entities having a relatively low oral bioavailability (F) and/or by employing formulations that are chemically and/or structurally predisposed to minimize systemic exposure of the chemical entity (e.g., the formulations can be designed to release the chemical entity at a pH that is present in the target area of the GI tract).

In view of the foregoing advantages and features delineated above, the chemical entities, methods, and compositions described herein are also expected to be functional in diverse patient populations and/or less sensitive to blocks in cell death mechanisms. Further, the ability to utilize traditional small molecules, such as niclosamide, can help reduce cost and facilitate patient administration.

In some embodiments, the methods and compositions described herein are suitable for use in combination therapy with various other therapeutic regimens (e.g., chemotherapy and/or radiation). In certain embodiments, the chemical entities and methods described herein can be used to treat side effects produced by such therapeutic regimens, e.g., inflammatory bowel diseases induced by chemotherapeutic immunomodulators, e.g., checkpoint inhibitors, which in some cases can be prohibitively severe. Additionally, the chemical entities, methods, and compositions described herein are also expected to be useful in certain treatment-resistant patient populations, e.g., one that is nonresponsive or resistant to treatment an anti-TNFalpha therapy (e.g., Humira, Enbrel, Remicade).

In one aspect, there is provided a solid pharmaceutical composition, which comprises: an inner phase which is a wet granulated solid preparation comprising niclosamide, or a pharmaceutically acceptable salt thereof; one or more disintegrants; one or more diluents; and one or more binders; and an external phase comprising one or more lubricants.

In another aspect, there is provided a solid pharmaceutical composition, which comprises: an inner phase which is a wet granulated solid preparation comprising niclosamide, or a pharmaceutically acceptable salt thereof; crospovidone; lactose monohydrate; and povidone; and an external phase comprising magnesium stearate and talc.

In another aspect, there is provided an enema preparation comprising a separately contained first component and a separately contained second component, wherein:

(i) the first component comprises a solid pharmaceutical composition, which comprises: an inner phase which is a wet granulated solid preparation comprising niclosamide, or a pharmaceutically acceptable salt thereof; one or more disintegrants; one or more diluents; and one or more binders; an external phase comprising one or more lubricants.; and

(ii) the second component comprises one or more liquids and optionally one or more other pharmaceutically acceptable excipients together forming a liquid carrier.

In another aspect, there is provided an enema formulation comprising water; methyl cellulose; povidone; methylparaben; propylparaben; sodium dihydrogen phospahate dehydrate; disodium phosphate dodecahydrate; crospovidone; lactose monohydrate; magnesium stearate; talc; and niclosamide, or a pharmaceutically acceptable salt thereof.

Disclosed are methods for inducing cell death of one or more T cells (e.g., in the digestive and/or gastrointestinal tract (GI), skin, eyes, or joints), of a subject are provided. The methods include contacting the one or more T cells with an effective amount of a chemical entity (e.g., a compound exhibiting activity as a mitochondrial uncoupling agent or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof; e.g., a compound, such as niclosamide or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof; e.g., a compound, such as a niclosamide analog, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof) as defined anywhere herein.

Disclosed are methods for treating a subject having a condition associated with unregulated (abnormal, elevated) recruitment and/or retention of one or more T cells (e.g., at the digestive and/or gastrointestinal tract (GI), skin, eyes, or joints) of the subject are

provided. The methods include contacting the one or more T cells with an effective amount of a chemical entity (e.g., a compound exhibiting activity as a mitochondrial uncoupling agent or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof; e.g., a compound, such as niclosamide or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof; e.g., a compound, such as a niclosamide analog, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof) as defined anywhere herein.

Disclosed are methods for treating a subject having a condition associated with unregulated (abnormal, elevated) activation of one or more T cells (e.g., in the digestive and/or gastrointestinal tract (GI), skin, eyes, or joints) of the subject are provided. The methods include contacting the one or more activated T cells with an effective amount of a cocrystal comprising **(i)** a mitochondrial uncoupling agent or a pharmaceutically acceptable salt and/or hydrate thereof; and **(ii)** one or more pharmaceutically acceptable coformers as defined anywhere herein.

Disclosed are methods for treating a condition (or one or more symptoms thereof) characterized by an abnormal inflammatory response in a subject in need thereof are provided (e.g., an autoimmune disorder, e.g., an inflammatory bowel disease). The methods include administering to the subject an effective amount of a chemical entity (e.g., a compound exhibiting activity as a mitochondrial uncoupling agent or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof; e.g., a compound, such as niclosamide or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof; e.g., a compound, such as a niclosamide analog, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof) as defined anywhere herein.

Disclosed are methods for treating a condition (or one or more symptoms thereof) characterized by an abnormal inflammatory response in a subject in need thereof are provided (e.g., an autoimmune disorder, e.g., an inflammatory bowel disease). The methods include topically and locally administering to the subject an effective amount of a chemical entity (e.g., a compound exhibiting activity as a mitochondrial uncoupling agent or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof; e.g., a compound, such as niclosamide or a pharmaceutically acceptable salt and/or hydrate and/or

cocrystal thereof; e.g., a compound, such as a niclosamide analog, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof) as defined anywhere herein.

Disclosed are methods for treating autoimmune colitis (or one or more symptoms thereof) in a subject are provided. The methods include topically and locally administering to the subject an effective amount of a chemical entity (e.g., a compound exhibiting activity as a mitochondrial uncoupling agent or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof; e.g., a compound, such as niclosamide or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof; e.g., a compound, such as a niclosamide analog, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof) as defined anywhere herein.

In another aspect, there is provided use of the enema formulation as described herein in the manufacture of a medicament for treating iatrogenic autoimmune colitis in a subject.

Disclosed are methods for treating a condition (or one or more symptoms thereof) selected from the group consisting of celiac disease, irritable bowel syndrome, mucositis, uveitis, collagenous colitis, lymphocytic colitis, microscopic colitis, radiation enteritis, rheumatoid arthritis, lupus, scleroderma, psoriasis, cutaneous T-cell lymphoma, acute graft vs. host disease and chronic graft vs. host disease in a subject are provided. The methods include topically and locally administering to the subject an effective amount of a chemical entity (e.g., a compound exhibiting activity as a mitochondrial uncoupling agent or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof; e.g., a compound, such as niclosamide or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof; e.g., a compound, such as a niclosamide analog, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof) as defined anywhere herein.

Disclosed is a cocrystal, which includes: **(i)** a mitochondrial uncoupling agent or a pharmaceutically acceptable salt and/or hydrate thereof; and **(ii)** one or more pharmaceutically acceptable coformers.

Definitions

To facilitate understanding of the disclosure set forth herein, a number of terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all technical

WHAT IS CLAIMED IS:

1. A solid pharmaceutical composition, which comprises:

an inner phase which is a wet granulated solid preparation comprising niclosamide, or a pharmaceutically acceptable salt thereof; one or more disintegrants; one or more diluents; and one or more binders; and

an external phase comprising one or more lubricants.

2. The composition of claim 1, wherein the composition comprises from about 40 weight percent to about 80 weight percent of niclosamide, or a pharmaceutically acceptable salt thereof.

3. The composition of claim 1, wherein the composition comprises from about 0.5 weight percent to about 5 weight percent of the one or more disintegrants.

4. The composition of claim 1, wherein each of the one or more disintegrants is independently selected from the group consisting of: carmellose calcium, low substituted hydroxypropyl cellulose (L-HPC), carmellose, croscarmellose sodium, partially pregelatinized starch, dry starch, carboxymethyl starch sodium, crospovidone, polysorbate 80 (polyoxyethylenesorbitan oleate), starch, sodium starch glycolate, hydroxypropyl cellulose pregelatinized starch, clays, cellulose, alginine, gums, and cross-linked PVP.

5. The composition of claim 1, wherein the one or more disintegrants is crospovidone.

6. The composition of claim 1, wherein the composition comprises from about 0.5 weight percent to about 5 weight percent of the one or more binders.

7. The composition of claim 1, wherein each of the one or more binders is independently selected from the group consisting of: starch, pregelatinized starch, gelatin, sugars (including sucrose, glucose, dxtrose, lactose and sorbitol), polyethylene glycol, waxes, natural and synthetic gums such as acacia tragacanth, sodium alginate cellulose, including hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, and veegum, and synthetic polymers such as acrylic acid and methacrylic acid copolymers, methacrylic acid copolymers, methyl methacrylate copolymers, aminoalkyl methacrylate copolymers, polyacrylic acid/polymethacrylic acid and polyvinylpyrrolidone (povidone).

8. The composition of claim 1, wherein the one or more binders is povidone.

9. The composition of claim 1, wherein the composition comprises from about 10 weight percent to about 50 weight percent of the one or more diluents.

10. The composition of claim 1, wherein each of the one or more diluents is independently selected from the group consisting of: dicalcium phosphate dihydrate, calcium sulfate, lactose (e.g., lactose monohydrate), sucrose, mannitol, sorbitol, cellulose, microcrystalline cellulose, kaolin, sodium chloride, dry starch, hydrolyzed starches, pregelatinized starch, silicone dioxide, titanium oxide, magnesium aluminum silicate and powdered sugar.

11. The composition of claim 1, wherein each of the one or more diluents is lactose monohydrate.

12. The composition of claim 1, wherein the composition comprises from about 0.05 weight percent to about 5 weight percent of the one or more glidants and/or lubricants.

13. The composition of claim 1, wherein each of the one or more glidants and/or lubricants is independently selected from the group consisting of: talc, magnesium stearate, calcium stearate, colloidal silica, stearic acid, aqueous silicon dioxide, synthetic magnesium silicate, fine granulated silicon oxide, starch, sodium laurylsulfate, boric acid, magnesium oxide, waxes, hydrogenated oil, polyethylene glycol, sodium benzoate, stearic acid glycerol behenate, polyethylene glycol, and mineral oil.

14. The composition of claim 1, wherein each of the one or more glidants and/or lubricants is independently selected from the group consisting of: magnesium stearate and talc.

15. A solid pharmaceutical composition, which comprises:

an inner phase which is a wet granulated solid preparation comprising niclosamide, or a pharmaceutically acceptable salt thereof; crospovidone; lactose monohydrate; and povidone; and

an external phase comprising magnesium stearate and talc.

16. The composition of claim 15, wherein the composition comprises from about 40 weight percent to about 80 weight percent of niclosamide, or a pharmaceutically acceptable salt thereof.

17. The composition of claim 15, wherein the composition comprises from about about 55 weight percent to about 70 weight percent of niclosamide, or a pharmaceutically acceptable salt thereof.

18. The composition of claim 15, wherein the composition comprises from about 0.5 weight percent to about 5 weight percent of crospovidone.

19. The composition of claim 15, wherein the composition comprises from about 1 weight percent to about 3 weight percent of crospovidone.

20. The composition of claim 15, wherein the composition comprises from about 0.5 weight percent to about 5 weight percent of povidone.

21. The composition of claim 15, wherein the composition comprises from about 1.5 weight percent to about 4.5 weight percent of povidone.

22. The composition of claim 15, wherein the composition comprises from about 10 weight percent to about 50 weight percent of lactose monohydrate.

23. The composition of claim 15, wherein the composition comprises from about 20 weight percent to about 40 weight percent of lactose monohydrate.

24. The composition of claim 15, wherein the composition comprises from about 0.5 weight percent to about 5 weight percent of talc.

25. The composition of claim 15, wherein the composition comprises from about 1 weight percent to about 3 weight percent of talc.

26. The composition of claim 15, wherein the composition comprises from about 0.05 weight percent to about 1 weight percent of magnesium stearate.

27. The composition of claim 15, wherein the composition comprises from about 0.1 weight percent to about 1 weight percent of magnesium stearate.

28. The composition of claim 15, wherein the composition comprises:

from about 40 weight percent to about 80 weight percent of niclosamide, or a pharmaceutically acceptable salt thereof;

from about 0.5 weight percent to about 5 weight percent of crospovidone;

from about 0.5 weight percent to about 5 weight percent of povidone;

from about 10 weight percent to about 50 weight percent of lactose monohydrate;

from about 0.5 weight percent to about 5 weight percent of talc; and

from about 0.05 weight percent to about 1 weight percent of magnesium stearate.

29. The composition of claim 15, wherein the composition comprises:

from about 50 weight percent to about 70 weight percent of niclosamide, or a pharmaceutically acceptable salt thereof;

from about 0.5 weight percent to about 3 weight percent of crospovidone;

from about 1.5 weight percent to about 4.5 weight percent of povidone;

from about 20 weight percent to about 40 weight percent of lactose monohydrate;

from about 0.5 weight percent to about 3 weight percent of talc; and

from about 0.1 weight percent to about 1 weight percent of magnesium stearate.

30. The composition of claim 15, wherein the composition comprises:

from about 60 weight percent to about 65 weight percent of niclosamide, or a pharmaceutically acceptable salt thereof;

from about 1 weight percent to about 3 weight percent of crospovidone;

from about 2 weight percent to about 3.5 weight percent of povidone;

from about 25 weight percent to about 35 weight percent of lactose monohydrate;

from about 1.5 weight percent to about 2.5 weight percent of talc; and

from about 0.1 weight percent to about 0.5 weight percent of magnesium stearate.

31. The composition of claim 15, wherein the composition comprises:

Ingredient	**Weight Percent**
niclosamide	about 62.1 weight percent)
Crospovidone	about 1.93 weight percent
lactose monohydrate	about 31.03 weight percent
Povidone	about 2.76 weight percent
talc	about 1.93 weight percent

Magnesium stearate	about 0.27 weight percent

32. An enema preparation comprising a separately contained first component and a separately contained second component, wherein:

(i) the first component comprises a solid pharmaceutical composition, which comprises:

an inner phase which is a wet granulated solid preparation comprising niclosamide, or a pharmaceutically acceptable salt thereof; one or more disintegrants; one or more diluents; and one or more binders;

an external phase comprising one or more lubricants.; and

(ii) the second component comprises one or more liquids and optionally one or more other pharmaceutically acceptable excipients together forming a liquid carrier.

33. The enema preparation of claim 32, wherein component (ii) comprises water and one or more of the following excipients:

(a') one or more thickeners, viscosity enhancing agents, binders, and/or mucoadhesive agents;

(b') one or more preservatives; and

(c') one or more buffers.

34. The enema preparation of claim 32, wherein component (ii) comprises water and one or more of the following excipients:

(a'') a first thickener, viscosity enhancing agent, binder, and/or mucoadhesive agent;

(a''') a second thickener, viscosity enhancing agent, binder, and/or mucoadhesive agent;

(b'') a first preservative;

(b'') a second preservative;

(c'') a first buffer; and(c''') a second buffer.

35. The enema preparation of claim 34, wherein component (**ii**) comprises: from about 0.05 weight percent to about 5 weight percent of (**a''**); from about 0.05 weight percent to about 5 weight percent of (**a'''**); from about 0.005 weight percent to about 0.1 weight percent of (**b''**); from about 0.05 weight percent to about 1 weight percent of (**b'''**); from about 0.05 weight percent to about 1 weight percent of (**c''**); and from about 0.005 weight percent to about 0.5 weight percent of (**c'''**); and up to 100% of water.

36. The enema preparation of claim 34, wherein (**a''**) and (**a'''**) are independently selected from the group consisting of: a cellulose or cellulose ester or ether or derivative or salt thereof and a polyvinyl polymer; (**b''**) and (**b''**) are each an independently selected paraben; and (**c''**) and (**c'''**) are each an independently selected phosphate buffer system.

37. The enema preparation of claim 32, wherein component (**ii**) comprises water; methyl cellulose; Povidone; propyl 4-hydroxybenzoate; methyl 4-hydroxybenzoate; disodium phosphate dodecahydrate; and sodium dihydrogen phospahate dehydrate.

38. The enema preparation of claim 37, wherein component (**ii**) comprises: from about 0.05 weight percent to about 5 weight percent of methyl cellulose; from about 0.05 weight percent to about 5 weight percent of Povidone; from about 0.005 weight percent to about 0.1 weight percent of propyl 4-hydroxybenzoate; from about 0.05 weight percent to about 1 weight percent of methyl 4-hydroxybenzoate; from about 0.05 weight percent to about 1 weight percent of disodium phosphate dodecahydrate; from about 0.005 weight percent to about 0.5 weight percent of sodium dihydrogen phospahate dihydrate; and up to 100% of water.

39. The enema preparation of claim 37, wherein component (**ii**) comprises: from about 0.1 weight percent to about 3 weight percent of methyl cellulose; from about 0.1 weight percent to about 2 weight percent of Povidone; from about 0.005 weight percent to about 0.05 weight percent of propyl 4-hydroxybenzoate; from about 0.05 weight percent to about 0.5 weight percent of methyl 4-hydroxybenzoate; from about 0.05

weight percent to about 0.5 weight percent of disodium phosphate dodecahydrate; from about 0.005 weight percent to about 0.3 weight percent of sodium dihydrogen phospahate dihydrate; and up to 100% of water.

40. The enema preparation of claim 37, wherein component **(ii)** comprises:

Ingredient	Weight Percent
methyl cellulose (Methocel A15C premium)	about 1.4 weight percent
Povidone (Kollidon K30)	about 1.0 weight percent
propyl 4-hydroxybenzoate	about 0.02 weight percent
methyl 4-hydroxybenzoate	about 0.20 weight percent
disodium phosphate dodecahydrate	about 0.15 weight percent
sodium dihydrogen phospahate dihydrate	about 0.15 weight percent
water	up to 100%

41. The enema preparation of claim 32, wherein the first component comprises the solid pharmaceutical composition as claimed in claim 15.

42. The enema preparation of claim 32, wherein the first component comprises the solid pharmaceutical composition as claimed in claim 28.

43. The enema preparation of claim 32, wherein the first component comprises the solid pharmaceutical composition as claimed in claim 29.

44. The enema preparation of claim 32, wherein the first component comprises the solid pharmaceutical composition as claimed in claim 30.

45. An enema formulation comprising water; methyl cellulose; povidone; methylparaben; propylparaben; sodium dihydrogen phospahate dehydrate; disodium phosphate dodecahydrate; crospovidone; lactose monohydrate; magnesium stearate; talc; and niclosamide, or a pharmaceutically acceptable salt thereof.

46. Use of the enema formulation as claimed in claim 45 in the manufacture of a medicament for treating iatrogenic autoimmune colitis in a subject.

47. The use of claim 46, wherein the iatrogenic autoimmune colitis is selected from the group consisting of colitis induced by one or more chemotherapeutic agents, colitis induced by treatment with adoptive cell therapy, and colitis associated by one or more alloimmune diseases (such as acute or chronic graft-vs-host disease).

48. The use of claim 47 wherein the iatrogenic autoimmune colitis is colitis induced by one or more chemotherapeutic agents.

49. The use of claim 48, wherein at least one of the one or more chemotherapeutic agents is a chemotherapeutic immunomodulator.

50. The use of claim 49, wherein the chemotherapeutic immunomodulator is an immune checkpoint inhibitor.

51. The use of claim 50, wherein the immune checkpoint inhibitor targets an immune checkpoint receptor selected from the group consisting of CTLA-4, PD-1, PD-L1, PD-1 – PD-L1, PD-1 – PD-L2, interleukin-2 (IL-2), indoleamine 2,3-dioxygenase (IDO), IL-10, transforming growth factor-β (TGFβ), T cell immunoglobulin and mucin 3 (TIM3 or HAVCR2), Galectin 9 – TIM3, Phosphatidylserine – TIM3, lymphocyte activation gene 3 protein (LAG3), MHC class II – LAG3, 4-1BB–4-1BB ligand, OX40–OX40 ligand, GITR, GITR ligand – GITR, CD27, CD70-CD27, TNFRSF25, TNFRSF25–TL1A, CD40L, CD40–CD40 ligand, HVEM–LIGHT–LTA, HVEM, HVEM

– BTLA, HVEM – CD160, HVEM – LIGHT, HVEM–BTLA–CD160, CD80, CD80 – PDL-1, PDL2 – CD80, CD244, CD48 – CD244, CD244, ICOS, ICOS–ICOS ligand, B7-H3, B7-H4, VISTA, TMIGD2, HHLA2–TMIGD2, Butyrophilins, including BTNL2, Siglec family, TIGIT and PVR family members, KIRs, ILTs and LIRs, NKG2D and NKG2A, MICA and MICB, CD244, CD28, CD86 – CD28, CD86 – CTLA, CD80 – CD28, CD39, CD73 Adenosine–CD39–CD73, CXCR4–CXCL12, Phosphatidylserine, TIM3, Phosphatidylserine – TIM3, SIRPA–CD47, VEGF, Neuropilin, CD160, CD30, and CD155.

52. The use of claim 51, wherein the immune checkpoint inhibitor is selected from the group consisting of: Urelumab, PF-05082566, MEDI6469, TRX518, Varlilumab, CP-870893, Pembrolizumab (PD1), Nivolumab (PD1), Atezolizumab (formerly MPDL3280A) (PDL1), MEDI4736 (PD-L1), Avelumab (PD-L1), PDR001 (PD1), BMS-986016, MGA271, Lirilumab, IPH2201, Emactuzumab, INCB024360, Galunisertib, Ulocuplumab, BKT140, Bavituximab, CC-90002, Bevacizumab, and MNRP1685A, and MGA271.

53. The use of claim 51, wherein the immune checkpoint inhibitor targets CTLA-4.

54. The use of claim 53, wherein the immune checkpoint inhibitor is an antibody.

55. The use of claim 54, wherein the antibody is ipilimumab or tremelimumab.

56. The use of claim 51, wherein the immune checkpoint inhibitor targets PD1 or PD-L1.

57. The use of claim 56, wherein the immune checkpoint inhibitor is selected from nivolumab, lambroizumab, and BMS-936559.

58. The use of claim 46, wherein the subject is a human.

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