravenous, intramuscular, intraperitoneal, intrathecal, and subcutaneous.

[00044] In some embodiments, such as those where TNF- α inhibitor antibody, such as certolizumab, is used, the TNF- α inhibitor antibody may be administered subcutaneously.

[00045] In some embodiments local administration may be employed. "Local administration" means that a pharmaceutical composition is administered directly to where its action is desired (e.g., at or near the site of a lung cancer), for example via direct intratumoral injection.

[00046] It is within the skill of one of ordinary skill in the art to select an appropriate route of administration taking into account the nature of the specific active agent being used and nature of the specific lung cancer to be treated.

Effective Amounts

[00047] As used herein the terms “effective amount” or “therapeutically effective amount” refer to an amount of an active agent as described herein that is sufficient to achieve, or contribute towards achieving, one or more desirable clinical outcomes, such as those described in the “treatment” and “prevention” descriptions above. An appropriate “effective” amount in any individual case may be determined using standard techniques known in the art, such as dose escalation studies, and may be determined taking into account such factors as the desired route of administration (e.g. systemic vs. local), the desired frequency of dosing, etc. Furthermore, an “effective amount” may be determined in the context of any other active agents that are also to be used in the treatment method. For example, in those embodiments where, for example, both a TNF- α inhibitor and one or more additional active agents are to be administered to a subject, rather than perform dosing studies using the TNF- α inhibitor alone, dosing studies may be performed using both the TNF- α inhibitor and the one or more additional active agents, because the effects of such agents may be synergistic. One of skill in the art can readily perform such dosing studies to determine appropriate doses to use, for example using assays such as those described in the Examples section of this patent application and/or other assays known in the art.

[00048] Exemplary doses, dosing schedules, and routes of administration are provided herein, including in this Detailed Description and also in the Examples section of this patent disclosure. Furthermore, one of skill in the art will recognize that the various active agents described herein can be administered at other doses, and using other dosing schedules, and using other routes of administration. It is within the skill of the ordinary artisan to vary the exemplary doses, dosing schedules, and routes of administration provided herein, and to arrive at other suitable doses, suitable dosing schedules, and suitable routes of administration for any chosen active agent or combination of active agents.

[00049] In some embodiments, the amount of any of the active agents described herein to be used for treatment may be about 100%, or about 90%, or about 80%, or about 70%, or about 60%, or about 50%, or about 40%, or about 30% of that agent's maximum tolerated dose in a subject.

[00050] In some embodiments, where the active agent is the TNF- α inhibitor antibody certolizumab, the effective amount of the antibody to be administered systemically (e.g. subcutaneously) to a human subject may be about 100 mg, or about 150 mg, or about 200 mg,

or about 250 mg, or about 300 mg, or about 350 mg, or about 400 mg, or about 450 mg, or about 500 mg, or about 550 mg, or about 600 mg, or about 650 mg, or about 700 mg, or about 750 mg, or about 800 mg, or more.

[00051] In some embodiments an effective amount of certolizumab to be administered systemically (e.g. subcutaneously) to a human subject may be about 100 mg - 500 mg. In some embodiments an effective amount of certolizumab to be administered systemically (e.g. subcutaneously) to a human subject may be about 200 mg - 400 mg. In some embodiments an effective amount of certolizumab to be administered systemically (e.g. subcutaneously) to a human subject may be about 200 mg. In some embodiments an effective amount of certolizumab to be administered systemically (e.g. subcutaneously) to a human subject may be about 400 mg.

[00052] Similarly, in some of those embodiments where the active agent is the TNF- α inhibitor antibody certolizumab, the antibody may be administered systemically (e.g. subcutaneously) to a human subject, once a week, or once every two weeks, or once every three weeks, or once a month, for as many treatment cycles as desired, for example for one cycle, or two cycles, or three cycles, or four cycles, or five cycles, or six or more cycles. In one such embodiment the TNF- α inhibitor antibody certolizumab may be administered systemically (e.g. subcutaneously) to a human subject once every two weeks for a month and then monthly thereafter for as long as desired.

[00053] In some of those embodiments where the active agent is the TNF- α inhibitor antibody certolizumab, the antibody may be administered to a subject using any of the dosages, dosage schedules, or administration routes described in the April 2016 certolizumab pegol (Cimzia) prescribing information, the contents of which are hereby incorporated by reference.

[00054] In embodiments in which more than one active agent is to be administered to a subject, the agents can be administered together (for example, in the same formulation and/or at the same time), or separately (for example, in different formulations and/or at different times). Where two or more active agents are used, it may be possible to use lower dosages or amounts of each active agent, as compared to the dosages necessary when each active agent is used alone.

Pharmaceutical Compositions

[00055] In certain embodiments, the present invention provides compositions, for example pharmaceutical compositions. The term “pharmaceutical composition,” as used herein, refers to a composition comprising at least one active agent as described herein, and one or more other components useful in formulating a composition for delivery to a subject, such as diluents, buffers, saline (such as phosphate buffered saline), cell culture media, carriers, stabilizers, dispersing agents, suspending agents, thickening agents, excipients, preservatives, and the like. “Pharmaceutical compositions” permit the biological activity of the active agent, and do not contain components that are unacceptably toxic to the living subject to which the composition would be administered.

[00056] Pharmaceutical compositions can be in numerous dosage forms, for example, tablet, capsule, liquid, solution, soft-gel, suspension, emulsion, syrup, elixir, tincture, film, powder, hydrogel, ointment, paste, cream, lotion, gel, mousse, foam, lacquer, spray, aerosol, inhaler, nebulizer, ophthalmic drops, patch, suppository, and/or enema. The choice of dosage forms and excipients will depend upon the active agent to be delivered and the specific disease or disorder to be treated or prevented, and can be selected by one of ordinary skill in the art without having to engage in any undue experimentation.

[00057] The present invention can be further understood by reference to the following “Examples” – which are non-limiting and provided for illustration purposes only. It will be apparent to those skilled in the art that many modifications, both to materials and methods, can be practiced without departing from the scope of the present disclosure.

EXAMPLES

[00058] Numbers in parentheses following text in these Examples represent the numbered references provided in the Reference List that follows.

Example 1

In Vitro Data and Animal Studies

[00059] While prior studies focused on the role of the TNF- α / CXCL1/2 / S100A8/9 axis in breast cancer (2), it has now been found that this pathway may play an important role in lung

adenocarcinoma. In particular, it has now been shown that S100A9 gene copy numbers are much higher in lung adeno carcinomas than in breast cancers. Indeed, S100A9 gene copy numbers were found to be higher in lung adenocarcinoma than in 51 other cancer subtypes tested. See **Fig. 1**. Immunostaining of tissue microarrays using S100A8/9 antibodies confirmed that higher levels of S100A8/9 protein are found in primary lung adenocarcinoma tumors relative to other histologic types. See **Fig. 2**. Furthermore, in a tissue microarray constructed from NSCLC surgical specimens, high TNF- α IHC scores (as compared to low scores (IHC ≥ 3 vs < 3 on a scale of 1-4)), predicted poor overall survival (2.0 vs 4.5 years, $p=0.04$).

[00060] To formally evaluate the role of the TNF- α / CXCL1/2 / S100A8/9 pathway in lung adenocarcinoma, S100A8/9 and CXCL1/2 expression was assessed in both brain metastatic H2030 and bone metastatic PC9 lung adenocarcinoma cells lines vs. their parental non-metastatic counterparts. mRNA expression of both was found to be significantly upregulated in the cells selected for metastatic potential. See **Fig. 3**.

[00061] To further elucidate the functional relevance of this pathway in lung cancer, shRNAs against RAGE, the receptor for S100A8/9, were generated. Knockdown of RAGE in PC9 brain metastatic lung adenocarcinoma cells using these shRNAs led to a substantial decrease in metastatic colony formation. See **Fig. 4**.

Example 2

Phase I Clinical Trial

[00062] Building on the pre-clinical data presented in Example 1, an investigator-initiated phase 1 clinical trial of cisplatin + pemetrexed + certolizumab pegol (Cimzia, a TNF- α monoclonal antibody) in patients with untreated stage IV lung adenocarcinomas (NCT02120807) was performed. The purpose of this study was to 1) establish the safety of the FDA-approved dose of certolizumab in conjunction with platinum-doublet chemotherapy and 2) determine whether the selected dose of certolizumab has the requisite *in vivo* pharmacodynamic effect of suppression of circulating TNF- α .

[00063] Patients with newly diagnosed untreated stage IV lung adenocarcinomas received cisplatin + pemetrexed chemotherapy every 3 weeks for 6 cycles (cis 75mg/m² and peme

500mg/m² q3wks for 6 cycles) along with certolizumab (200mg or 400mg) subcutaneously every 2 weeks for a month, then every month thereafter. A total of 18 patients were treated in the phase 1 study, 3 at the certolizumab 200mg dose and 15 at the FDA-approved 400mg dose. Serial blood was collected for cytokine analysis by ELISA. Response was assessed using RECIST v1.1. The primary endpoint was identification of a phase 2 dose (R2PD) by safety and pharmacodynamic criteria (suppression of TNF- α). The median age of patients in the trial was 63 (42-71). 61% were female. 94% were former/current smokers. The median KPS was 80%.

[00064] Treatment was well-tolerated with no dose limiting toxicities (DLTs) observed. 16 patients were evaluable for response with 9 partial responses (PR) (56%), 6 incomplete responses / stable disease (SD) (44%), and 1 progressive disease (PD) (6%). See **Fig. 5**. Most patients with SD had >20% reduction in their sum tumor dimension. With a median follow-up of 8.2 months, 12 patients (66%) remain on maintenance pemetrexed. One patient subsequently developed a complete response to therapy while on maintenance therapy. No patients developed a new site of metastatic disease. Importantly, all patients had a significant reduction in serum TNF- α from baseline with an 8.5-fold mean decrease ($p < 0.001$). This was significantly different from a control group treated with chemotherapy alone (16-fold mean increase, $p = 0.001$ compared to the experimental group). This pharmacodynamic effect occurred quickly - with a nadir in TNF- α by C1D8 in nearly all patients.

[00065] The most common any-grade related adverse events (AEs) were nausea (67%), anemia (61%), constipation (61%), and leukopenia (50%). Grade ≥ 3 related AEs occurred in 61% of pts and were mostly hematologic: i.e. decreased neutrophil count (22%), anemia (6%), and thrombocytopenia (6%). There were no febrile neutropenia events. There were 3 unrelated SAEs (grade 3 lung infection, grade 2 skin infection, grade 5 cardiac arrest). No patient had CTCAE weight loss; 16% had grade 1 weight gain.

[00066] These results demonstrate that certolizumab 400mg is tolerable when given with cis+peme with promising anti-tumor efficacy and suppression of TNF- α .

Example 3

Phase II Clinical Trial

[00067] Having demonstrated adequate safety, promising efficacy, and a significant pharmacodynamic effect from treatment with certolizumab in a phase I clinical trial, phase II trials are conducted to determine if the addition of certolizumab to cisplatin + pemetrexed chemotherapy can improve the disease-free survival (DFS) of patients with stage IIIA lung adenocarcinomas by inhibiting the chemotherapy-induced paracrine inflammatory loop mediated by TNF- α that promotes the development of metastatic disease and chemotherapy resistance.

[00068] Studies are performed to (a) determine the 18 month DFS of patients treated with cisplatin + pemetrexed + certolizumab pegol followed by surgical resection as compared to historical controls from previous neoadjuvant studies, (b) determine the frequency and nature of metastatic recurrence in these patients, and (c) to characterize the kinetics of circulating tumor DNA (ctDNA) at baseline, during therapy, and after surgical resection as a potential prognostic biomarker for recurrence.

[00069] Patients with stage IIIA lung adenocarcinoma (confirmed N2 disease by mediastinal staging) undergo up to 4 cycles of neoadjuvant cisplatin 75mg/m² + pemetrexed 500mg/m² + 400mg certolizumab pegol every 3 weeks. CT imaging is performed after 2 cycles of therapy. If there is at least stable disease (RECIST 1.1), patients receive 2 additional cycles of treatment followed by pre-operative evaluation and surgical resection of their cancer. Patients undergo post-op RT as indicated. Patients are followed every 6 months for 3 years with CT CAP + MRI brain to assess for recurrence, followed by annual scans thereafter.

[00070] A single arm phase II design is employed. Two previous studies of patients with stage IIIA lung adenocarcinomas are used as a historical control for determination of landmark DFS end-points (5, 6). The 18 month DFS for stage IIIA patients (N=54) in these previous studies was 50%, with a median DFS of 15 months. A sample size of 23 patients (N=23) is used to enable detection of a 50% increase (to 75%) in the 18 month DFS of patients in this trial compared to historical controls.

[00071] Two prior studies showing 25% and 37% rates of recurrence in IIIA patients who underwent resection (7, 8) serve as historical references against which secondary endpoints are compared. Detection of ctDNA is used as a clinical standard for assessing the presence of EGFR T790M mutations. A hybrid-capture next-generation sequencing (NGS) platform

(MSK-IMPACT) is used for the detection of somatic variants in more than 400 oncogenes and tumor suppressors in ctDNA. Standard of care MSK-IMPACT testing is performed for all patients in this study so that the exact mutational fingerprint of each patient's cancer in ctDNA can be tracked before treatment, during therapy, at the time of surgery, and serially during observation. Changes in ctDNA can be observed and describes over time and secondary analysis can be performed to link DFS and patterns of recurrence, providing data on the use of ctDNA in early stage patients as a surrogate prognostic marker.

[00072] This trial addresses a critically important but understudied aspect of cancer treatment - the pathophysiology of metastatic propagation. This treatment strategy can be paradigm-shifting - as such a strategy has not yet been employed in cancer therapy.

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CLAIMS

1. A method of treating lung adenocarcinoma, the method comprising administering to a subject in need thereof an effective amount of either: (a) a TNF- α inhibitor, (b) a CXCL1/2 inhibitor, or (c) a S100A8/9 inhibitor.
2. A method of treating lung adenocarcinoma, the method comprising administering to a subject in need thereof an effective amount of a TNF- α inhibitor.
3. The method of claim 1 or claim 2, further comprising administering to the subject an effective amount of a chemotherapeutic agent.
4. The method of claim 1 or claim 2, further comprising administering to the subject an effective amount of a platinum-based chemotherapeutic agent and a non platinum-based chemotherapeutic agent.
5. The method of claim 4, wherein the platinum-based chemotherapeutic agent is cisplatin or carboplatin.
6. The method of claim 4, wherein the non-platinum-based chemotherapeutic agent is selected from the group consisting of paclitaxel, gemcitabine, and pemetrexed.
7. The method of claim 1 or claim 2, wherein the TNF- α inhibitor is selected from the group consisting of certolizumab, certolizumab pegol (Cimzia), infliximab (Remicade), etanercept (Enbrel), adalimumab (Humira), golimumab (Simponi), thalidomide (Immunoprin), lenalidomide (Revlimid), xanthine derivatives, pentoxifylline, and bupropion.
8. The method of claim 1 or claim 2, wherein the TNF- α inhibitor is a TNF- α inhibitory antibody.
9. The method of claim 1 or claim 2, wherein the TNF- α inhibitor is a TNF- α inhibitory antibody selected from the group consisting of certolizumab, certolizumab pegol (Cimzia), infliximab (Remicade), adalimumab (Humira), and golimumab (Simponi).

10. The method of claim 1 or claim 2, comprising administering to a subject in need thereof an effective amount of: (a) the TNF- α inhibitory antibody certolizumab, (b) the platinum-based chemotherapeutic agent cisplatin, and (c) the non-platinum-based chemotherapeutic agent pemetrexed.
11. The method of claim 1 or claim 2, wherein the subject is a mammal.
12. The method of claim 1 or claim 2, wherein the subject is a human.
13. The method of claim 1 or claim 2, wherein the subject has a stage IIIA or greater lung adenocarcinoma.
14. The method of claim 1 or claim 2, wherein the subject has a stage IV or greater lung adenocarcinoma.
15. The method of claim 1 or claim 2, wherein the subject has a metastatic lung adenocarcinoma.
16. The method of claim 1 or claim 2, wherein the subject has a lung adenocarcinoma comprising a S100A9 gene amplification.
17. The method of claim 1 or claim 2, wherein the subject has a TNF- α over-expressing lung adenocarcinoma.
18. The method of claim 1 or claim 2, wherein the subject has a CXCL1/2 over-expressing lung adenocarcinoma.
19. The method of claim 1 or claim 2, wherein the subject is a human and the TNF- α inhibitor is the TNF- α inhibitory antibody certolizumab, and wherein the certolizumab is administered at a dose of from about 200mg to about 400mg.
20. The method of claim 19, wherein the certolizumab is administered every 2 weeks for a month, then every month thereafter.
21. The method of claim 19, wherein the TNF- α inhibitor is administered subcutaneously.

22. The method of claim 10, wherein the cisplatin is administered at about 75mg/m^2 approximately every 3 weeks for about 6 cycles.
23. The method of claim 10, wherein the pemetrexed is administered at about 500mg/m^2 approximately every 3 weeks for about 6 cycles.
24. The method of claim 1 or claim 2, further comprising performing surgical resection of the lung adenocarcinoma.
25. The method of claim 1 or claim 2, further comprising performing radiation therapy of the lung adenocarcinoma.
26. A method of treating lung adenocarcinoma, the method comprising administering to a human subject in need thereof an effective amount of (a) a TNF- α inhibitory antibody and (b) one or more chemotherapeutic agents.
27. A method of treating lung adenocarcinoma, the method comprising administering to a human subject in need thereof an effective amount of (a) a TNF- α inhibitory antibody, (b) a platinum-based chemotherapeutic agent, and (c) a non-platinum-based chemotherapeutic agent.
28. A method of treating lung adenocarcinoma, the method comprising administering to a human subject in need thereof an effective amount of (a) a TNF- α inhibitory antibody, (b) cisplatin, and (c) pemetrexed.
29. The method of claim 26, 27 or 28, wherein the TNF- α inhibitory antibody is certolizumab.
30. The method of claim 29, wherein the certolizumab is certolizumab pegol.
31. A method of treating lung adenocarcinoma, the method comprising administering to a human subject in need thereof an effective amount of (a) certolizumab pegol, and (b) one or more chemotherapeutic agents.
32. A method of treating lung adenocarcinoma, the method comprising administering to a human subject in need thereof an effective amount of (a) certolizumab pegol, (b) a

platinum-based chemotherapeutic agent, and (c) a non-platinum-based chemotherapeutic agent

33. A method of treating lung adenocarcinoma, the method comprising administering to a human subject in need thereof an effective amount of (a) certolizumab pegol, (b) cisplatin, and (c) pemetrexed.
34. The method of claim 31, 32, or 33, wherein the certolizumab pegol is administered to the subject subcutaneously.
35. The method of claim 31, 32, or 33, wherein the certolizumab pegol is administered to the subject subcutaneously at a dose of about 100-500 mg.
36. The method of claim 31, 32, or 33, wherein the certolizumab pegol is administered to the subject subcutaneously at a dose of about 100-500 mg at weekly intervals.
37. The method of claim 31, 32, or 33, wherein the certolizumab pegol is administered to the subject subcutaneously at a dose of about 100-500 mg at two-weekly intervals.
38. The method of claim 31, 32, or 33, wherein the certolizumab pegol is administered to the subject subcutaneously at a dose of about 100-500 mg at three-weekly intervals.
39. The method of claim 31, 32, or 33, wherein the certolizumab pegol is administered to the subject subcutaneously at a dose of about 100-500 mg at monthly intervals.
40. The method of claim 31, 32, or 33, wherein the certolizumab pegol is administered to the subject subcutaneously at a dose of about 200-400 mg.
41. The method of claim 31, 32, or 33, wherein the certolizumab pegol is administered to the subject subcutaneously at a dose of about 200-400 mg at weekly intervals.
42. The method of claim 31, 32, or 33, wherein the certolizumab pegol is administered to the subject subcutaneously at a dose of about 200-400 mg at two-weekly intervals.
43. The method of claim 31, 32, or 33, wherein the certolizumab pegol is administered to the subject subcutaneously at a dose of about 200-400 mg at three-weekly intervals.

44. The method of claim 31, 32, or 33, wherein the certolizumab pegol is administered to the subject subcutaneously at a dose of about 200-400 mg at monthly intervals.
45. A pharmaceutical composition comprising an effective amount of (a) either a TNF- α inhibitor, a CXCL1/2 inhibitor, or a S100A8/9 inhibitor, and (b) a chemotherapeutic agent.
46. A pharmaceutical composition comprising an effective amount of a TNF- α inhibitor and a chemotherapeutic agent.
47. The pharmaceutical composition of claim 45 or claim 46, comprising a platinum-based chemotherapeutic agent and a non-platinum-based chemotherapeutic agent.
48. The pharmaceutical composition of claim 47, wherein the platinum-based chemotherapeutic agent is cisplatin or carboplatin.
49. The pharmaceutical composition of claim 47, wherein the non-platinum-based chemotherapeutic agent is selected from the group consisting of paclitaxel, gemcitabine, and pemetrexed.
50. The pharmaceutical composition of claim 45 or claim 46, wherein the TNF- α inhibitor is selected from the group consisting of certolizumab, certolizumab pegol (Cimzia), infliximab (Remicade), etanercept (Enbrel), adalimumab (Humira), golimumab (Simponi), thalidomide (Immunoprin), lenalidomide (Revlimid), xanthine derivatives, pentoxifylline, and bupropion.
51. The pharmaceutical composition of claim 45 or claim 46, wherein the TNF- α inhibitor is a TNF- α inhibitory antibody.
52. The pharmaceutical composition of claim 45 or claim 46, wherein the TNF- α inhibitor is a TNF- α inhibitory antibody selected from the group consisting of certolizumab, certolizumab pegol (Cimzia), infliximab (Remicade), adalimumab (Humira), and golimumab (Simponi).

53. The pharmaceutical composition of claim 45 or claim 46, comprising: (a) the TNF- α inhibitory antibody certolizumab, (b) the platinum-based chemotherapeutic agent cisplatin, and (c) the non-platinum-based chemotherapeutic agent pemetrexed.
54. The pharmaceutical composition of claim 53, wherein the certolizumab is certolizumab pegol.

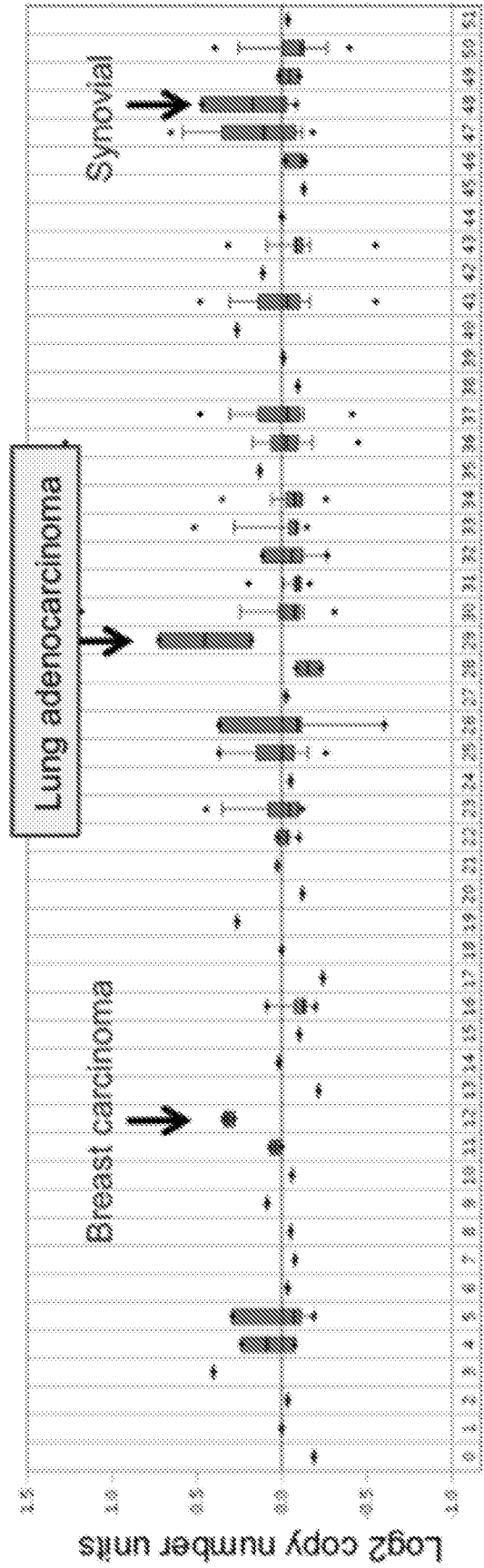


Fig. 1

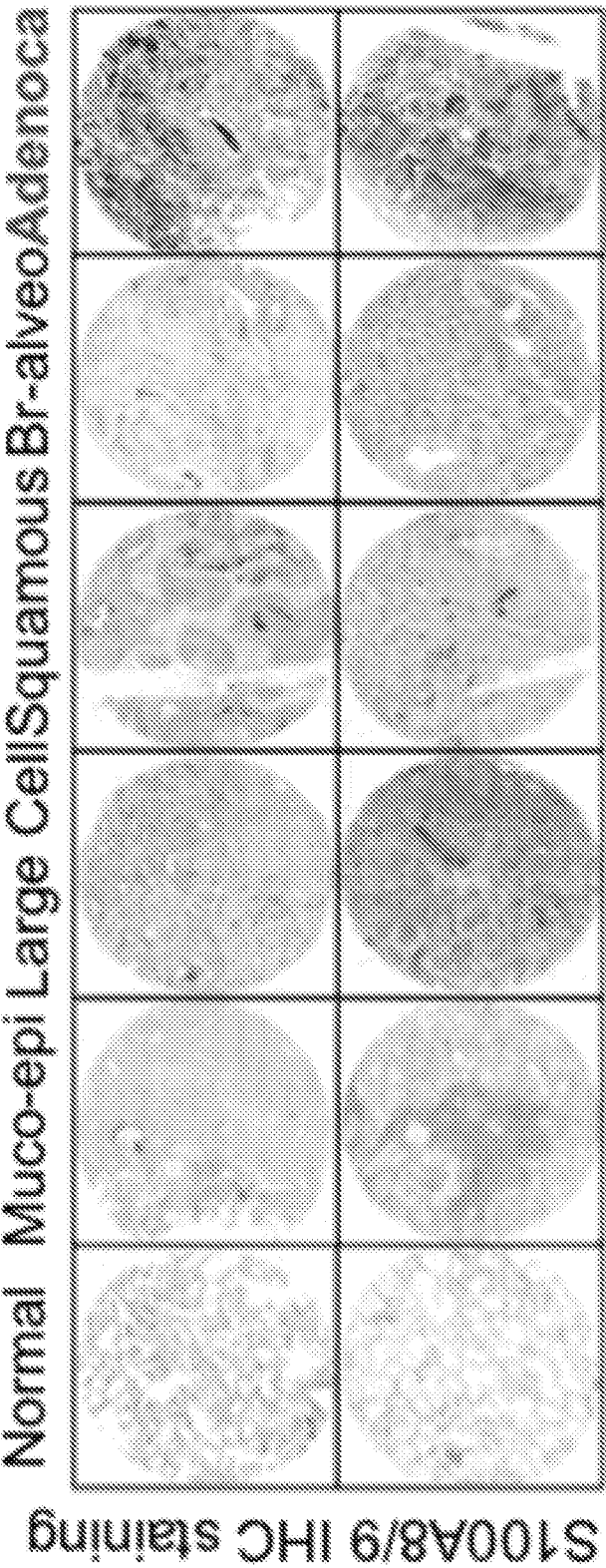


Fig. 2

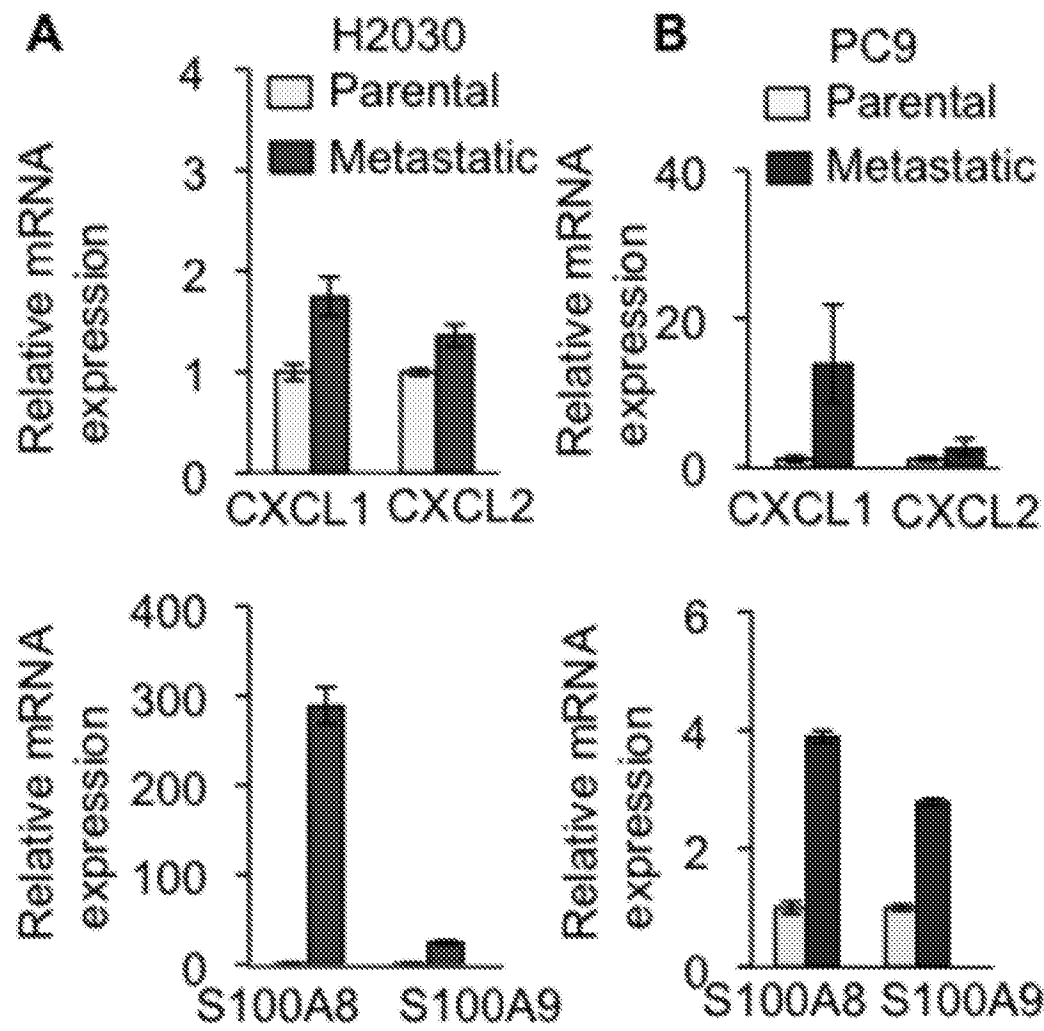


Fig. 3A-B

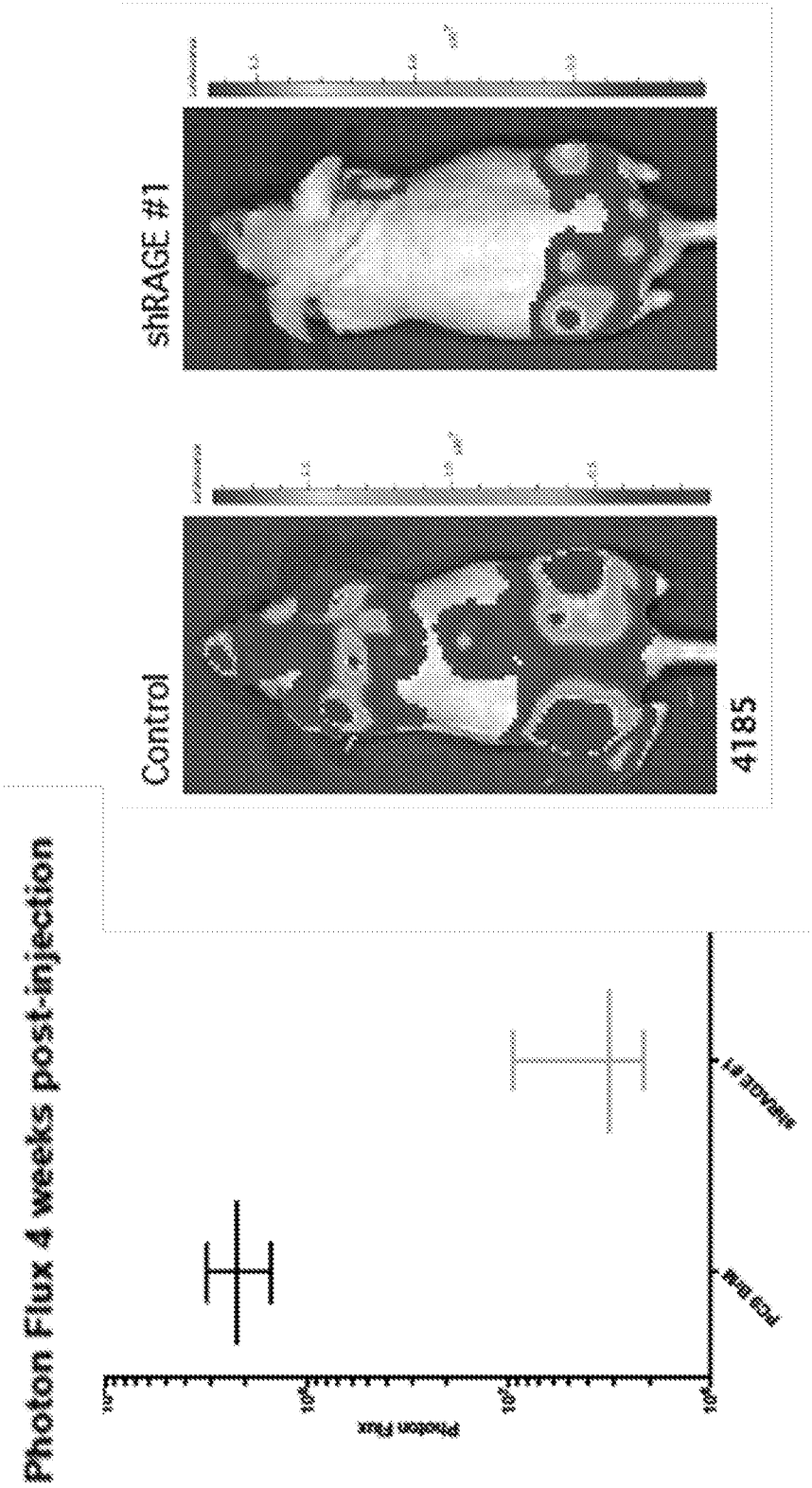


Fig. 4

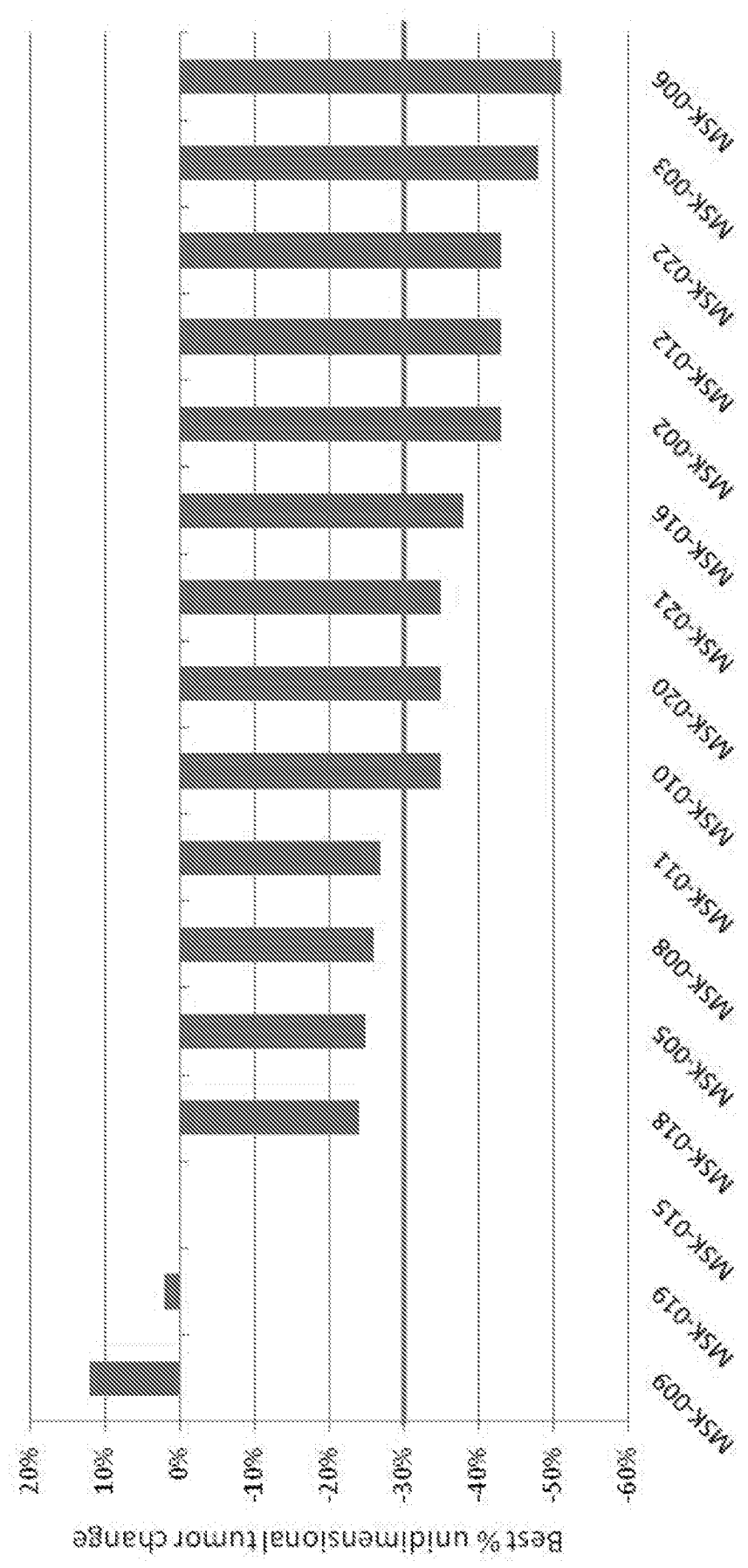


Fig. 5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/33062

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - A61K 38/17, C07K 14/00 (2017.01)
 CPC - C12N 9/6489, A61K 38/4886, C12Y 304/24086

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	ClinicalTrials.gov "NCT02120807 on 2016_03_10" 10 March 2016 (10.03.2016) < https://clinicaltrials.gov/archive/NCT02120807/2016_03_10 >; pg. 1, para 1-2, 5-6, pg. 2, para 2	1-49, 51-54
X	Hernandez-Flores et al. "Pentoxifylline sensitizes human cervical tumor cells to cisplatin-induced apoptosis by suppressing NF-kappa B and decreased cell senescence" BMC cancer. 2011, vol 11, pg. 1-15; pg. 3, left col, para 1, abstract	45-46, 50
A	WO 2011/056590 A1 (PROMETHEUS LABORATORIES INC.) 12 May 2011 (12.05.2011); para [0006]	1-54
A	Arai et al. "Immunohistochemical investigation of S100A9 expression in pulmonary adenocarcinoma: S100A9 expression is associated with tumor differentiation" Oncology Reports. 01 May 2001 (01.05.2001) vol 8, pg. 591-596; abstract	1-54
A	Saintigny et al. "CXCR2 Expression in Tumor Cells Is a Poor Prognostic Factor and Promotes Invasion and Metastasis in Lung Adenocarcinoma" Cancer Research. 30 November 2012 (30.11.2012) vol 73, pg. 571-582; pg. 580, left col, para 2	1-54
A	US 2015/0284470 A1 (ZYMEWORKS, INC.) 08 October 2015 (08.10.2015); entire document	1-54

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

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Date of the actual completion of the international search

19 July 2017

Date of mailing of the international search report

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