receptors, ion channels, the secretory pathway, DNA repair and biogenesis of organelles.

[0005] Aberrations in the process have recently been implicated in the pathogenesis of several diseases, both inherited and acquired. These diseases fall into two major groups: (a) those that result from loss of function with the resultant stabilization of certain proteins, and (b) those that result from gain of function, i.e. abnormal or accelerated degradation of the protein target.

[0006] The UPP is used to induce selective protein degradation, including use of fusion proteins to artificially ubiquitinate target proteins and synthetic small-molecule probes to induce proteasome-dependent degradation. Bifunctional compounds composed of a target protein-binding ligand and an E3 ubiquitin ligase ligand, induced proteasome-mediated degradation of selected proteins via their recruitment to E3 ubiquitin ligase and subsequent ubiquitination. These drug-like molecules offer the possibility of temporal control over protein expression. Such compounds are capable of inducing the inactivation of a protein of interest upon addition to cells or administration to an animal or human, and could be useful as biochemical reagents and lead to a new paradigm for the treatment of diseases by removing pathogenic or oncogenic proteins (Crews C, Chemistry & Biology, 2010, 17(6):551-555; Schnnekloth JS Jr., Chembiochem, 2005, 6(l):40-46).

[0007] An ongoing need exists in the art for effective treatments for disease, especially hyperplasias and cancers, such as multiple myeloma. However, non-specific effects, and the inability to target and modulate certain classes of proteins altogether, such as transcription factors, remain as obstacles to the development of effective anti-cancer agents. As such, small molecule therapeutic agents that leverage E3 ligase mediated protein degradation to target cancer-associated proteins such as interleukin-1 receptor-associated kinases (“IRAK”) hold promise as therapeutic agents. Accordingly, there remains a need to find compounds that are IRAK degraders useful as therapeutic agents.

SUMMARY

[0007a] In an aspect of the present disclosure, there is provided a use of an IRAK4 degrader in the manufacture of a medicament for treating hidradenitis suppurativa patient and/or atopic dermatitis in a patient having an elevated level of an inflammatory biomarker.

[0007b] In another aspect of the present disclosure, there is provided a use of an IRAK4 degrader in the manufacture of a medicament for treating hidradenitis suppurativa patient and/or

atopic dermatitis in a patient, wherein a patient having an elevated level of an inflammatory biomarker is selected, and the IRAK4 degrader is to be administered to the patient.

[0007c] In a further aspect of the present disclosure, there is provided a use of an IRAK4 degrader in the manufacture of a medicament for treating hidradenitis suppurativa patient and/or atopic dermatitis in a patient, wherein an inflammatory biomarker level in a sample of a patient is measured, a patient having an elevated level of an inflammatory biomarker is selected, and the IRAK4 degrader is to be administered to the patient.

[0007d] In another aspect of the present disclosure, there is provided a use of an IRAK4 degrader in the manufacture of a medicament for treating hidradenitis suppurativa patient and/or atopic dermatitis in a patient having a reduced level of an inflammatory biomarker after a treatment with an IRAK4 degrader.

[0007e]In a further aspect of the present disclosure, there is provided a use of an IRAK4 degrader in the manufacture of a medicament for treating hidradenitis suppurativa patient and/or atopic dermatitis in a patient, wherein a patient having a reduced level of an inflammatory biomarker after a treatment with an IRAK4 degrader is selected, and the IRAK4 degrader is to be administered to the patient.

[0007f] In another aspect of the present disclosure, there is provided a use of an IRAK4 degrader in the manufacture of a medicament for treating hidradenitis suppurativa patient and/or atopic dermatitis in a patient, wherein an inflammatory biomarker level in a sample of a patient after a treatment with an IRAK4 degrader is measured, a patient having a reduced level of an inflammatory biomarker after a treatment with an IRAK4 degrader is selected, and the IRAK4 degrader is to be administered to the patient.

[0007g] In a further aspect of the present disclosure, there is provided a use of an IRAK4 degrader in the manufacture of a medicament for treating hidradenitis suppurativa patient and/or atopic dermatitis in a patient, wherein an IRAK4 degrader is to be administered to a patient, an inflammatory biomarker level in a sample of a patient after a treatment with the IRAK4 degrader is measured, a patient having a reduced level of an inflammatory biomarker after a treatment with the IRAK4 degrader is selected, and an IRAK4 degrader is to be further administered to the patient.

[0008] As described herein, the inventors have discovered that levels of certain inflammatory biomarkers in hidradenitis suppurativa (HS) and atopic dermatitis (AD) patients are indicative of patient responsiveness to treatment with IRAK degraders, including, for example, those as described herein. The inflammatory biomarkers can be cutaneous and circulating inflammatory

biomarkers. As shown herein, certain inflammatory biomarkers levels can be used, for example, for selecting patients for a treatment using IRAK degraders.

[0009] Accordingly, in one example, the present disclosure provides a method of identifying or selecting a patient having an elevated level of an inflammatory biomarker, comprising measuring a level of an inflammatory biomarker in a sample of a patient, and selecting a patient having an elevated level of an inflammatory biomarker in the sample. In some examples, a patient is a hidradenitis suppurativa patient. In some examples, a patient is an atopic dermatitis patient.

[0010] In another example, the present disclosure provides a method of identifying or selecting a patient having a reduced level of an inflammatory biomarker after a treatment with an IRAK degrader, comprising measuring a level of an inflammatory biomarker in a sample of a patient after a treatment with an IRAK degrader, and selecting a patient having a reduced level of an inflammatory biomarker in a sample. In some examples, a patient is a hidradenitis suppurativa patient. In some examples, a patient is an atopic dermatitis patient.

[0011] In another example, the present disclosure provides a method of treating a disease or disorder in a patient having an elevated level of an inflammatory biomarker, comprising administering to the patient a therapeutically effective amount of an IRAK degrader. In some examples, a disease or disorder is hidradenitis suppurativa. In some examples, a disease or disorder is an atopic dermatitis.

[0012] In another example, the present disclosure provides a method of treating a disease or disorder in a patient having a reduced level of an inflammatory biomarker after a treatment with an IRAK degrader, comprising administering to the patient a therapeutically effective amount of an IRAK degrader. In some examples, a disease or disorder is hidradenitis suppurativa. In some examples, a disease or disorder is an atopic dermatitis.

[0013] In another example, the present disclosure provides a method of treating a disease or disorder in a patient, comprising selecting a patient having an elevated level of an inflammatory biomarker, and administering to the patient a therapeutically effective amount of an IRAK degrader. In some examples, a disease or disorder is hidradenitis suppurativa. In some examples, a disease or disorder is an atopic dermatitis.

[0014] In another example, the present disclosure provides a method of treating a disease or disorder in a patient, comprising selecting a patient having a reduced level of an inflammatory biomarker after a treatment with an IRAK degrader, and administering to the patient a

therapeutically effective amount of an IRAK degrader. In some examples, a disease or disorder is hidradenitis suppurativa. In some examples, a disease or disorder is an atopic dermatitis.

[0015] In some examples, an inflammatory biomarker is selected from those as described herein. In some examples, an IRAK degrader is selected from those as described herein.

BRIEF DESCRIPTION OF FIGURES

[0016] **FIG. 1** depicts potent and selective degraders of IRAK4.

[0017] **FIG. 2** depicts orally active IRAK4 degrader blocks IL-1 driven neutrophilic infiltration in MSU air pouch model.

[0018] **FIG. 3** depicts full degradation of IRAK4 in skin and lymphoid tissues in higher species.

[0019] **FIG. 4** depicts that IRAK4 degradation has broader and more potent effect on TIR activation compared to kinase inhibition.

[0020] **FIG. 5** depicts that IRAK4 degradation reduces skin thickening and inhibits cytokine signaling in imiquimod induced psoriasis mouse model.

[0021] **FIG. 6** depicts HS patient responses to Degrader 2 ex vivo in PBMC subsets.

[0022] **FIG. 7** depicts IRAK signal at baseline and following ex vivo treatment with Degrader 2 in HS patients.

[0023] **FIG. 8** depicts IRAK4 immunofluorescence (IF) of patient biopsies (A) and cell count by intensity per biopsy location (B).

[0024] **FIG. 9** depicts absolute quanification of IRAK4 by mass spectrometry (MS) in patient biopsies normalized to PARK7.

[0025] **FIG. 10** shows IRAK4 expression in peripheral blood mononuclear cells is highest in monocytes.

[0026] **FIG. 11** shows that IRAK4 degrader downregulates IRAK4 expression across all PBMC subsets with comparison to IRAK4 inhibitor.

[0027] **FIG. 12** shows methods for measuring IRAK4 protein and pro-inflammatory gene transcripts in HS skin biopsies (A) and healthy subject skin/monocytes (B).

[0028] **FIG. 13** shows IRAK4 protein expression is elevated in HS skin compared to skin from healthy subjects.

CLAIMS

1. Use of an IRAK4 degrader in the manufacture of a medicament for treating hidradenitis suppurativa patient and/or atopic dermatitis in a patient having an elevated level of an inflammatory biomarker.

2. Use of an IRAK4 degrader in the manufacture of a medicament for treating hidradenitis suppurativa patient and/or atopic dermatitis in a patient, wherein a patient having an elevated level of an inflammatory biomarker is selected, and the IRAK4 degrader is to be administered to the patient.

3. Use of an IRAK4 degrader in the manufacture of a medicament for treating hidradenitis suppurativa patient and/or atopic dermatitis in a patient, wherein an inflammatory biomarker level in a sample of a patient is measured, a patient having an elevated level of an inflammatory biomarker is selected, and the IRAK4 degrader is to be administered to the patient.

4. Use of an IRAK4 degrader in the manufacture of a medicament for treating hidradenitis suppurativa patient and/or atopic dermatitis in a patient having a reduced level of an inflammatory biomarker after a treatment with an IRAK4 degrader.

5. Use of an IRAK4 degrader in the manufacture of a medicament for treating hidradenitis suppurativa patient and/or atopic dermatitis in a patient, wherein a patient having a reduced level of an inflammatory biomarker after a treatment with an IRAK4 degrader is selected, and the IRAK4 degrader is to be administered to the patient.

6. Use of an IRAK4 degrader in the manufacture of a medicament for treating hidradenitis suppurativa patient and/or atopic dermatitis in a patient, wherein an inflammatory biomarker level in a sample of a patient after a treatment with an IRAK4 degrader is measured, a patient having a reduced level of an inflammatory biomarker after a treatment with an IRAK4 degrader is selected, and the IRAK4 degrader is to be administered to the patient.

7. Use of an IRAK4 degrader in the manufacture of a medicament for treating hidradenitis suppurativa patient and/or atopic dermatitis in a patient, wherein an IRAK4 degrader is to be administered to a patient, an inflammatory biomarker level in a sample of a patient after a treatment with the IRAK4 degrader is measured, a patient having a reduced level of an inflammatory biomarker after a treatment with the IRAK4 degrader is selected, and an IRAK4 degrader is to be further administered to the patient.

8. The use of any one of claims 3, 6, and 7, wherein the sample is a blood sample or a skin sample.

9. The use of any one of claims 1-8, wherein the inflammatory biomarker is IRAK4 in circulating peripheral blood mononuclear cells (PBMC).

10. The use of claim 9, wherein the circulating PBMC is selected from B cells, CD4–/CD8– (double-negative, DN) T cells, CD4+ T cells, CD8+ T cells, monocytes, and NK cells.

11. The use of any one of claims 1-8, wherein the inflammatory biomarker is a chemokine selected from CCL2, CCL20, CSF3, CXCL1, CXCL2, CXCL6, CXCL8, CXCL11, and CXCL13.

12. The use of any one of claims 1-8, wherein the inflammatory biomarker is selected from GZMB and PRF1.

13. The use of any one of claims 1-8, wherein the inflammatory biomarker is a cytokine selected from IFNG, IL10, IL1B, IL32, IL36G, IL6, IRF7, SOCS3, and TNF.

14. The use of any one of claims 1-8, wherein the inflammatory biomarker is a cytokine receptor selected from IL2RA, IL2RB, and IL18RAP.

15. The use of any one of claims 1-8, wherein the inflammatory biomarker is selected from MYD88, TLR1, TLR2, TLR3, TLR4, TLR6, TLR8, and TLR9.

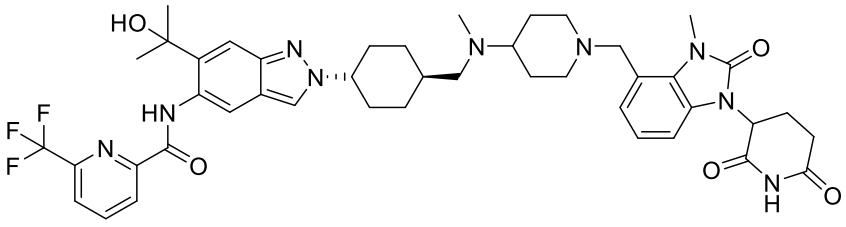
16. The use of any one of claims 1-8, wherein the inflammatory biomarker is selected from NLRP3 and PTGS2.

17. The use of any one of claims 1-8, wherein the inflammatory biomarker is selected from CXCL6, CXCL8, CXCL1, CGAS, SOCS3, CXCL13, and CTSL.

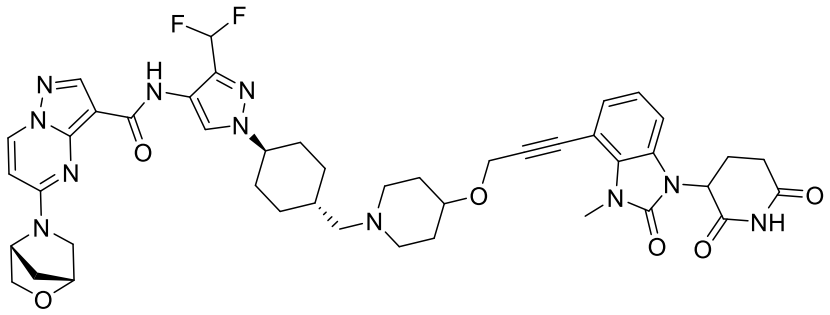
18. The use of any one of claims 1-3, wherein the elevated level of the inflammatory biomarker refers to that the amount or concentration of the inflammatory biomarker in the patient is about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 100%, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, about 10-fold, about 20-fold, about 25-fold, about 50-fold, about 100-fold, or higher, relative to the amount or concentration of the inflammatory biomarker in a healthy person.

18. The use of any one of claims 4-7, wherein the reduced level of the inflammatory biomarker refers to that the amount or concentration of the inflammatory biomarker in the patient is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95%, after a treatment with an IRAK4 degrader.

19. The use of any one of claims 1-18, wherein the IRAK4 degrader is Degrader 1:



, or a pharmaceutically acceptable salt thereof, or Degrader 2:



, or a pharmaceutically acceptable salt thereof.