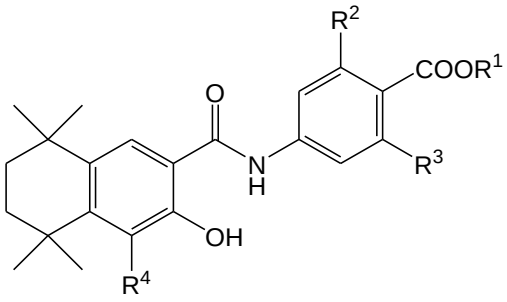
the bone marrow. However, the use of retinoid analogs which are not inactivated by CYP26 enables such retinoids to terminally differentiate, and thus eliminate, the cancer HSCs from the protective bone marrow niche. Since such differentiation is mediated by RARα and the use of RARα specific analogs, which are CYP26 resistant, enables the therapeutic differentiation-inducing activity without inactivation by the CYP26 enzyme.

[0005] Thus, the combination of RAR agonists, to induce differentiation of cancer stem cells, and targeted immunotherapy can be particularly useful in treating cancer.

SUMMARY

[0006] Disclosed herein are compounds for potentiation of targeted cancer immunotherapeutics. Compounds which act on retinoic acid receptors (RAR) are used in combination with chimeric antigen receptor (CAR)-modified immune cells (sometimes abbreviated as CAR-MIC) to potentiate the anti-cancer activity of the CAR-modified immune cells and/or immune checkpoint targeted therapeutics.

[0006a] In one aspect, the present disclosure refers to a use of at least one differentiating retinoic acid receptor (RAR) active agent in the manufacture of a medicament for ~~potentiating chimeric antigen receptor-modified immune cells (CAR-MIC)~~ cancer immunotherapy, wherein the differentiating RAR active agent is a RARα agonist, wherein the RARα agonist is a CYP26 metabolism-resistant, RARα selective agonist having a structure of general formula (I)

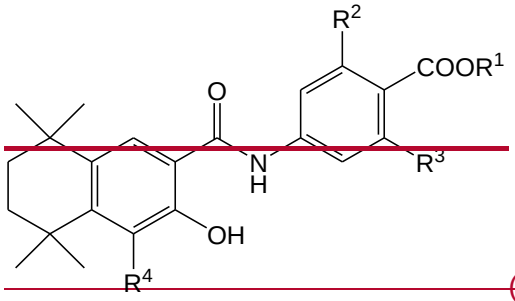


(I)

wherein R^1 is H or C_{1-6} alky, R^2 and R^3 are independently H or F, and R^4 is a halogen wherein the medicament is to be administered to a cancer patient, and wherein the cancer patient is receiving, has received, or is scheduled to receive, chimeric antigen receptor-modified immune cells (CAR-MIC).

[0006b] In another aspect, the present disclosure refers to a use at least one differentiating RAR active agent in the manufacture of a medicament for cancer immunotherapy , wherein the differentiating RAR active agent is a RARα agonist, wherein the RARα agonist is a CYP26 metabolism-resistant, RARα selective agonist having a structure of general formula (I)

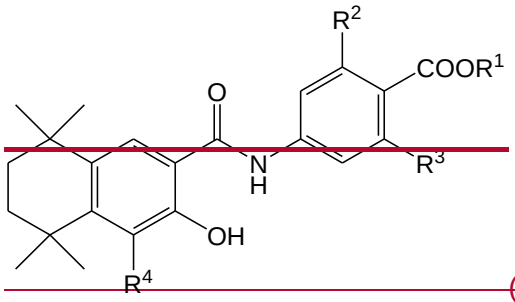
[0006d] In another aspect, the present disclosure refers to a method of augmenting the production of chimeric antigen receptor-modified immune cells (CAR-MIC) comprising culturing the CAR-MIC in a culture medium comprising at least one differentiating retinoic acid receptor (RAR) active agent, wherein the differentiating RAR active agent is a RARα agonist, wherein the RARα agonist is a CYP26 metabolism-resistant, RARα selective agonist having a structure of general formula (I)



(I)

wherein R^1 is H or C_{1-6} alky, R^2 and R^3 are independently H or F, and R^4 is a halogen.

[0006e] In another aspect, the present disclosure refers to a use of a culture of chimeric antigen receptor-modified immune cells (CAR-MIC) in the manufacture of a medicament for CAR-MIC cancer immunotherapy, wherein production of the culture of CAR-MIC is augmented by culturing CAR-MIC in a culture medium comprising at least one differentiating retinoic acid receptor (RAR) active agent, wherein the differentiating RAR active agent is a RARα agonist, wherein the RARα agonist is a CYP26 metabolism-resistant, RARα selective agonist having a structure of general formula (I)

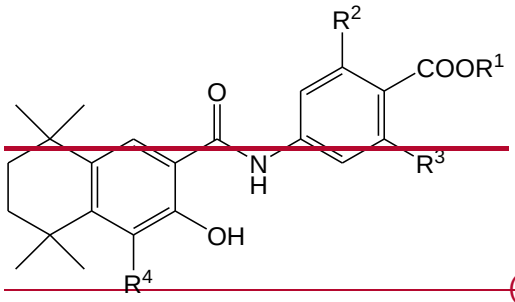


(I)

wherein R^1 is H or C_{1-6} alky, R^2 and R^3 are independently H or F, and R^4 is a halogen, and wherein the medicament is to be administered directly to a subject.

[0006f] In another aspect, the present disclosure refers to a use of a cryopreserved culture of chimeric antigen receptor-modified immune cells (CAR-MIC) in the manufacture of a medicament for CAR-MIC cancer immunotherapy, wherein the culture of CAR-MIC is cryopreserved for future administration to a subject, wherein production of the culture of CAR-MIC is augmented by culturing the CAR-MIC in a culture medium comprising at least one differentiating retinoic acid receptor (RAR) active agent, wherein the differentiating RA

~~active agent is a RARα agonist, wherein the RARα agonist is a CYP26 metabolism-resistant, RARα selective agonist having a structure of general formula (I)~~



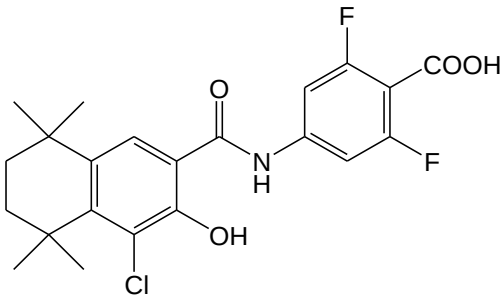
~~(I)~~

~~wherein R^1 is H or C_{1-6} alky, R^2 and R^3 are independently H or F, and R^4 is a halogen.~~

[0007] Retinoids and rexinoids have diverse activities. Particular retinoids have an anticancer effect based in terminally differentiating cancer stem cells. These differentiating retinoids, or differentiating RAR active agents, can be used in combination with CAR-MIC to increase the overall effectiveness of the immunotherapy. In some examples the differentiating retinoid is a RARα agonist. In some examples the RARα agonist is a RARα specific or selective agonist. In some examples the RARα agonists are CYP26 resistant.

[0008] In some examples, the CAR-modified immune cells are, or comprise, CAR-modified T cells. In some examples, the CAR-modified immune cells are, or comprise, CAR-modified NK cells. In some examples, the CAR-modified immune cells are, or comprise, CAR-modified NKT cells. In some examples, the CAR-modified immune cells are, or comprise, CAR-modified macrophages. Further examples can comprise mixtures of these cell types. Most typically such cellular preparations are administered by infusion, for example intravenous infusion. In contrast, the RARα agonists are small molecules that can be administered orally, for example as pills or capsules and the like. Thus the RARα agonists and the CAR-modified immune cells may be administered on independent schedules.

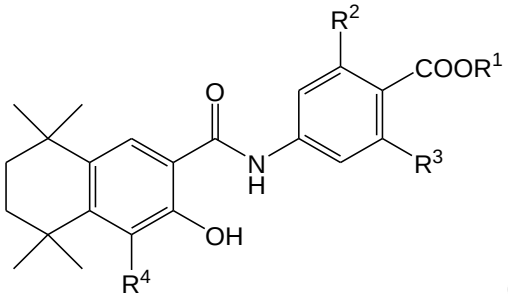
[0009] In some examples, the RARα agonist is:



(III) (IRX5183).

What is claimed is:

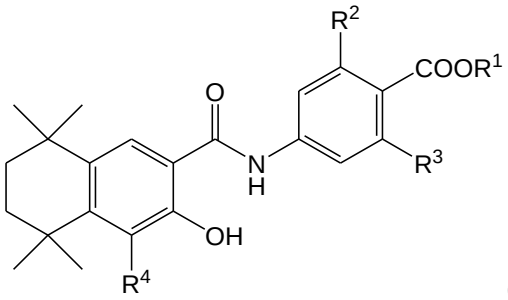
1. Use of at least one differentiating retinoic acid receptor (RAR) active agent in the manufacture of a medicament for ~~potentiating chimeric antigen receptor-modified immune cells (CAR-MIC)~~ cancer immunotherapy, wherein the differentiating RAR active agent is a RARα agonist, wherein the RARα agonist is a CYP26 metabolism-resistant, RARα selective agonist having a structure of general formula (I)



(I)

wherein R^1 is H or C_{1-6} alky, R^2 and R^3 are independently H or F, and R^4 is a halogen
wherein the medicament is to be administered to a cancer patient,
and wherein the cancer patient is receiving, has received, or is scheduled to receive, chimeric antigen receptor-modified immune cells (CAR-MIC).

2. Use of at least one differentiating RAR active agent in the manufacture of a medicament for cancer immunotherapy , wherein the differentiating RAR active agent is a RARα agonist, wherein the RARα agonist is a CYP26 metabolism-resistant, RARα selective agonist having a structure of general formula (I)

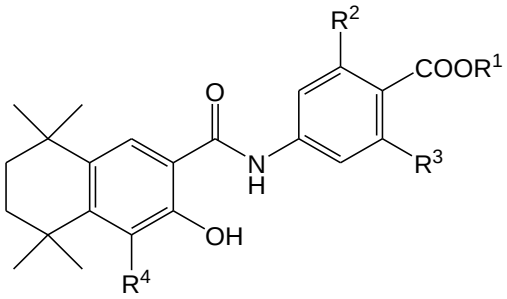


(I)

wherein R^1 is H or C_{1-6} alky, R^2 and R^3 are independently H or F, and R^4 is a halogen,
wherein the medicament is to be administered to a subject in need thereof,
and wherein the medicament is to be administered with CAR-MIC.

3. Use of at least one RARα agonist in the manufacture of a medicament for decreasing toxicity of CAR-modified immune cells, wherein the medicament is to be administered in combination with the CAR-modified immune cells such that as a result of the

combination, a lower dose of CAR-modified immune cells is administered but the efficacy is not decreased, as compared to administration of the CAR-modified immune cells alone, wherein the RARα agonist is a CYP26 metabolism-resistant, RARα selective agonist having a structure of general formula (I)

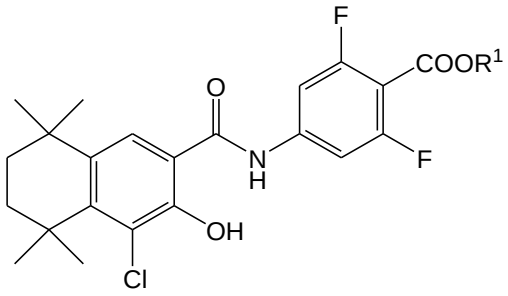


(I)

wherein R^1 is H or C_{1-6} alky, R^2 and R^3 are independently H or F, and R^4 is a halogen.

4. The use according to any one of claims 1-3, wherein R^4 is F, Cl, Br or I.

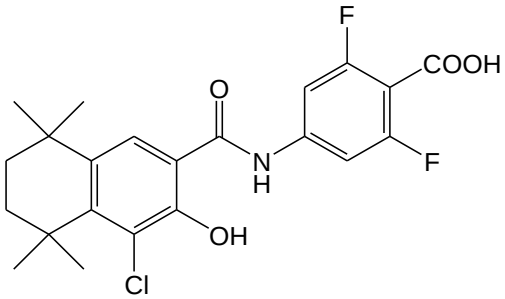
5. The use according to any one of claims 1-3, wherein the RARα agonist is a compound having a structure of formula (II):



(II)

wherein R^1 is H or C_{1-6} alkyl.

6. The use according to claim 5, wherein the RARα agonist is a compound having a structure of formula (III):



(III) (IRX5183).

7. The use according to any one of claims 1-3, wherein the CAR-modified immune cells are CAR-modified T cells.

8. The use according to any one of claims 1-3, wherein the CAR-modified immune cells are CAR-modified NK cells.

9. The use according to any one of claims 1-3, wherein the CAR-modified immune cells are CAR-modified macrophages.

10. The use according to any one of claims 1-3, wherein the cancer is a hematologic malignancy.

11. The use according to claim 10, wherein the hematologic malignancy is acute myeloid leukemia, chronic myelogenous leukemia (CML), accelerated CML, CML blast phase (CML-BP), acute lymphoblastic leukemia, chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, follicular lymphoma, mantle cell lymphoma, B-cell lymphoma, T-cell lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, myelodysplastic syndromes (MDS), refractory anemia (RA), RA with ringed sideroblasts, RA with excess blasts (RAEB), RAEB in transformation, or a myeloproliferative syndrome.

12. The use according to claim 10, wherein the hematologic malignancy is acute myeloid leukemia.

13. The use according to claim 10, wherein the hematologic malignancy is multiple myeloma.

14. The use according to any one of claims 1-3, wherein the cancer is a solid tumor.

15. The use according to claim 14, wherein the cancer is a solid tumor which can metastasize to the bone, wherein the solid tumor is pancreatic cancer; bladder cancer; colorectal cancer; breast cancer, including metastatic breast cancer; prostate cancer, including androgen-dependent and androgen-independent prostate cancer; renal cancer, metastatic renal cell carcinoma; hepatocellular cancer; lung cancer, non-small cell lung cancer (NSCLC), small cell lung cancer, bronchoalveolar carcinoma (BAC), and adenocarcinoma of the lung; ovarian cancer, progressive epithelial, primary peritoneal cancer; cervical cancer; gastric cancer; esophageal cancer; head and neck cancer, squamous cell carcinoma of the head and neck; melanoma; neuroendocrine cancer, metastatic neuroendocrine tumor; brain tumor, glioma, anaplastic oligodendroglioma, adult glioblastoma multiforme, adult anaplastic astrocytoma; bone cancer; and soft tissue sarcoma.

16. The use according to any one of claims 1-3, wherein the medicament is to be administered for at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days,

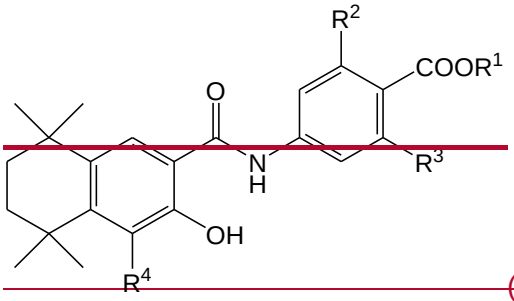
at least 6 days, at least 1 week, at least 2 weeks, at least 3 weeks, or at least one month before administration of the CAR-modified immune cells.

17. The use according to any one of claims 1-3, wherein administration of the medicament is to be discontinued before administration of CAR-modified immune cells.

18. The use according to claim 17, wherein bortezomib is to be further administered.

19. The use according to claim 18, wherein the cancer patient has multiple myeloma.

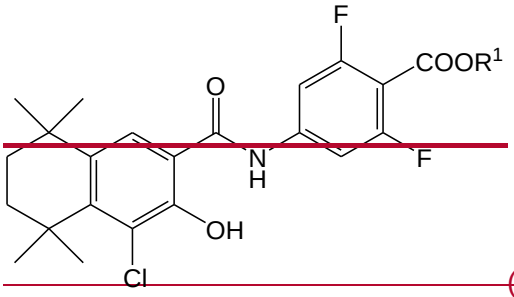
~~20. A method of augmenting the production of chimeric antigen receptor-modified immune cells (CAR-MIC) comprising culturing the CAR-MIC in a culture medium comprising at least one differentiating retinoic acid receptor (RAR) active agent, wherein the differentiating RAR active agent is a RARα agonist, wherein the RARα agonist is a CYP26 metabolism-resistant, RARα selective agonist having a structure of general formula (I)~~



~~(I)~~

~~wherein R^1 is H or C_{1-6} alky, R^2 and R^3 are independently H or F, and R^4 is a halogen.~~

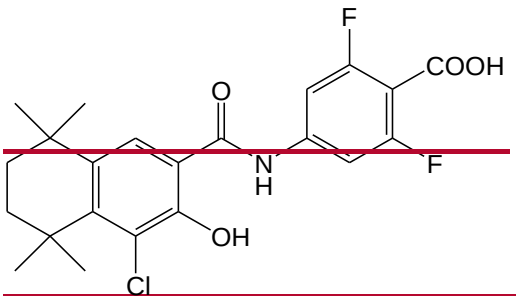
~~21. The method of claim 20, wherein the RARα agonist is a compound having a structure of formula (II):~~



~~(II)~~

~~wherein R^1 is H or C_{1-6} alkyl.~~

22. The method of claim 20, wherein the RARα agonist is a compound having a structure of formula (III):

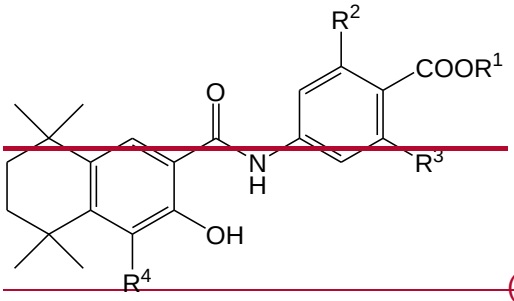


(III) (IRX5183).

23. The method of claim 20, wherein augmenting the production CAR-MIC comprises expansion of CAR-MIC numbers.

24. The method of claim 20, wherein augmenting the production CAR-MIC comprises maintenance of the CAR phenotype.

25. Use of a culture of chimeric antigen receptor-modified immune cells (CAR-MIC) in the manufacture of a medicament for CAR-MIC cancer immunotherapy, wherein production of the culture of CAR-MIC is augmented by culturing CAR-MIC in a culture medium comprising at least one differentiating retinoic acid receptor (RAR) active agent, wherein the differentiating RAR active agent is a RARα agonist, wherein the RARα agonist is a CYP26 metabolism-resistant, RARα selective agonist having a structure of general formula (I)

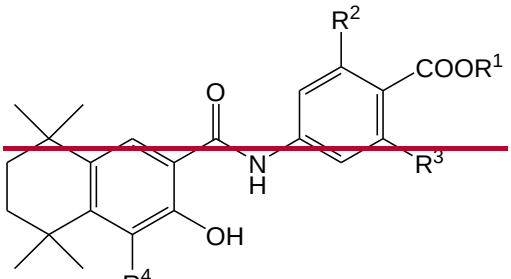


(I)

wherein R^1 is H or C_{1-6} alky, R^2 and R^3 are independently H or F, and R^4 is a halogen, and wherein the medicament is to be administered directly to a subject.

26. Use of a cryopreserved culture of chimeric antigen receptor-modified immune cells (CAR-MIC) in the manufacture of a medicament for CAR-MIC cancer immunotherapy, wherein the culture of CAR-MIC is cryopreserved for future administration to a subject, wherein production of the culture of CAR-MIC is augmented by culturing the CAR-MIC in a culture medium comprising at least one differentiating retinoic acid receptor (RAR) active agent, wherein the differentiating RAR active agent is a RARα agonist, wherein the RARα agonist is a

~~CYP26 metabolism-resistant, RARα selective agonist having a structure of general formula (I)~~



~~(I)~~

~~wherein R^1 is H or C_{1-6} alky, R^2 and R^3 are independently H or F, and R^4 is a halogen.~~

~~27. The method of claim 20, wherein the CAR-MIC is a CAR-T cell.~~