METHODS OF TREATING CANCER

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/789,164 filed January 7, 2019, which is incorporated by reference herein in its entirety.

BACKGROUND

[0002] Various immunotherapeutic approaches are being evaluated for the treatment of a number of cancers. However, there remains a need for immunotherapies and regimens capable of producing a robust immune response directed specifically to cancer cells.

SUMMARY

[0002a] The present disclosure refers to a use of a first recombinant microorganism and a second recombinant microorganism in the manufacture of a medicament for treating a tumor in a subject, wherein the first recombinant microorganism is to be administered to the subject, wherein the first recombinant microorganism replicates in a tumor cell and does not replicate in a non-tumor cell or displays attenuated replication in a non-tumor cell, and wherein the first recombinant microorganism is a bacterium; wherein the second recombinant microorganism is to be administered to the subject, wherein the second recombinant microorganism replicates in a tumor cell and does not replicate in a non-tumor cell or displays attenuated replication in a non-tumor cell, and wherein the second recombinant microorganism is a virus; and wherein an immune response to a protein expressed by a tumor associated cell that is not coded for or expressed by the first recombinant microorganism and the second recombinant microorganism is enhanced or elicited.

[0003] The methods described herein feature, *inter alia*, methods of treating cancer by administering a heterologous prime-boost regimen of oncolytic microorganisms that enhances or elicits an immune response to a tumor protein that is not coded for by the oncolytic microorganisms.

[0004] One example provides a method of treating a tumor in a subject, comprising: administering to the subject a first recombinant microorganism, wherein the first recombinant microorganism replicates in a tumor cell and does not replicate in a non-tumor cell or displays attenuated replication in a non-

CLAIMS:

1. Use of a first recombinant microorganism and a second recombinant microorganism in the manufacture of a medicament for treating a tumor in a subject,

wherein the first recombinant microorganism is to be administered to the subject,

wherein the first recombinant microorganism replicates in a tumor cell and does not replicate in a non-tumor cell or displays attenuated replication in a non-tumor cell, and

wherein the first recombinant microorganism is a bacterium;

wherein the second recombinant microorganism is to be administered to the subject,

wherein the second recombinant microorganism replicates in a tumor cell and does not replicate in a non-tumor cell or displays attenuated replication in a non-tumor cell, and

wherein the second recombinant microorganism is a virus; and

wherein an immune response to a protein expressed by a tumor associated cell that is not coded for or expressed by the first recombinant microorganism and the second recombinant microorganism is enhanced or elicited.

2. The use of claim 1, wherein the immune response is demonstrated by one or more of a decrease in the volume of the tumor in the subject, a decrease in the level of expression of one or more tumor proteins in the subject or a sample from the subject, a decrease in the number of tumor sites in the subject, a change in viral load in the subject or the sample from the subject, a change in population of immune cells in the subject or the sample from the subject, a change in expression levels of an immune cell marker in the subject or the sample from the subject, an enhancement of B-cell proliferation in the subject or the sample from the subject, an enhancement of CD4+ T cell proliferation in the subject or the sample from the subject, an enhancement of CD8+ T cells proliferation in the subject or the sample from the subject, an enhancement of cytokine production in the subject or the sample from the subject, an enhancement of antigen presenting cell proliferation in the subject or the sample from the subject, or any combinations thereof .

3. The use of claim 2, wherein the immune response is demonstrated by the decrease in the level of expression of one or more tumor proteins, the change in population of immune cells, the change in expression levels of an immune cell marker, the enhancement of B-cell proliferation, the enhancement of CD4+ T cell proliferation, the enhancement of CD8+ T cells proliferation, the

enhancement of cytokine production, the enhancement of antigen presenting cell proliferation, or any combinations thereof, in the subject or the sample from the subject, wherein the sample from the subject is a blood, tissue, urine, or saliva sample.

4. The use of any preceding claim, wherein the immune response can be detected at a time point at or after the administration of the first or second recombinant microorganism.

5. The use of any preceding claim, wherein the first recombinant microorganism does not replicate in the non-tumor cell.

6. The use of any one of claims 1-4, wherein the first recombinant microorganism displays attenuated replication in the non-tumor cell.

7. The use of any preceding claim, wherein the second recombinant microorganism does not replicate in the non-tumor cell.

8. The use of any one of claims 1-6, wherein the second recombinant microorganism displays attenuated replication in the non-tumor cell.

9. The use of claim 1, wherein the bacterium is an enterobacterium, a listeriaceae bacterium, or a streptococcaceae bacterium.

10. The use of claim 1, wherein the second recombinant microorganism is of family viridae.

11. The use of claim 13, wherein the second recombinant microorganism is a poxvirus, a picornavirus, an adenovirus, a parvovirus, a herpesvirus, a reovirus, a paramyxovirus, a rhabdovirus, an orthomyxovirus, or a coxsackievirus.

12. The use of any preceding claim, wherein the first recombinant microorganism and the second recombinant microorganism are administered to the subject simultaneously.

13. The use of claim 15, wherein the first recombinant microorganism is formulated in a delayed release composition, a sustained release composition, an immediate release composition, a stealth release composition, or any combinations thereof.

14. The use of any one of claims 1-14, wherein the second recombinant microorganism is administered to the subject after the first recombinant microorganism is administered to the subject.

15. The use of claim 17, wherein the second recombinant microorganism is administered from about 1-60 days, from 1-45 days, from 1-30 days, from 1-15 days, from 1-10 days, or from 1-7 days after administration of the first recombinant microorganism.

16. The use of claim 17, wherein the second recombinant microorganism is administered about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 21, 28, 35, 56, or 60 days after administration of the first recombinant microorganism.

17. The use of claim 17, wherein the second recombinant microorganism is administered to the subject one, two, three, three, four, five or more times.

18. The use of claim 17, wherein the second recombinant microorganism is administered to the subject two, three, three, four, five or more times with about 1-60 days, 1-45 days, 1-30 days, 1-15 days, 1-10 days, 1-7, 1-5 days, or 1-3 days between each administration.

19. The use of any preceding claim, wherein the first recombinant microorganism is to be administered intra-tumorally, intradermally, subcutaneously, intraperitoneally, intramuscularly or intravenously; and the second recombinant microorganism is to be administered intra-tumorally, intradermally, subcutaneously, intraperitoneally, intrathecally, intramuscularly or intravenously.

20. The use of any preceding claim, wherein an anti-cancer therapy is to be further administered.

21. The use of claim 1, wherein an immune response to a protein expressed by a non-tumorous cell present within a tumor microenvironment that is not coded for or expressed by the first recombinant microorganism and the second recombinant microorganism is further enhanced or elicited.