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- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- of inventorship (Rule 4.17(iv))

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- with international search report (Art. 21(3))
- with sequence listing part of description (Rule 5.2(a))

(54) Title: METHOD FOR TREATING CANCERS EXPRESSING PROLACTIN RECEPTOR

(57) Abstract: The present invention discloses methods and compositions for control of pituitary and peripheral autocrine sources of prolactin to improve efficacy of prolactin receptor antagonists for the treatment of cancers expressing prolactin receptor.



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METHOD FOR TREATING CANCERS EXPRESSING
PROLACTIN RECEPTOR

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of United States Provisional Patent Application No. 62/637,860, filed March 2, 2018, the full disclosure of which is incorporated herein by reference.

INCORPORATION BY REFERENCE OF A
SEQUENCE LISTING PROVIDED AS A TEXT FILE

[0002] A sequence listing is provided herewith as a text file “010464-5021-Sequence-Listing” created on March 1, 2019 and having a size of 4KB. The contents of the text file are incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

[0003] The present invention is directed to methods and compositions for simultaneous control of both pituitary and peripheral sources of PRL to improve the efficacy of PRLR antagonists in the treatment of cancers expressing PRLRs prolactin in receptors (PRLR).

BACKGROUND OF THE INVENTION

[0004] Breast cancer represents as much as 25% of all cancers occurring in women. Despite well-developed surgical, chemotherapeutic, and radiotherapeutic methods of treatment, there are high levels of relapse due to tumor resistance.

[0005] That PRL plays a key role in breast cancer is not surprising and was suggested almost forty years ago from data initially obtained in mouse and rat studies. Unfortunately, rodents have proven to be poor general models for PRL effects in humans, in part due to the fact that the significant differences in peripheral autogenic

PRL production between rodents and human tissue development was not recognized in early breast cancer studies.

[0006] Clinical trials using bromocriptine to modulate pituitary production of PRL to reduce overall serum PRL levels, as suggested by the rodent data, were largely unsuccessful in treating human breast cancer patients. More recent studies have identified peripherally produced PRL as a key player in human breast cancer. These studies also found that even high-normal circulating levels of PRL increase breast cancer risk, and that there is a causal relationship between PRLR expression and breast cancer.

[0007] Prostate cancer is the most frequently diagnosed cancer in men. PRL plays a key role in development of the prostate. Inhibition of pituitary PRL production in rats during embryonic development results in severely limited prostate development, indicating that PRL plays a role in development of the prostate. There is also significant evidence for peripheral PRL autocrine functions within the prostate.

[0008] Treatment of prostate cancer frequently includes radical prostatectomy, radiation, and androgen deprivation therapy. However, as with breast cancer, resistance to hormone therapy is also common in prostate cancer, although both malignant and healthy prostates produce PRL. Tissues producing high PRL correlate strongly with high Gleason scores based on a microscopic analysis of cancer cells in prostate biopsy samples. Furthermore, prostatic fluid from patients with prostate cancer has higher PRL levels than such fluids from control subjects. Many of the effects of PRL on prostate cancer cells are similar to those on breast cancer cells. *In vitro*, PRL induces proliferation and inhibits apoptosis in some tumor cell lines. PRLRs are expressed in the human prostate, and PRL expression is particularly elevated in prostate cancer patients and in prostate tumor cells.

[0009] Serum PRL in ovarian and endometrial cancer patients are also known to be elevated, indicating a role for PRL in gynecological cancers. Expression of PRLR in ovarian and endometrial tumors, as well as in cases of endometrial hyperplasia is also significantly elevated, suggesting the importance of PRL signaling in malignant and premalignant conditions. PRL mRNA transcripts are abundant in ovarian and

endometrial tumors, indicating the presence of an autocrine loop in such cells. Serum PRL levels are also significantly elevated in women with a strong family history of ovarian cancer.

[0010] Although the exact mechanisms through which PRL leads to increased cancer risk remain unclear, PRL is thought to promote cancer via the JAK2/STAT5 pathway and may increase survival of cancer cells by stimulating the proliferation of cancer cells and interfering with apoptotic signals. PRL has been shown to increase cell motility and promote the spread of cancer in both *in vitro* and *in vivo* studies. PRL is also implicated in adaptive drug resistance to cytotoxic drugs such as cisplatin or paclitaxel.

[0011] In healthy humans the pituitary is not the only source of circulating PRL. Many organs such as the mammary gland, prostate, skin, and brain tissue also express PRL. PRL derived from such tissues is involved in development of breast tissue, the prostate, dermatological bio-regulation, and perception of pain. While peripheral extra-pituitary PRL secretion is also observed in animal models, it appears to be much more common in humans. Such extra-pituitary PRL secretion is dopamine independent. While only small amounts of PRL may be produced locally, relative to the amounts produced by the pituitary, such localized PRL production is important for tumor formation due to local availability.

[0012] Breast cancer and prostate cancer patients treated with a monoclonal antibody directed to PRLR (LFA102) exhibit an unexpected increase in circulating serum PRL levels. This increase in serum PRL has been ascribed to increased pituitary production of PRL due to disruption of feedback from peripheral non-tumoral PRLR inhibition. Although it is not possible to directly differentiate PRL from peripheral and pituitary sources, blocking PRLR should effectively reduce all autocrine sources of PRL, and thus the increase in PRL observed on administration of a PRLR antagonist is thought to provide a valuable biomarker for PRLR inhibition.

[0013] United States Patent Numbers 7,115,556; 8,754,031; 8,754,031; 8,648,046; 7,632,809; 7,201,905 and 7,339,027 which describe various aspects of PRLR antagonists are incorporated herein by reference in their entirety.

[0014] All documents and references cited herein and in the referenced patent documents, are hereby incorporated herein by reference.

DESCRIPTION OF THE INVENTION

[0015] PRL sensitive tumors express higher levels of PRLR when compared to healthy tissue. PRLR comprises as many as six different isoforms. These six isoforms are variably expressed in different tissues and tumor types. Multiple studies suggest that low turnover of the PRLR in cancer cells increases invasive proliferation. PRLR antagonists such as G129R, a human PRL variant in which the glycine at position 129 is replaced with arginine, reduce cancer cell proliferation and enhance the action of many anti-cancer drugs. G129R sterically blocks the sequential dimerization and subsequent activation of PRLR, and induces cell death (either apoptosis or autophagy) of many different breast, prostate, and ovarian cancer cell lines. Although G129R disrupts autocrine production of PRL in such cancer cells it is not known to affect pituitary sources of PRL at all.

[0016] Treatment of ovarian cancer patients with G129R results in an increase in circulating PRL similar to that observed when breast and prostate cancer patients are treated with LFA102. This indicates that G129R effectively blocks PRLR, but provokes increased expression of pituitary derived PRL. The ability to monitor the situation is further confused by the lack of simple clinical tests to differentiate endogenously produced PRL (whether from the pituitary or from peripheral sources) from G129R itself.

[0017] The present invention discloses that when administered in combination with G129R, dopamine agonists allow differentiation of exogenously administered G129R from pituitary derived PRL. Further, co-administration of PRLR antagonists, such as G129R, with a dopamine agonist provides a surprisingly synergistic improvement to existing cancer treatments relative to treatments based on administration of such compounds individually.

A. DEFINITIONS

[0018] As used herein, the term "PLR" refers to human prolactin with the amino acid sequence shown in SEQ ID NO. 1.

[0019] As used herein, the term "G129R" refers to PRL in which the glycine at position 129 is replaced with arginine. The complete sequence of G129R is provided in SIG ID NO. 2.

[0020] As used herein, the term "prolactin receptor antagonist" or "PRLR antagonist" refers to agents and compounds that block or dampen the biological response of the PRLR within a cell by binding to and blocking a receptor rather than activating it like an agonist. There are several forms of PRLR antagonists that have been studied in animal models of cancer, including G129R. As used here, we include antibodies to regions of the PRLR which achieve a similar effect, such as the antibody LFA102.

[0021] The term "dopamine agonist" as used herein refers to agents and compounds that activate dopamine receptors thereby reducing pituitary driven production of PRL. Dopamine agonists as described herein include, without limitation, apomorphine, aripiprazole, bromocriptine (Parlodel® or Cycloset®), cabergoline (Dostinex®), ciladopa, dihedrexidine, dinapsoline, doxanthrine, epicriptine, lisuride, pergolide, phencyclidine, priribedil, pramipexole, propylnorapomorphine, quinagolide, quinpirole, ropinirole, rotigotine, roxindole, salvinorin A, sumanirole.

[0022] The Summary of the Invention is not intended to define the claims nor is it intended to limit the scope of the invention in any manner.

[0023] Other features and advantages of the invention disclosed herein will be apparent from the following, Description of the Invention, and the Claims.

[0024] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates

otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

[0025] As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present invention. Any recited method can be carried out in the order of events recited or in any other order which is logically possible.

B. EMBODIMENTS

[0026] In one embodiment, an effective dose of a PRLR antagonist and an effective dose of a dopamine agonist are co-administered to a human subject suffering from a cancer expressing PRLR. The PRLR antagonist and the dopamine agonist may be administered to the subject simultaneously or separately.

[0027] In another embodiment, an effective dose of G129R is co-administered with an effective amount of a dopamine agonist to a human subject suffering a cancer expressing PRLR. The effective dose of G129R may be administered as a single injection or in multiple injections. Such injections may be any parenteral route such as, without limitation, intramuscular, intradermal, subcutaneous, intravenous, intrathecal, intracranial or intratumoral. An effective dose of may be 50 mg of G129R per kg of patient body weight per day (50 mg/kg/day), 10 mg/kg/day, 5 mg/kg/day, 2.5 mg/kg/day, 1 mg/kg/day, 0.5 mg/kg/day, 0.25 mg/kg/day, 0.1 mg/kg/day, 0.05 mg/kg/day, 0.01 mg/kg/day, 0.005 mg/kg/day.

[0028] In another embodiment, an effective dose of a monoclonal antibody that inhibits PRLR activity is coadministered with an effective amount of a dopamine agonist to a human subject suffering a cancer expressing PRLR. The effective dose of the monoclonal antibody may be administered as a single injection or multiple injections. Such injections may be any parenteral route such as, without limitation, intramuscular, intradermal, intravenous, or intratumoral. In a preferred embodiment the monoclonal antibody is LFA102. An effective dose of may be 10 mg of G129R per kg of patient body weight per day (10 mg/kg/day), 5 mg/kg/day, 2.5 mg/kg/day, 1 mg/kg/day, 0.5 mg/kg/day, 0.25 mg/kg/day, 0.1 mg/kg/day, 0.05 mg/kg/day, 0.025 mg/kg/day, 0.001 mg/kg/day.

[0029] In yet another embodiment, an effective dose of a PRLR antagonist is co-administered with an effective amount of bromocriptine (a dopamine receptor agonist) to a human subject suffering a cancer expressing PRLR. The effective dose of bromocriptine may be administered as singly or in multiple doses. Such administration may be any enteral or parenteral route. An effective oral dose of bromocriptine may be 5 mg per kg of patient body weight per day (5 mg/kg/day), 1 mg/kg/day, 0.5 mg/kg/day, 0.25 mg/kg/day, 0.1 mg/kg/day, 0.05 mg/kg/day, 0.025 mg/kg/day, 0.01 mg/kg/day.

[0030] In still another embodiment, an effective dose of a PRLR antagonist is co-administered with an effective amount of cabergoline (a dopamine receptor agonist) to a human subject suffering a cancer expressing PRLR. The effective dose of cabergoline may be administered as singly or in multiple doses. Such administration may be any enteral or parenteral route. An effective oral dose of cabergoline may be 50 µg per kg of patient body weight per week (50 µg/kg/wk), 25 µg/kg/wk, 10 µg/kg/wk, 5 µg/kg/wk, 1 µg/kg/wk, 0.5 µg/kg/wk, 0.25 µg/kg/day, 0.1 µg/kg/wk.

[0031] In some embodiments, the cancer expressing PRLR may be breast cancer, prostate cancer, ovarian cancer or endometrial cancer.

EXAMPLES

[0032] The following Examples are meant to be illustrative and are not intended to limit the scope of the invention as set forth in the appended Claims.

Example 1**Administration of PRL antagonist G129R increases circulating PRL levels.**

[0033] Human subjects with ovarian cancers expressing PRLR were treated with the PRLR antagonist G129R and the effect of such treatment on circulating PRL was measured. Treatment comprised subcutaneous administration of G129R at 0.5 mg/kg/day. In all cases a sharp increase in circulating PRL was observed within one week of initiating treatment.

[0034] **Table 1.** Circulating PRL (ng/ml) before and after administration of G129R in three subjects with ovarian cancer expressing PRLR.

Patient	Screen (Day < 1)	Day 1 (Pre)	Day 8	Day 15	Day 22	Day 29
1	17.3	13.4	41.9	48.4	68.8	66.9
2	7.7	11.2	67.9	66.4	94.3	36.0
3	14.0	12.9	90.4	110.4	43.9	72.9

[0035] While the subjects experienced stable disease initially during treatment with G129R, by the end of the study each exhibited progressive disease. It was apparent that the increased PRL levels provided increased competition with the fixed dose of G129R administered. While the half-life of G129R was not determined in ovarian cancer subjects, it was previously determined as ranging from 1.7 to 5.3 hours in cynomolgus monkeys.

Example 2

Co-administration of PRL antagonist G129R with a dopamine agonist produces no increase in circulating PRL levels and improves the anti-tumor properties of G129R.

[0036] Human subjects with cancers expressing PRLR are treated with the PRLR antagonist G129R as in Example 1 and are further treated with bromocriptine and the effect of such treatment on circulating PRL was measured. Treatment comprised intravenous administration of G129R at 0.5 mg/kg/day and daily oral administration of an effective amount of dopamine agonist. In all cases circulating PRL will be depressed from the starting (naïve) values due to the action of the dopamine agonist in suppressing pituitary derived PRL.

[0037] Tumor suppression markers as measured by RECIST (Response Evaluation Criteria In Solid Tumors) using imaging methods will indicate increased inhibition of growth and proliferation of the subject cancers relative to treatment with G129R alone. The combination of G129R suppression of peripheral autocrine sources of PRL and suppression of pituitary sources of PRL by the dopamine agonist is a direct demonstration that G129R anti-tumor activity is enhanced by overall suppression of circulating PRL levels.

[0038] The preceding merely illustrates the principles of the invention. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the invention and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions.

CLAIMS

What is claimed is:

1. A method for inhibiting proliferation of cancer cells expressing a prolactin receptor in a patient, the method comprising administering to the patient an effective amount of human prolactin receptor antagonist in combination with a dopamine agonist.
2. The method of claim 1, wherein the human prolactin receptor antagonist comprises a human prolactin in which the glycine at position 129 is substituted with another amino acid.
3. The human prolactin receptor antagonist of claim 2, wherein the substitute amino acid is arginine (G129R).
4. The method of claim 1, wherein the human prolactin receptor antagonist of claim 1 comprises a monoclonal antibody that binds to the prolactin receptor.
5. The human prolactin receptor antagonist of claim 4, wherein the monoclonal antibody is LFA102.
6. The method of claim 1, wherein the dopamine agonist is selected from the group consisting of apomorphine, aripiprazole, bromocriptine, cabergoline, ciladopa, dihedrexidine, dinapsoline, doxanthrine, epicriptine, lisuride, pergolide, phencyclidine, piribedil, pramipexole, propylnorapomorphine, quinagolide, quinpirole, ropinirole, rotigotine, roxindole, salvinorin A, sumanirole.
7. The method of claim 1 wherein the dopamine agonist is bromocriptine.
8. The method of claim 1 wherein the human prolactin receptor antagonist is G129R and the dopamine agonist is bromocriptine.
9. The method of claim 1 wherein the human prolactin receptor antagonist is LFA102 and the dopamine agonist is bromocriptine.
10. The method of claim 1 wherein the cancer cells are ovarian cancer cells.
11. The method of claim 1 wherein the cancer cells are breast cancer cells.
12. The method of claim 1 wherein the cancer cells are prostate cancer cells.
13. The method of claim 1 wherein the cancer cells are endometrial cancer cells.

14. The method of claim 11 wherein the breast cancer cells are triple negative breast cancer cells.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2019/020402

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07K 14/575; C07K 16/28 (2019.01)

CPC - C07K 14/57554; C07K 16/2869; C07K 2317/73; C07K 2317/76 (2019.02)

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

USPC - 435/334; 514/11.5; 514/19.3 (keyword delimited)

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 -- Y	US 2015/0133383 A1 (PROREC BIO AB) 14 May 2015 (14.05.2015) entire document	1-4, 10-14 ----- 5, 8, 9
X -- Y	US 2008/0038369 A1 (CLARK) 14 February 2008 (14.02.2008) entire document	1, 6, 7 ----- 8, 9
Y	US 2014/0227294 A1 (ABBVIE INC.) 14 August 2014 (14.08.2014) entire document	5, 9
A	US 2013/0022606 A1 (BAYER IP GMBH et al) 24 January 2013 (24.01.2013) entire document	1-14
A	US 2013/0231286 A1 (CHEN et al) 05 September 2013 (05.09.2013) entire document	1-14

☐ 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

23 April 2019

Date of mailing of the international search report

10 MAY 2019

Name and mailing address of the ISA/US

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PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2019/020402

Box No. 1 Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments: