(De Nardo et al., J. Bio. Chem. 2018, 293(39):15195; Cushing et al., J. Bio. Chem. 2014, 289(15):10865). The NF-kB activation is particularly dependent on the scaffolding function of IRAK4 and is a key driver of cellular proliferation and proinflammatory cytokine and chemokine production mediated by myddosome activation.

[0005] There are numerous cutaneous, rheumatic, and GI autoinflammatory/autoimmune disease indications whose pathogenesis involves IL-1 family cytokines as well as TLR stimulation and where the pleiotropic effects of an IRAK4 degrader on these pathways can provide a significant advantage over current treatment options. Further there are multiple cutaneous indications where there is clinical proof of concept for targeting the IL-1R/TLR pathway but continued high unmet need for more effective therapeutics.

SUMMARY

[0006] It has been found that IRAK4 degrader 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(3-(difluoromethyl)-1-((1r,4R)-4-((4-((3-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)prop-2-yn-1-yl)oxy)piperidin-1-yl)methyl)cyclohexyl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Compound A) formulations and unit dosage forms of the disclosure have certain advantages in treating autoimmune/autoinflammatory diseases.

[0006a] In an aspect of the present disclosure, there is provided a spray-dried formulation comprising Compound A or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable polymer;

wherein Compound A is 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(3-(difluoromethyl)-1-((1r,4R)-4-((4-((3-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)prop-2-yn-1-yl)oxy)piperidin-1-yl)methyl)cyclohexyl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide.

[0006b] In another aspect of the present disclosure, there is provided a unit dosage form comprising the spray-dried formulation disclosed herein.

[0006c] In a further aspect of the present disclosure, there is provided a use of the spray-dried formulation disclosed herein, or the unit dosage form disclosed herein, in the manufacture of a medicament for treating an autoimmune/autoinflammatory disease or a hematological malignancy in a patient.

[0006d] In another aspect of the present disclosure, there is provided a spray-dried formulation disclosed herein, or the unit dosage form disclosed herein, for use in therapy.

[0007] In one example of the present disclosure, there is provided a spray-dried formulation comprising Compound A or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable polymer. In some examples, the spray-dried formulation comprises Compound A free base. In other examples, the spray-dried formulation comprises Compound A HCl. In some instances, the pharmaceutically acceptable polymer is selected from PVP-VA, HPMC, HPMCP-55, HPMCAS-M, TPGS, HPMCAS-L, and MCC, preferably HPMCAS-M. The spray-dried formulation may include about 20-40% wt/wt Compound A, or a pharmaceutically acceptable salt thereof and about 60-80% wt/wt of pharmaceutically acceptable polymer. In certain examples, the spray-dried formulation comprises 25:75 (% wt/wt) Compound A free base : HPMCAS-M.

[0008] In one example of the present disclosure, there is provided a unit dosage form comprising the spray-dried formulation disclosed herein. In some examples, the spray-dried formulation is about 45-55 % wt/wt of the unit dosage form. In other examples, the unit dosage form

further comprises a filler, wherein the filler is selected from mannitol, microcrystalline cellulose, or a mixture thereof. In certain examples, the unit dosage form further comprises a glidant, wherein the glidant is colloidal silicon dioxide. In certain examples, the unit dosage form further comprises a disintegrant, wherein the disintegrant is croscarmellose sodium. In certain examples, the unit dosage form further comprises a solubility enhancer, wherein the solubility enhancer is hydroxypropyl-beta-cyclodextrin (HPβCD). In certain examples, the unit dosage form further comprises a lubricant, wherein the lubricant is stearyl fumarate sodium.

[0009] In another example of the present compositions and methods, the unit dosage form comprises 10-500 mg of Compound A or a pharmaceutically acceptable salt thereof, for example, the unit dosage form comprises 25 mg or 100 mg of Compound A or a pharmaceutically acceptable salt thereof.

[0010] In further examples of the present disclosure, there is provided a method for treating an autoimmune/autoinflammatory disease or a hematological malignancy in a patient, comprising administering (e.g., orally) to the patient a therapeutically effect amount of the spray-dried formulation or the unit dosage form described herein In some examples, the autoimmune/autoinflammatory disease is selected from a cutaneous, rheumatic, and gastrointestinal autoimmune/autoinflammatory disease. In some examples, the autoimmune/autoinflammatory disease is a cutaneous autoimmune/autoinflammatory disease selected from atopic dermatitis (AD) and hidradenitis suppurativa (HS).

[0011] In some examples, the method comprises administering (e.g., orally) up to about 1600 mg of Compound A or a pharmaceutically acceptable salt thereof to a patient, such as up to about 1400 mg (e.g., per day). In some examples, the method comprises administering about 25-1400 mg (for example, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 800 mg, about 1000 mg, about 1200 mg, or about 1400 mg) of compound A or a pharmaceutically acceptable salt thereof to a patient (e.g., per day).

[0012] These and other examples of this disclosure will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain background information and procedures and are each hereby incorporated by reference in their entirety.

CLAIMS

1. A spray-dried formulation comprising Compound A or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable polymer;

wherein Compound A is 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(3-(difluoromethyl)-1-((1r,4R)-4-((4-((3-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)prop-2-yn-1-yl)oxy)piperidin-1-yl)methyl)cyclohexyl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide.

2. The spray-dried formulation of claim 1, comprising Compound A free base.

3. The spray-dried formulation of claim 1, comprising Compound A HCl.

4. The spray-dried formulation of any one of claims 1-3, wherein the pharmaceutically acceptable polymer is selected from PVP-VA, HPMC, HPMCP-55, HPMCAS-M, TPGS, HPMCAS-L, and MCC.

5. The spray-dried formulation of any one of claims 1-4, comprising about 20-40% wt/wt Compound A, or a pharmaceutically acceptable salt thereof.

6. The spray-dried formulation of any one of claims 1-5, comprising about 60-80% wt/wt of pharmaceutically acceptable polymer.

7. The spray-dried formulation of any one of claims 1-6, comprising 25:75 (% wt/wt) Compound A free base : HPMCAS-M.

8. A unit dosage form comprising the spray-dried formulation of any one of claims 1-7.

9. The unit dosage form of claim 8, wherein the spray-dried formulation is about 45-55 % wt/wt of the unit dosage form.

10. The unit dosage form of claim 8 or 9, further comprising a filler, wherein the filler is selected from mannitol, microcrystalline cellulose, or mixtures thereof.

11. The unit dosage form of any one of claims 8-10, further comprising a glidant, wherein the glidant is colloidal silicon dioxide.

12. The unit dosage form of any one of claims 8-11, further comprising a disintegrant, wherein the disintegrant is croscarmellose sodium.

13. The unit dosage form of any one of claims 8-12, further comprising a solubility enhancer, wherein the solubility enhancer is hydroxypropyl-beta-cyclodextrin (HPβCD).

14. The unit dosage form of any one of claims 8-13, further comprising a lubricant, wherein the lubricant is stearyl fumarate sodium.

15. The unit dosage form of any one of claims 8-14, comprising about 10-500 mg of Compound A or a pharmaceutically acceptable salt thereof.

16. The unit dosage form of any one of claims 8-15, comprising about 25 mg or about 100 mg of Compound A or a pharmaceutically acceptable salt thereof.

17. The unit dosage form of any one of claims 8-16, which is a tablet of about 208 mg, comprising:

i) a tablet core of about 200 mg, comprising

intragranularly: about 25 mg Compound A free base, about 75 mg HPMCAS-M, about 15 mg mannitol, about 15 mg microcrystalline cellulose, about 40 mg hydroxypropyl-beta-cyclodextrin, about 19.34 mg croscarmellose sodium, about 2 mg stearyl fumarate sodium, and about 2 mg colloidal silicon dioxide; and

extragranularly: about 4.66 mg croscarmellose sodium, about 1 mg stearyl fumarate sodium, and about 1 mg colloidal silicon dioxide; and

ii) Opadry® II Yellow Film Coating of about 8 mg, comprising about 3.2 mg Polyvinyl Alcohol, 1.616 mg Macrogol/PEG, 1.872 mg Titanium Dioxide, 0.128 mg Iron Oxide, and 1.184 mg Talc.

18. The unit dosage form of any one of claims 8-16, which is a tablet of about 824 mg, comprising:

i) a tablet core of about 800 mg, comprising
intragranularly: about 100 mg Compound A free base, about 300 mg HPMCAS-M, about 45 mg mannitol, about 45 mg microcrystalline cellulose, about 160 mg hydroxypropyl-beta-cyclodextrin, about 77.36 mg croscarmellose sodium, about 8 mg stearyl fumarate sodium, and about 8 mg colloidal silicon dioxide; and
extragranularly: about 18.64 mg croscarmellose sodium, about 4 mg stearyl fumarate sodium, and about 4 mg colloidal silicon dioxide; and

ii) Opadry® II Yellow Film Coating of about 24 mg, comprising about 9.6 mg Polyvinyl Alcohol, 4.848 mg Macrogol/PEG, 5.616 mg Titanium Dioxide, 0.384 mg Iron Oxide, and 3.552 mg Talc.

19. Use of the spray-dried formulation of any one of claims 1-7, or the unit dosage form of any one of claims 8-18, in the manufacture of a medicament for treating an autoimmune/autoinflammatory disease or a hematological malignancy in a patient.

20. The use of claim 19, wherein the autoimmune/autoinflammatory disease is selected from a cutaneous, rheumatic, and gastrointestinal autoimmune/autoinflammatory disease.

21. The use of claim 20, wherein the autoimmune/autoinflammatory disease is a cutaneous autoimmune/autoinflammatory disease selected from atopic dermatitis (AD)
and hidradenitis suppurativa (HS).

22. The use of any one of claim 18-21, wherein up to about 1600 mg of Compound A or a pharmaceutically acceptable salt thereof is to be administered to the patient.

23. The use of any one of claims 19-22, wherein up to about 1400 mg of Compound A or a pharmaceutically acceptable salt thereof is to be administered to the patient.

24. The use of any one of claims 19-23, wherein about 25-1400 mg (for example, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 500 mg, about 1000 mg, or about 1400 mg) of compound A or a pharmaceutically acceptable salt thereof is to be administered to the patient per day.

25. The use of any one of claims 19-23, wherein up to 100 mg, up to 150 mg, or up to 200 mg of Compound A, or a pharmaceutically acceptable salt thereof is to be administered to the patient.

26. The spray-dried formulation of any one of claims 1-7, or the unit dosage form of any one of claims 8-18, for use in therapy.