cases, a genetic mutation, such as mutation in the Jak2 protein, may be present in stem cells from a patient with an MPN.

[005] MPNs may lead to increases in certain blood cells, abnormal blood cells, and enlargement of the spleen (splenomegaly). MPNs may damage the bone marrow and result in bone marrow fibrosis (myelofibrosis or MF). Anemia, fatigue, and weakness may occur due to changes in blood cell counts in MPN. Thrombohemorrhagic complications, such as thrombosis, are also a risk of MPN. Progression of MPNs can lead to development of further conditions, such as acute myeloid leukemia.

[006] The present application describes improved methods for treating MPNs with a diphtheria toxin-human interleukin-3 conjugate (DT-IL3) and one or more Jak inhibitors and/or one or more hypomethylating agents.

SUMMARY

[007] In accordance with the description, this application describes methods of treatment with a DT-IL3 and (a) one or more Jak inhibitors and/or (b) one or more hypomethylating agents.

[008] In one example, the present application provides a method for treating or inhibiting a myeloproliferative neoplasm (MPN) in a subject in need thereof, comprising administering to the subject a diphtheria toxin-human interleukin-3 conjugate (DT-IL3) and a) one or more Jak inhibitors and/or b) one or more hypomethylating agents.

[008a] In one aspect, the present disclosure refers to the use of a diphtheria toxin-human interleukin-3 conjugate (DT-IL3) in the manufacture of a medicament for use in combinatorial therapy for treating or inhibiting a myeloproliferative neoplasm (MPN) in a human subject in need thereof, wherein said medicament is to be administered in combination with

a. one or more Jak inhibitors selected from ruxolitinib and pacritinib; and/or

b. one or more hypomethylating agents selected from azacitidine and decitabine,

wherein the DT-IL3 is a chemical conjugate and/or a recombinantly expressed protein.

[009] In some examples, the DT-IL3 is administered at a dose of 1 p[μg/kg or greater, 2 μg/kg or greater, or 4 μg/kg or greater. In some examples, the DT-IL3 is administered at a dose of 2 μg/kg to 20 μg/kg or 9 μg/kg to 20 μg/kg. In some examples, the DT-IL3 is administered at a dose of 4 μg/kg to 12 μg/kg or 9 μg/kg to 12 μg/kg. In some examples, the DT-IL3 is administered at a dose of 5, 7, 9, or 12 μg/kg. In some examples, the DT-IL3 is administered at a dose that is the maximum tolerated dose.

What is Claimed is:

1. Use of a diphtheria toxin-human interleukin-3 conjugate (DT-IL3) in the manufacture of a medicament for use in combinatorial therapy for treating or inhibiting a myeloproliferative neoplasm (MPN) in a human subject in need thereof, wherein said medicament is to be administered in combination with

   a. one or more Jak inhibitors selected from ruxolitinib and pacritinib; and/or

   b. one or more hypomethylating agents selected from azacitidine and decitabine,

wherein the DT-IL3 is a chemical conjugate and/or a recombinantly expressed protein.

2. The use of claim 1, wherein the medicament comprises a dose of DT-IL3 of:

   a. 1 μg/kg or greater, 2 μg/kg or greater, or 4 μg/kg or greater;

   b. 2 μg/kg to 20 μg/kg or 9 μg/kg to 20 μg/kg;

   c. 4 μg/kg to 12 μg/kg, or 9 μg/kg to 12 μg/kg;

   d. 5 μg/kg, 7 μg/kg, 9 μg/kg, or 12 μg/kg; or

   e. the maximum tolerated dose.

3. The use of claim 1 or claim 2, wherein the DT-IL3 and the one or more Jak inhibitors and/or hypomethylating agents are indicated for administration:

   a. at least once a week, at least two times a week, or at least three times a week;

   b. over a period of one week or more, or over a period of two weeks or more;

   c. for at least 3 consecutive days; and/or

d. in multiple treatment cycles.

4. The use of claim 3, wherein the treatment cycles are at least 1 week apart, at least 2 weeks apart, at least 3 weeks apart, at least 4 weeks apart, at least 5 weeks apart, or a combination thereof.

5. The use of claim 3 or claim 4, wherein:

a. the DT-IL3 is indicated for administration for at least 3 consecutive days every 21 days for four cycles, followed by every 28 days for 3 cycles, and then every 42 days;

b. the one or more Jak inhibitors are indicated for administration for at least once daily, or at least twice daily; and/or

c. the one or more hypomethylating agents are indicated for administration for at least the first 3 days, at least the first 4 days, at least the first 5 days, at least the first 6 days, or at least the first 7 days of at least one cycle;

d. the one or more hypomethylating agents are indicated for administration for at least the first 3 days, at least the first 4 days, at least the first 5 days, at least the first 6 days, or at least the first 7 days of a 28-day cycle for 3 cycles following administration of DT-IL3 for four 21-day cycles; and/or

the DT-IL3 and the a) one or more Jak inhibitors and/or b) one or more hypomethylating agents are indicated for administration until disease progression and/or unacceptable toxicity is obtained.

6. The use of any one of claims 1-5, wherein the human subject has unfavorable cytogenetics.

7. The use of any one of claims 1-6, wherein the DT-IL3 is a recombinantly expressed protein expressed as a single polypeptide comprising the catalytic and translocation domains of diphtheria toxin and human IL-3.

8. The use of claim 7, wherein the DT-IL3 comprises amino acid residues 1 to 388 of diphtheria toxin linked via a peptide bond to human IL-3.

9. The use of any one of claims 1-8, wherein the inhibition results in a reduction in the proliferation of MPN cells, a stabilization in the amount of MPN cells, a reduction in the amount of MPN cells, and/or a reduction in spleen and/or liver size.

10. The use of any one of claims 1-9, wherein the MPN is polycythemia vera, essential thrombocytosis, myelofibrosis, chronic myelomonocytic leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia, systemic mastocytosis, symptomatic hypereosinophilic disorder, or other bone marrow disorder that causes the production of excess red blood cells, white blood cells, and/or platelets.

11. The use of claim 10, wherein the MPN is myelofibrosis (MF).

12. The use of claim 11, wherein the myelofibrosis is primary myelofibrosis, post-polycythemia vera myelofibrosis, post-essential thrombocythemia myelofibrosis, blast phase primary myelofibrosis, post-polycythemia vera myelofibrosis in blast phase, or post-ET myelofibrosis in blast phase.

13. The use of any one of claims 1-12, wherein the MPN is in blast phase.

14. The use of claim 13, wherein the MPN is primary myelofibrosis in blast phase, post-polycythemia vera myelofibrosis in blast phase, or post-ET myelofibrosis in blast phase.

15. The use of any one of claims 1-14, wherein the one or more Jak inhibitors comprises ruxolitinib.

16. The use of any one of claims 1-15, wherein the medicament comprises at least one Jak inhibitor selected from ruxolitinib and pacritinib, and at least one hypomethylating agent selected from azacitidine and decitabine.

17. The use of any one of claims 1-16, wherein:

a. the human subject was refractory to prior treatment with one or more Jak inhibitors and/or one or more hypomethylating agents;

b. the human subject could not tolerate the full dose of a prior treatment with one or more Jak inhibitors and/or one or more hypomethylating agents;

c. the human subject has low platelets counts or was not eligible for treatment with ruxolitinib;

d. the human subject previously responded to a Jak inhibitor and/or a hypomethylating agent; and/or

e. the human subject has mutations in the JAK2, MPL, ASXL1, TET2, or CALR gene.

18. The use of claim 17, wherein (a) the Jak inhibitor was ruxolitinib or pacritinib and/or (b) the subject has the JAK2V617F mutation.

19. The use of claim 18, wherein the human subject has MF.