combination thereof; e.g., a compound, such as a niclosamide analog, or a pharmaceutically acceptable salt, and/or hydrate, and/or drug combination, and/or cocrystal thereof) that are useful, e.g., for treating one or more symptoms of a pathology characterized by an abnormal inflammatory response (e.g., inflammatory bowel diseases) in a subject (e.g., a human). This disclosure also features compositions as well as other methods of using and making the same.

This disclosure is based, in part, on the finding that niclosamide kills pathogenic T cells isolated from IBD patients and is effective in murine models of IBD. While not wishing to be bound by theory, it is believed that the chemical entities described herein (e.g., niclosamide or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof) uncouple mitochondrial respiration from oxidative phosphorylation in one or more T cells, thereby disrupting the mitochondrial energy cycle in the one or more T cells and inducing cell death of the one or more T cells (e.g., activated T cells). It has been surprisingly found that the chemical entities described herein selectively target and kill T cells associated with pathologies characterized by an abnormal inflammatory response (e.g., pathogenic T cells in the intestinal mucosa).

The chemical entities, methods, and compositions described herein not only provide treatment options that are highly efficient and effective at killing T cells, but also ones that address the toxicity, cost, and convenience issues associated with some standard methods of treatment.

In certain examples, the methods described herein can be carried out using niclosamide, a small molecule that has an established and good safety profile and is an FDA approved anthelmintic drug.

Additionally, the chemical entities described herein can be readily and efficiently administered locally, such that the resultant systemic bioavailability of the administered chemical entity is relatively low, and the resultant local bioavailability of the administered chemical entity is relatively high. Local (non-systemic) administration of the chemical entity at a desired area of treatment (e.g., gastrointestinal tract) significantly reduces the likelihood that a patient will experience systemic toxicities associated with some current standards of care. The foregoing can be achieved, for example, by selecting chemical

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 examples, 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 examples, 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: (i) an internal 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 (ii) an external phase comprising one or more glidants and/or 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 glidants and/or 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

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 preparation as described herein in the manufacture of a medicament for treating inflammatory bowel disease 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:

(i) an internal 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

(ii) an external phase comprising one or more glidants and/or one or more lubricants.

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

3. The composition of claim 1, wherein the composition comprises from 0.5 weight percent to 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 0.5 weight percent to 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 10 weight percent to 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 0.05 weight percent to 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 40 weight percent to 80 weight percent of niclosamide, or a pharmaceutically acceptable salt thereof.

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

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

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

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

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

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

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

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

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

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

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

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

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

from 0.5 weight percent to 5 weight percent of crospovidone;

from 0.5 weight percent to 5 weight percent of povidone;

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

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

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

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

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

from 0.5 weight percent to 3 weight percent of crospovidone;

from 1.5 weight percent to 4.5 weight percent of povidone;

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

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

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

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

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

from 1 weight percent to 3 weight percent of crospovidone;

from 2 weight percent to 3.5 weight percent of povidone;

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

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

from 0.1 weight percent to 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 glidants and/or 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 0.05 weight percent to 5 weight percent of (**a''**); from 0.05 weight percent to 5 weight percent of (**a'''**); from 0.005 weight percent to 0.1 weight percent of (**b''**); from 0.05 weight percent to 1 weight percent of (**b'''**); from 0.05 weight percent to 1 weight percent of (**c''**); and from 0.005 weight percent to 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 0.05 weight percent to 5 weight percent of methyl cellulose; from 0.05 weight percent to 5 weight percent of Povidone; from 0.005 weight percent to 0.1 weight percent of propyl 4-hydroxybenzoate; from 0.05 weight percent to 1 weight percent of methyl 4-hydroxybenzoate; from 0.05 weight percent to 1 weight percent of disodium phosphate dodecahydrate; from 0.005 weight percent to 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 0.1 weight percent to 3 weight percent of methyl cellulose; from 0.1 weight percent to 2 weight percent of Povidone; from 0.005 weight percent to 0.05 weight percent of propyl 4-hydroxybenzoate; from 0.05 weight percent to 0.5 weight percent of methyl 4-hydroxybenzoate; from 0.05

weight percent to 0.5 weight percent of disodium phosphate dodecahydrate; from 0.005 weight percent to 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 preparation as claimed in claim 32 in the manufacture of a medicament for treating inflammatory bowel disease in a subject.

47. The use of claim 46, wherein the inflammatory bowel disease is ulcerative colitis.

48. The use of claim 47 wherein the inflammatory bowel disease is Crohn's disease.

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