

SUMMARY

[0010a] In an aspect of the present disclosure, there is provided a use of a heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator (GRM) in the manufacture of a medicament for treating a neuroendocrine tumor in a patient hosting a neuroendocrine tumor without increasing cortisol levels or risk of hypokalemia in said patient, the tumor having a baseline level of somatostatin receptor expression, wherein:

a) at least one dose of a heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator (GRM) is to be administered, effective to stimulate the expression of somatostatin receptors (SRs) in said neuroendocrine tumor; and

b) at least one dose of somatostatin or a somatostatin analog is to be administered;

whereby the neuroendocrine tumor is treated, without leading to significant increases in cortisol, and without increasing the risk of hypokalemia in the patient.

[0010b] In another aspect of the present disclosure, there is provided a use of a heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator (GRM) in the manufacture of a medicament for localizing a neuroendocrine tumor in a patient hosting a neuroendocrine tumor without increasing cortisol levels or risk of hypokalemia in said patient, the tumor having a baseline level of somatostatin receptor expression, wherein:

a) at least one dose of a heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator (GRM) is to be administered, effective to stimulate the expression of somatostatin receptors (SRs) in said neuroendocrine tumor;

b) at least one dose of somatostatin or a somatostatin analog is to be administered; and

c) the patient is to be imaged, effective to provide an image of the tumor within the patient,

whereby the neuroendocrine tumor is localized, without leading to significant increases in cortisol, and without increasing the risk of hypokalemia in the patient.

[0011] Applicant has surprisingly discovered that the heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator (GRM) termed “relacorilant” is an effective glucocorticoid receptor antagonist (GRA) that can inhibit glucocorticoid receptor (GR) activation without raising cortisol levels, and thus without increasing the risk of hypokalemia in patients.

Administration of heteroaryl-ketone fused azadecalin GRMs effective to block GR activation

also stimulates somatostatin receptor (SR) expression. Provided herein are methods for treating, identifying and localizing tumors expressing SR, including methods of enhancing the efficacy of imaging techniques by increasing SR expression in tumors. In preferred methods, the heteroaryl-ketone fused azadecalin GRM is relacorilant. In examples, the methods include selecting patients who may derive benefit from the treatment methods disclosed herein. Patients who may derive benefit from the treatment methods disclosed herein include those suspected of hosting a tumor, where the suspected tumor expresses low levels of somatostatin receptors, or where the suspected tumor is not visible, or is poorly visible, with imaging techniques such as techniques used to image somatostatin receptors, or where increasing said somatostatin receptor expression in the tumor would improve imaging, identification, or localization of the tumor, and combinations thereof.

[0012] Applicant discloses herein methods of treating a tumor in a patient hosting a tumor without increasing cortisol levels or risk of hypokalemia in the patient, the tumor having a baseline level of somatostatin receptor expression, the method comprising: a) Administering to the patient at least one dose of a heteroaryl-ketone fused azadecalin GRM, effective stimulate the expression of SRs in said tumor; and b) administering to the patient at least one dose of somatostatin or a somatostatin analog; whereby the tumor is treated without increasing cortisol levels or risk of hypokalemia in the patient. In examples, administration of a heteroaryl-ketone fused azadecalin GRM compound is effective to enhance SR expression and improve treatment, identification, and localization of a tumor while not leading to significant increases in cortisol, and while not increasing the risk of, or causing, hypokalemia. The tumors may be, e.g., neuroendocrine tumors. In examples, the tumor is a neuroendocrine tumor, and the methods include methods of treating a neuroendocrine tumor in a patient hosting a neuroendocrine tumor without increasing cortisol levels or risk of hypokalemia in the patient, the tumor having a baseline level of somatostatin receptor expression, the method comprising: a) Administering to the patient at least one dose of a heteroaryl-ketone fused azadecalin GRM, effective stimulate the expression of

somatostatin receptors (SRs) in said neuroendocrine tumor; and b) administering to the patient at least one dose of somatostatin or a somatostatin analog; whereby the neuroendocrine tumor is treated, without leading to significant increases in cortisol, and while not increasing the risk of, or causing, hypokalemia. These methods are useful for treating, locating and identifying tumors suspected of causing Cushing's syndrome in patients.

[0013] Poor SR expression in a tumor may be determined by low-level (faint) or non-existent images of the tumor with SR imaging. In examples, a patient suffering from Cushing's syndrome having a tumor that expresses no, or only small amounts of, somatostatin receptor (SR) is selected for the methods disclosed herein in order to enhance imaging of a tumor by increasing SR expression in the tumor. In examples, these methods are useful for enhancing imaging techniques so as to improve imaging, locating, or identifying tumors in a patient, such as a Cushing's syndrome patient. In examples, these methods are useful in some cases, so as to make it possible to obtain usable images of a tumor, or to determine the location of a tumor, or to identify a tumor, where i) such images, location, or identification of a tumor would otherwise would not have been possible, or ii) where obtaining such images, location, or identification of a tumor would otherwise would not have been possible without increasing cortisol levels or risk of hypokalemia in the patient, or both i) and ii). Heteroaryl-ketone fused azadecalin GRMs bind to glucocorticoid receptors (GRs) and may increase somatostatin receptor expression, particularly may increase expression of somatostatin receptor type 2 (sst2) in tumors. SR, including sst2, bind octreotide and other SR ligands. Treatment of patients hosting a tumor with a heteroaryl-ketone fused azadecalin GRM may be, by itself, effective to treat such a tumor. Treatment of patients hosting a tumor with a heteroaryl-ketone fused azadecalin GRM is shown to be effective to enhance SR-based imaging of such a tumor, improving diagnosis and localization of the tumor. Such enhanced imaging allows better determination of the further course of tumor treatment, whether surgery, radiation, chemotherapy, or combinations thereof, than was provided by prior methods. Improved localization of the tumor by such enhanced imaging allows for improved surgery, radiation, or both.

[0014] Enhancement of SR expression by GRM administration also enhances treatment of tumors, such as neuroendocrine tumors, in combination with somatostatin analogs or with peptide receptor radionuclide therapy. In examples, the treatment of neuroendocrine tumors comprises administration of a heteroaryl-ketone fused azadecalin GRM and a

somatostatin receptor agonist, such as, e.g., somatostatin or a somatostatin analog (SSA). In examples, the somatostatin or SSA is a radiolabeled somatostatin or SSA.

[0015] In some examples, the method comprises administering a somatostatin analog (SSA). In some cases, the SSA is selected from the group consisting of octreotide, octreotate, pasireotide, lanreotide, pentetreotide, and derivatives thereof. In some cases, the SSA is labeled with a radionuclide, such as, e.g., ¹¹¹Indium, ⁹⁰Yttrium, ¹⁷⁷Lutetium, ²¹³Bismuth, or other radionuclides. Examples of radiolabeled SSAs include, for example, ¹²³I-Tyr³-octreotide, ¹¹¹In-DTPA-*D*-Phe¹-octreotide, [¹¹¹In-DTPA⁰]octreotide, [⁹⁰Y-DOTA, Tyr³]octreotide, ¹¹¹In-octreotide, ¹¹¹In-pentetreotide, and [¹⁷⁷Lu-DOTA, Tyr³]octreotate. Such radiolabeled SSAs are used, for example, in peptide receptor radionuclide imaging for observing, localizing, or identifying tumors in patients. In examples, such tumors may be, e.g., neuroendocrine tumors, and may be inoperable and/or metastatic neuroendocrine tumors. Such radiolabeled SSAs are used, for example, in peptide receptor radionuclide therapy (PRRT) for patients with inoperable and/or metastatic tumors, such as inoperable and/or metastatic neuroendocrine tumors. Administration of a SSA in combination with heteroaryl-ketone fused azadecalin GRM administration, or following heteroaryl-ketone fused azadecalin GRM administration, or both, enhances SSA imaging and PRRT as compared to such imaging in the absence of heteroaryl-ketone fused azadecalin GRM administration.

[0016] In some cases, the SSA is administered in a sustained release formulation. In some cases, the SSA is administered as octreotide LAR (such as, e.g., Sandostatin[®] LAR depot, a composition of octreotide acetate formulated for injection, as a suspension).

[0017] Enhancement of SR expression by a heteroaryl-ketone fused azadecalin GRM compound has advantages as compared to administration of other GRM compounds, in that administration of a heteroaryl-ketone fused azadecalin GRM compound does not lead to significant increases in cortisol. For example, as disclosed herein, administration of the heteroaryl-ketone fused azadecalin GRM compound “relacorilant” did not lead to significant increases in cortisol in Cushing’s syndrome patients to whom it was administered; this is important since Cushing’s syndrome patients already suffer from excess cortisol, leading to risk of hypokalemia, a serious condition requiring immediate medical attention. Relacorilant administration thus did not lead to further increased risk of hypokalemia; however, such increased risk of hypokalemia may follow administration of other GRMs; for example,

hypokalemia was observed in 44% of subjects during treatment with mifepristone (Korlym[®]) (Korlym FDA Label, section 5.2) administration also enhances treatment of neuroendocrine tumors in combination with somatostatin analogs or with peptide receptor radionuclide imaging or peptide receptor radionuclide therapy. Excess cortisol may also lead to endometrial hypertrophy, vaginal bleeding, or other complications in female patients, and the risk, or severity, of such adverse events may be increased by mifepristone administration in female Cushing's syndrome patients. However, the heteroaryl-ketone fused azadecalin GRM compound relacorilant also binds to GR and modulates the effects of cortisol, but does not significantly increase cortisol levels, and thus would not significantly increase adverse events associated with further increases in cortisol levels. Thus, heteroaryl-ketone fused azadecalin GRM compounds, such as relacorilant, may be administered and used to image tumors, enhance tumor images, localize tumors, and treat tumors yet would not be expected to significantly increase cortisol levels, and thus may be administered and used for imaging, diagnosis, and therapy where modulation of GR, modulation of somatostatin receptor expression, or both, is involved, without significantly increasing adverse events associated with further increases in cortisol levels.

[0018] Administration of a heteroaryl-ketone fused azadecalin GRM compound, such as relacorilant, is thus useful to image, to localize, to identify, and to treat tumors, such as neuroendocrine tumors while not leading to significant increases in cortisol, and while not increasing the risk of, or causing, hypokalemia. Administration of a heteroaryl-ketone fused azadecalin GRM, such as relacorilant, provides the diagnostic and therapeutic benefits of GRM administration without such increased risks. Accordingly, the present methods provide advantages as compared to prior methods.

[0019] The methods disclosed herein provide advantages of treating Cushing's syndrome in a patient suffering from Cushing's syndrome, while at the same time providing further diagnostic information useful for imaging, localization, or identification of a tumor associated with, or causing, Cushing's syndrome while not leading to significant increases in cortisol, and while not increasing the risk of, or causing, hypokalemia. Such a tumor associated with, or causing, Cushing's syndrome may be a pituitary tumor, an adrenal tumor, may be a tumor located elsewhere in the body of the patient, and may be one of more than one tumor associated with, or causing, Cushing's syndrome. In examples, the tumor may be a neuroendocrine tumor.

[0020] In examples, identifying information, localization information, and diagnostic information obtained by the methods disclosed herein may be useful to aid in providing the patient with appropriate treatment; may avoid unnecessary delay in treating a serious medical condition; may aid in determining whether or not further treatment is needed; and may aid in determining what type of further treatment may be needed (e.g., typically transsphenoidal surgery for patients identified as having ACTH-dependent Cushing's syndrome; adrenal surgery for an adrenal tumor for patients identified as having adrenal Cushing's syndrome; or other surgery for a tumor identified or localized as other than a pituitary or adrenal tumor). All these advantages may be obtained while not leading to significant increases in cortisol, and while not increasing the risk of, or causing, hypokalemia, providing advantages over prior treatments and imaging methods.

[0021] Other objects, features, and advantages of the methods disclosed herein will be apparent to one of skill in the art from the following detailed description and figures.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] Fig. 1 shows an indium octreoscan image of a Cushing's Syndrome patient having an ectopic tumor, showing faint indications of the ectopic tumor (the dark dot in the right lung/mediastinum shows a mildly octreotide positive lesion). Computer tomography (CT) and magnetic resonance imaging (MRI) images of the patient failed to identify an ectopic tumor in the patient.

[0023] Fig. 2 shows an indium octreoscan image of the same Cushing's Syndrome patient following treatment with relacorilant, a heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator; this image, taken after relacorilant treatment, shows clear images of the ectopic tumor. The relacorilant treatment enhanced the indium octreoscan images of the ectopic tumor.

DETAILED DESCRIPTION

I. INTRODUCTION

[0024] Applicant provides novel methods for identifying and localizing tumors expressing somatostatin receptors, including methods of enhancing the efficacy of imaging techniques by increasing somatostatin receptor (SR) expression in tumors while not leading to significant increases in cortisol, and while not increasing the risk of, or causing, hypokalemia.

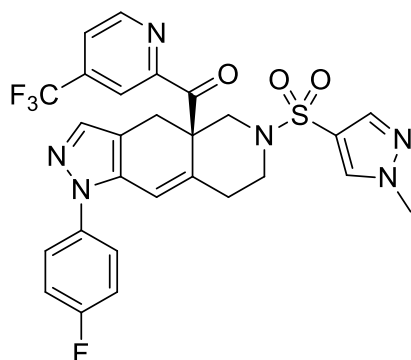
WE CLAIM:

1. Use of a heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator (GRM) in the manufacture of a medicament for treating a neuroendocrine tumor in a patient hosting a neuroendocrine tumor without increasing cortisol levels or risk of hypokalemia in said patient, the tumor having a baseline level of somatostatin receptor expression, wherein:

a) at least one dose of a heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator (GRM) is to be administered, effective to stimulate the expression of somatostatin receptors (SRs) in said neuroendocrine tumor; and

b) at least one dose of somatostatin or a somatostatin analog is to be administered; whereby the neuroendocrine tumor is treated, without leading to significant increases in cortisol, and without increasing the risk of hypokalemia in the patient.

2. The use of claim 1, wherein the heteroaryl-ketone fused azadecalin is (R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (relacorilant) having the structure:



3. The use of claim 1, wherein somatostatin is to be administered.

4. The use of claim 1, wherein a somatostatin analog (SSA) selected from the group consisting of octreotide, radiolabeled octreotide, octreotate, pasireotide, lanreotide, pentetreotide, vapreotide, seglitide, cortistatin, and radiolabeled derivatives thereof selected from the group consisting of ^{123}I -Tyr³-octreotide, ^{111}In -DTPA-*D*-Phe¹-octreotide, [^{111}In -DTPA⁰]octreotide, [^{90}Y -DOTA, Tyr³]octreotide, ^{111}In -octreotide, ^{111}In -pentetreotide, and [^{177}Lu -DOTA, Tyr³]octreotate is to be administered.

5. The use of claim 1, wherein said baseline level of somatostatin receptor expression is undetectable, or only poorly detectable, with imaging.

6. The use of claim 1, wherein labeled somatostatin or somatostatin analogs in the patient is to be imaged, effective to localize the tumor within the patient.

7. The use of claim 5, wherein labeled somatostatin or somatostatin analogs in the patient is to be imaged following said administration of said heteroaryl-ketone fused azadecalin GRM, effective to localize the tumor within the patient.

8. The use of claim 1, wherein said at least one dose of somatostatin or a somatostatin analog is to be administered to the patient, effective to increase the tumor's expression of somatostatin receptors above the baseline amount of somatostatin receptor expression in the tumor.

9. The use of claim 1, wherein said patient suffers from Cushing's syndrome, and said use is effective to treat said Cushing's syndrome.

10. The use of claim 9, wherein said patient suffers from Cushing's Disease, and said use is effective to treat said Cushing's Disease.

11. Use of a heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator (GRM) in the manufacture of a medicament for localizing a neuroendocrine tumor in a patient hosting a neuroendocrine tumor without increasing cortisol levels or risk of hypokalemia in said patient, the tumor having a baseline level of somatostatin receptor expression, wherein:

a) at least one dose of a heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator (GRM) is to be administered, effective to stimulate the expression of somatostatin receptors (SRs) in said neuroendocrine tumor;

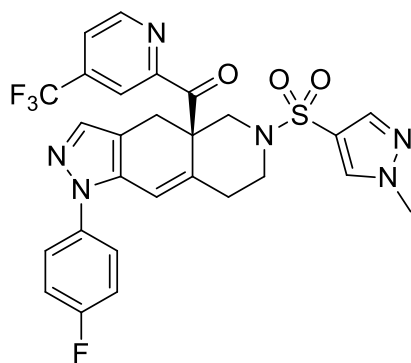
b) at least one dose of somatostatin or a somatostatin analog is to be administered; and

c) the patient is to be imaged, effective to provide an image of the tumor within the patient,

whereby the neuroendocrine tumor is localized, without leading to significant increases in cortisol, and without increasing the risk of hypokalemia in the patient.

12. The use of claim 11, wherein the heteroaryl-ketone fused azadecalin is (R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-

pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (relacorilant) having the structure:



13. The use of claim 11, wherein somatostatin is to be administered.
14. The use of claim 11, wherein a somatostatin analog (SSA) selected from the group consisting of octreotide, radiolabeled octreotide, octreotate, pasireotide, lanreotide, pentetreotide, vapreotide, seglitide, cortistatin, and radiolabeled derivatives thereof selected from the group consisting of ^{123}I -Tyr³-octreotide, ^{111}In -DTPA-*D*-Phe¹-octreotide, [^{111}In -DTPA⁰]octreotide, [^{90}Y -DOTA, Tyr³]octreotide, ^{111}In -octreotide, ^{111}In -pentetreotide, and [^{177}Lu -DOTA, Tyr³]octreotate is to be administered.
15. The use of claim 11, wherein said baseline level of somatostatin receptor expression is undetectable, or only poorly detectable, with imaging.
16. The use of claim 11, wherein labeled somatostatin or somatostatin analogs in the patient is to be imaged, effective to localize the tumor within the patient.
17. The use of claim 15, wherein labeled somatostatin or somatostatin analogs in the patient is to be imaged following said administration of said heteroaryl-ketone fused azadecalin GRM, effective to localize the tumor within the patient.
18. The use of claim 11, wherein said at least one dose of somatostatin or a somatostatin analog is to be administered to the patient, effective to increase the tumor's expression of somatostatin receptors above the baseline amount of somatostatin receptor expression in the tumor.
19. The use of claim 11, wherein said patient suffers from Cushing's syndrome, and said use is effective to treat said Cushing's syndrome.

20. The use of claim 19, wherein said patient suffers from Cushing's Disease, and said use is effective to treat said Cushing's Disease.