host, variability in patterns of somatic alterations in tumor cells, and environmental differences with the potential to impact on systemic immunity.

SUMMARY

Provided herein is the use of a bacterial formulation comprising bacteria of the genus *Bifidobacterium* in the manufacture of a medicament for treating cancer, wherein the medicament is to be co-administered with a separate pharmaceutical composition comprising an immune checkpoint inhibitor.

Provided herein are methods of treatment and/or prevention of cancer by manipulation of commensal microflora. In particular, the amount, identity, presence, and/or ratio of microflora (e.g., gut microflora) in a subject is manipulated to facilitate one or more co-treatments.

In some embodiments, provided herein are methods of treating or preventing cancer in a subject, comprising modulating levels of one or more commensal microbes within the subject to: (A) enhance an immune response by the subject, (B) inhibit the growth or spread of the cancer, (C) inhibit immune evasion by the cancer, and/or (D) enhance the efficacy of a therapeutic. In some embodiments, the levels of one or more commensal microbes are modulated within the gut of the subject. In some embodiments, modulating the levels of one or more commensal microbes comprises increasing and/or decreasing levels of one or more bacterial selected from the genera *Adlercreutzia, Oscillopira, Mollicutes, Butyrivibrio, Bacteroides, Clostridium, Fusobacterium, Eubacterium, Ruminococcus, Peptococcus, Peptostreptococcus, Bifidobacterium, Rikenella, Alistipes, Marinilabilia, Anaerostipes, Escherichia*, and/or *Lactobacillus.*

In some embodiments, modulating the levels of one or more commensal microbes comprises administering a beneficial microbes to the subject. In some embodiments, the beneficial microbes are bacteria. In some embodiments, the bacteria are selected from the genera *Adlercreutzia, Oscillopira, Mollicutes, Butyrivibrio, Bacteroides, Clostridium, Fusobacterium, Eubacterium, Ruminococcus, Peptococcus, Peptostreptococcus, Bifidobacterium, Rikenella, Alistipes, Marinilabilia, Anaerostipes, Escherichia*, and/or *Lactobacillus.* In some embodiments, the bacteria are *Bifidobacterium*. In some embodiments, the *Bifidobacterium* include bacteria selected from the group consisting of *Bifidobacterium lactis, Bifidobacterium bifidium, Bifidobacterium longum, Bifidobacterium animalis, Bifidobacterium breve, Bifidobacterium infantis, Bifidobacterium catenulatum, Bifidobacterium pseudocatenulatum, Bifidobacterium adolescentis,* and *Bifidobacterium angulatum.* In some embodiments, the beneficial microbes are administered as a probiotic composition or via microflora transplant from a donor.

CLAIMS

We claim:

1. Use of a bacterial formulation comprising bacteria of the genus *Bifidobacterium* in the manufacture of a medicament for treating cancer, wherein the medicament is to be co-administered with a separate pharmaceutical composition comprising an immune checkpoint inhibitor.

2. The use of claim 1, wherein at least 50% of the bacteria in the bacterial formulation are of the genus *Bifidobacterium*.

3. The use of claim 1, wherein at least 90% of the bacteria in the bacterial formulation are of the genus *Bifidobacterium*.

4. The use of claim 1, wherein the bacteria of the genus *Bifidobacterium* comprise bacteria of the species *Bifidobacterium lactis, Bifidobacterium bifidium, Bifidobacterium longum, Bifidobacterium animalis, Bifidobacterium breve, Bifidobacterium infantis, Bifidobacterium catenulatum, Bifidobacterium pseudocatenulatum, Bifidobacterium adolescentis, Bifidobacterium angulatum, Bifidobacterium asteroides, Bifidobacterium boum, Bifidobacterium choerinum, Bifidobacterium coryneforme, Bifidobacterium cuniculi, Bifidobacterium denticolens, Bifidobacterium dentium, Bifidobacterium gallicum, Bifidobacterium gallinarum, Bifidobacterium indicum, Bifidobacterium inopinatum, Bifidobacterium magnum, Bifidobacterium merycicum, Bifidobacterium minimum, Bifidobacterium pseudolongum, Bifidobacterium pullorum, Bifidobacterium psychraerophilum, Bifidobacterium ruminantium, Bifidobacterium saeculare, Bifidobacterium scardovii, Bifidobacterium simiae, Bifidobacterium subtile, Bifidobacterium therammcidophilum, Bifidobacterium thermophilum, Bifidobacterium tsurumiense, Bifidobacterium urinalis* or *Bifidobacterium sp.*.

5. The use of claim 1, wherein the bacterial formulation is to be administered by oral administration or rectal administration.

6. The use of claim 5, wherein the bacterial formulation is to be administered by oral administration.

7. The use of claim 1, wherein the bacterial formulation comprises at least $5x10^6$ CFU of bacteria of the genus *Bifidobacterium*.

8. The use of claim 1, wherein the bacterial formulation is to be administered to the subject in two or more doses.

9. The use of claim 8, wherein the administration of the two or more doses are to be separated by at least 1 week.

10. The use of claim 1, wherein an antibiotic is to be administered prior to the administration of the bacterial formulation.

11. The use of claim 10, wherein the antibiotic is to be administered to the subject at least 1 day before the bacterial formulation is to be administered to the subject.

12. The use of claim 1, wherein the immune checkpoint inhibitor is a protein or polypeptide that binds to an immune checkpoint protein.

13. The use of claim 12, wherein the immune checkpoint protein is CTLA4, PD-1, PD-L1, PD-L2, A2AR, B7-H3, B7-H4, BTLA, KIR, LAG3, TIM-3 or VISTA.

14. The use of claim 13, wherein the immune checkpoint protein is PD-1 or PD-L1.

15. The use of claim 1, wherein the immune checkpoint inhibitor is an antibody or antigen binding fragment thereof that binds to an immune checkpoint protein.

16. The use of claim 15, wherein the immune checkpoint protein is CTLA4, PD-1, PD-L1, PD-L2, A2AR, B7-H3, B7-H4, BTLA, KIR, LAG3, TIM-3 or VISTA.

17. The use of claim 16, wherein the immune checkpoint protein is PD-1 or PD-L1.

18. The use of claim 1, wherein the immune checkpoint inhibitor is nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, STI-A1110, TSR-042, RG-7446, BMS-936559, BMS-936558, MK-3475, CT Ol l, MPDL3280A, MEDI-4736, MSB-0020718C, AUR-012 and STI-A1010.

19. The use of claim 1, wherein the pharmaceutical composition comprising the immune checkpoint inhibitor is to be administered by intravenous injection, intramuscular injection, intratumoral injection or subcutaneous injection.

20. The use of claim 1, wherein the bacterial formulation comprises at least $5x10^6$ CFU of bacteria of the genus *Bifidobacterium,* and wherein at least 50% of the bacteria in the bacterial formulation are of the genus *Bifidobacterium*.

21. The use of claim 20, wherein at least 90% of the bacteria in the bacterial formulation are of the genus *Bifidobacterium*.

22. The use of claim 20, wherein the bacteria of the genus *Bifidobacterium* comprise bacteria of the species *Bifidobacterium lactis, Bifidobacterium bifidium, Bifidobacterium longum, Bifidobacterium animalis, Bifidobacterium breve, Bifidobacterium infantis, Bifidobacterium catenulatum, Bifidobacterium pseudocatenulatum, Bifidobacterium adolescentis, Bifidobacterium angulatum, Bifidobacterium asteroides, Bifidobacterium boum, Bifidobacterium choerinum, Bifidobacterium coryneforme, Bifidobacterium cuniculi, Bifidobacterium denticolens, Bifidobacterium dentium, Bifidobacterium gallicum, Bifidobacterium gallinarum, Bifidobacterium indicum, Bifidobacterium inopinatum, Bifidobacterium magnum, Bifidobacterium merycicum, Bifidobacterium minimum, Bifidobacterium pseudolongum, Bifidobacterium pullorum, Bifidobacterium psychraerophilum, Bifidobacterium ruminantium, Bifidobacterium saeculare, Bifidobacterium scardovii, Bifidobacterium simiae, Bifidobacterium subtile, Bifidobacterium therammcidophilum, Bifidobacterium thermophilum, Bifidobacterium tsurumiense, Bifidobacterium urinalis* or *Bifidobacterium sp.*.

23. The use of claim 20, wherein the bacterial formulation is to be administered by oral administration or rectal administration.

24. The use of claim 23, wherein the bacterial formulation is to be administered by oral administration.

25. The use of claim 20, wherein the bacterial formulation is to be administered to the subject in two or more doses.

26. The use of claim 20, wherein an antibiotic is to be further administered to the subject before the bacterial formulation is to be administered to the subject.

27. The use of claim 20, wherein the immune checkpoint inhibitor is an antibody or antigen binding fragment thereof that binds to CTLA4, PD-1, PD-L1, PD-L2, A2AR, B7-H3, B7-H4, BTLA, KIR, LAG3, TIM-3 or VISTA.

28. The use of claim 20, wherein the immune checkpoint inhibitor is an antibody or antigen binding fragment thereof that binds to PD-1 or PD-L1.

29. The use of claim 20, wherein the immune checkpoint inhibitor is nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, STI-A1110, TSR-042, RG-7446, BMS-936559, BMS-936558, MK-3475, CT Ol l, MPDL3280A, MEDI-4736, MSB-0020718C, AUR-012 and STI-A1010.