physiological immune responses in peripheral tissues, and minimizing collateral tissue damage. It is believed that tumor cells can activate the immune checkpoint signaling pathways to decrease the effectiveness of the immune response against tumor tissues. Many of these immune checkpoint signaling pathways are initiated by interactions between checkpoint proteins present on the surface of the cells participating in the immune responses, e.g., T cells, and their ligands, thus they can be readily blocked by agents or modulated by recombinant forms of the checkpoint proteins or ligands or receptors. The agents blocking the immunosuppression pathway induced by checkpoint proteins are commonly referred to as checkpoint inhibitors and a few have been commercialized. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4, or CTLA-4) antibodies, blocking the immunosuppression pathway by the checkpoint protein CTLA4, were the first of this class of immunotherapeutics to achieve US Food and Drug Administration (FDA) approval. Clinical findings with blockers of additional immune-checkpoint proteins, such as programmed cell death protein 1 (PD-1), indicate broad and diverse opportunities to enhance anti-tumor immunity with the potential to produce durable clinical responses.

[0004] GR is expressed in most human cells and is particularly abundant in immune cells. The effects of, and degree of, endogenous cortisol's effects on the immune system, and their possible consequences for immune responses, including anti-tumor immune responses, are not fully understood. Accordingly, improved methods and treatments for disorders related to cortisol excess, cortisol effects on the immune systems, and for enhancing immune-related treatments are needed.

SUMMARY

[0004a] In one aspect of the present disclosure, there is provided a use of a nonsteroidal selective glucocorticoid receptor modulator (SGRM) in the manufacture of a medicament for improving immune function in a cancer patient having a solid tumor, wherein an effective amount of a cancer treatment and an effective amount of the nonsteroidal selective glucocorticoid receptor modulator (SGRM) is to be administered to said cancer patient, whereby the patient's immune function is improved.

[0005] Applicant discloses herein methods of improving immune function in a cancer patient having a solid tumor, comprising administering an effective amount of a cancer treatment and an effective amount of a nonsteroidal glucocorticoid receptor (GR) modulator (GRM), preferably a selective glucocorticoid receptor modulator (SGRM), to said cancer patient,

whereby the patient's immune function is improved. In examples, the improvement in immune function is effective to elicit an anti-cancer effect in said patient having a solid tumor, thereby slowing tumor growth, stopping tumor growth, reducing tumor load, or combinations thereof. In examples, improved immune function comprises increased CD8+ T-cell activation as compared to CD8+ T-cell activation prior to administration of said nonsteroidal SGRM; improved immune function comprises increased pro-inflammatory cytokine secretion as compared to pro-inflammatory cytokine secretion prior to

administration of said nonsteroidal SGRM; improved immune function comprises increased tumor necrosis factor alpha (TNFα) secretion as compared to TNFα secretion prior to administration of said nonsteroidal SGRM; improved immune function comprises increased interferon gamma IFNγ secretion as compared to IFNγ secretion prior to administration of said nonsteroidal SGRM; and combinations thereof. In examples, immune function is improved after a few to several days of administration of said nonsteroidal GRM or SGRM (e.g., 1, 2,3, 4, 5, 6, 7, 10, 14, or more days of administration).

[0006] In some cases, the GRM (e.g., a SGRM) is a nonsteroidal compound comprising a fused azadecalin structure, wherein the fused azadecalin structure is as described and disclosed in U.S. Patent 7,928,237 and in U.S. Patent 8,461,172. In some cases, the GRM (e.g., a SGRM) is a nonsteroidal compound comprising a heteroaryl ketone fused azadecalin structure, wherein the heteroaryl ketone fused azadecalin structure is as described and disclosed in U.S. Patent 8,859,774. In some cases, the GRM (e.g., a SGRM) is a nonsteroidal compound comprising an octahydro fused azadecalin structure, wherein the octahydro fused azadecalin structure is as described and disclosed in U.S. Patent 10,047,082.

[0007] In some cases, the GRM (e.g., a SGRM, such as a nonsteroidal SGRM) is orally administered.

[0008] In examples, the GRM is administered with a cancer treatment. In examples, the cancer treatment comprises one or more of cancer radiation therapy, administration of growth factor inhibitors, and administration of anti-angiogenesis factors. In examples, the cancer treatment comprises administration of a chemotherapeutic agent or an antibody checkpoint inhibitor. In examples, the GRM is administered with at least one chemotherapeutic agent. In examples, the chemotherapeutic agent is an agent selected from taxanes, alkylating agents, topoisomerase inhibitors, endoplasmic reticulum stress inducing agents, antimetabolites, mitotic inhibitors and combinations thereof. For example, in examples, the chemotherapeutic agent is a taxane, such as nab-paclitaxel. In examples, the antibody checkpoint inhibitor directed against a protein target selected from PD-1, PD-L1, PD-L2, CTLA-4, LAG3, B7-H3, B7-H4, OX-40, CD137, and TIM3.

[0009] To better understand the role of endogenous cortisol in immune suppression, we applied the selective GR antagonist relacorilant to in vitro, in vivo, and ex vivo systems that recapitulate the physiological effects of normal GC activity. These data indicate that

CLAIMS:

1. Use of a nonsteroidal selective glucocorticoid receptor modulator (SGRM) in the manufacture of a medicament for improving immune function in a cancer patient having a solid tumor, wherein an effective amount of a cancer treatment and an effective amount of the nonsteroidal selective glucocorticoid receptor modulator (SGRM) is to be administered to said cancer patient,

whereby the patient's immune function is improved.

2. The use of claim 1, wherein said improvement in immune function is effective to elicit an anti-cancer effect in said patient having a solid tumor, thereby slowing tumor growth, stopping tumor growth, reducing tumor load, or combinations thereof.

3. The use of claim 1 or claim 2, wherein said improved immune function comprises increased CD8+ T-cell activation as compared to CD8+ T-cell activation prior to administration of said nonsteroidal SGRM.

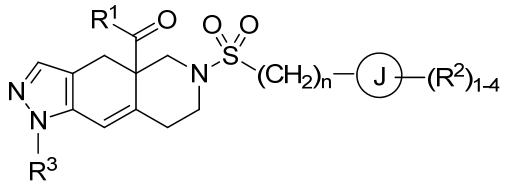
4. The use of claim 1 or claim 2, wherein said improved immune function comprises increased pro-inflammatory cytokine secretion as compared to pro-inflammatory cytokine secretion prior to administration of said nonsteroidal SGRM.

5. The use of claim 1 or claim 2, wherein said improved immune function comprises increased TNFα secretion as compared to TNFα secretion prior to administration of said nonsteroidal SGRM.

6. The use of claim 1 or claim 2, wherein said improved immune function comprises increased IFNγ secretion as compared to IFNγ secretion prior to administration of said nonsteroidal SGRM.

7. The use of any of claims 1 to 6, wherein said immune function is improved after administration of said nonsteroidal SGRM for a number of days selected from 1, 2, 3, 4, 5, 6, 7, 10, 14, or more days.

8. The use of any of claims 1 to 6, wherein said nonsteroidal SGRM is a compound comprising a heteroaryl ketone fused azadecalin structure having the formula:



wherein

R^1 is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S, optionally substituted with 1-4 groups each independently selected from R^{1a};

each R^{1a} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, CN, N-oxide, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl;

ring J is selected from the group consisting of a cycloalkyl ring, a heterocycloalkyl ring, an aryl ring and a heteroaryl ring, wherein the heterocycloalkyl and heteroaryl rings have from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S;

each R^2 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, $C_{1\ 6}$ haloalkyl, $C_{1\ 6}$ alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkyl-C_{1-6} alkoxy, CN, OH, $NR^{2a}R^{2b}$, $C(O)R^{2a}$, $C(O)OR^{2a}$, $C(O)NR^{2a}R^{2b}$, SR^{2a}, $S(O)R^{2a}$, $S(O)_2R^{2a}$, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl, wherein the heterocycloalkyl groups are optionally substituted with 1-4 R^{2c} groups;

alternatively, two R^2 groups linked to the same carbon are combined to form an oxo group (=O);

alternatively, two R^2 groups are combined to form a heterocycloalkyl ring having from 5 to 6 ring members and from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S, wherein the heterocycloalkyl ring is optionally substituted with from 1 to 3 R^{2d} groups;

R^{2a} and R^{2b} are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

each R^{2c} is independently selected from the group consisting of hydrogen, halogen, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkoxy, CN, and $NR^{2a}R^{2b}$;

each R^{2d} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl, or two R^{2d} groups attached to the same ring atom are combined to form (=O);

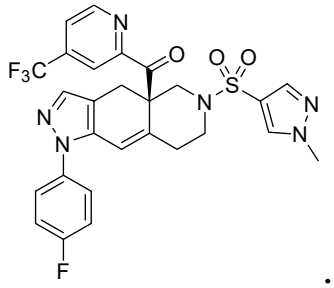
R^3 is selected from the group consisting of phenyl and pyridyl, each optionally substituted with 1-4 R^{3a} groups;

each R^{3a} is independently selected from the group consisting of hydrogen, halogen, and C_{1-6} haloalkyl; and

subscript n is an integer from 0 to 3;

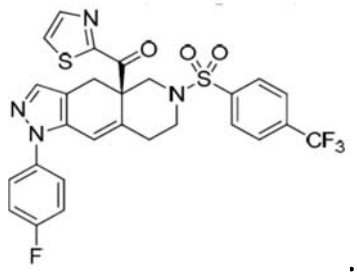
or salts and isomers thereof.

9. The use of claim 8, wherein the nonsteroidal SGRM 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, termed relacorilant, which has the following structure:



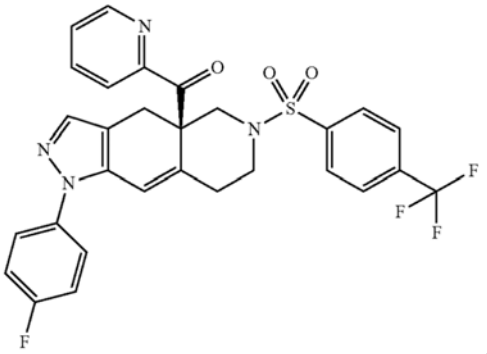
.

10. The use of claim 8, wherein the nonsteroidal SGRM is (R)-(1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl)sulfonyl)-4,4a,5,6,- 7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(thiazol-2-yl)methanone, termed CORT122928, which has the following structure:



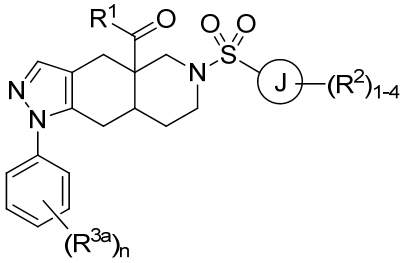
.

11. The use of claim 8, wherein the nonsteroidal SGRM is (R)-(1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl) sulfonyl)-4, 4a, 5,6,7,8-hexahydro-1-H-pyrazolo 1,4-g]isoquinolin-4a-yl) (pyridin-2-yl)methanone, termed CORT113176, which has the following structure:



.

12. The use of any of claims 1 to 6, wherein the nonsteroidal SGRM comprises an octahydro fused azadecalin structure compound having the formula:



wherein R^1 is selected from the group consisting of pyridine and thiazole, optionally substituted with 1-4 groups each independently selected from R^{1a};

each R^{1a} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, N-oxide, and C_{3-8} cycloalkyl;
ring J is selected from the group consisting of phenyl, pyridine, pyrazole, and triazole;

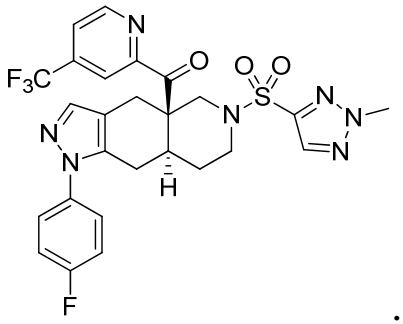
each R^2 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and -CN;

R^{3a} is F;

subscript n is an integer from 0 to 3,

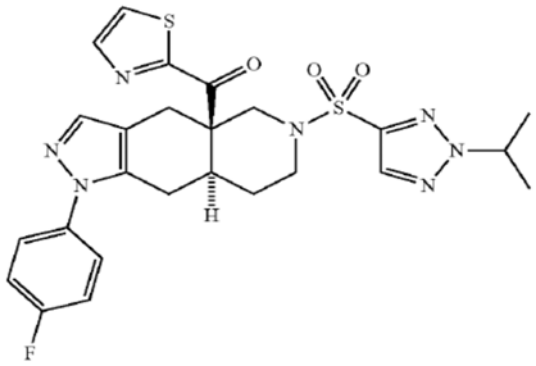
or salts and isomers thereof.

13. The use of claim 12, wherein the nonsteroidal SGRM is ((4aR,8aS)-1-(4-fluorophenyl)-6-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone, termed exicorilant, which has the structure:



.

14. The use of claim 12, wherein the nonsteroidal SGRM is ((4aR,8aS)-1-(4-fluorophenyl)-6-((2-isopropyl-2H-1,2,3-triazol-4-yl)sulfonyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(thiazol-2-yl)methanone, termed “CORT125329”, having the formula:



15. The use of any of claims 1 to 14, wherein the cancer treatment comprises a chemotherapeutic agent.

16. The use of claim 15, wherein the chemotherapeutic agent is selected from the group consisting of taxanes, alkylating agents, topoisomerase inhibitors, endoplasmic reticulum stress inducing agents, antimetabolites, mitotic inhibitors and combinations thereof.

17. The use of claim 15, wherein the chemotherapeutic agent is a taxane.

18. The use of claim 17, wherein the chemotherapeutic agent is nab-paclitaxel.

19. The use of any of claims 1 to 14, wherein the cancer treatment comprises an immunotherapeutic agent.

20. The use of claim 19, wherein the immunotherapeutic agent comprises administration of an antibody checkpoint inhibitor directed against a protein target selected from PD-1, PD-L1, CTLA-4, LAG3, B7-H3, B7-H4, OX-40, CD137, and TIM3.

21. The use of any of claims 1 to 14, wherein the cancer treatment comprises one or more of cancer radiation therapy, growth factor inhibitors, and anti-angiogenesis factors.

22. The use of any of claims 1 to 21, wherein said selective glucocorticoid receptor modulator is a selective glucocorticoid receptor antagonist.