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(54) SELECTIVELY ALTERING MICROBIOTA FOR IMMUNE MODULATION

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Related U.S. Application Data

(63) Continuation of application No. 16/192,752, filed on Nov. 15, 2018, now Pat. No. 10,363,308, which is a continuation of application No. 15/820,296, filed on Nov. 21, 2017, now Pat. No. 10,195,273, which is a continuation of application No. PCT/EP2017/063593, filed on Jun. 4, 2017.

(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**

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(52) **U.S. Cl.**
CPC ***A61K 39/3955*** (2013.01); ***A61K 31/7105*** (2013.01); ***A61K 35/15*** (2013.01); ***A61K 35/17*** (2013.01); ***A61P 35/00*** (2018.01); ***A61P 37/00*** (2018.01); *A61K 39/0011* (2013.01); *A61K 2039/505* (2013.01); *C12N 2320/30* (2013.01); *C12N 2320/50* (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

To view the complete listing of prior art documents cited during the proceeding for Reexamination Control Number 90/015,047, please refer to the USPTO's Patent Electronic System.

Primary Examiner — Padmashri Ponnaluri

(57) **ABSTRACT**

The invention relates to methods of modulating immune cells in a patient by altering microbiota of the patient. The invention also relates to methods of modulating treatments or therapies in a subject organism by altering microbiota of the subject. The invention also relates to cell populations, systems, arrays, cells, RNA, kits and other means for effecting this. In an example, advantageously selective targeting of a particular species in a human gut microbiota using guided nucleic acid modification is carried out to effect the alteration.

EX PARTE REEXAMINATION CERTIFICATE

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims **11-16** are cancelled.

Claims **1** and **5** are determined to be patentable as amended.

Claims **2-4**, **6-10** and **17-20**, dependent on an amended claim, are determined to be patentable.

1. A method of enhancing efficacy of **[a]** *an* immunotherapy for a colon cancer in a human or animal subject, wherein the subject comprises a gut microbiota that comprises host bacterial cells, the method comprising administering a treatment comprising an antibacterial agent to the subject that kills host bacterial cells or inhibits the growth of host bacterial cells comprised by the gut microbiota, wherein the host bacterial cells are *Fusobacterium* cells,

and wherein:

(i) the antibacterial agent comprises a nucleic acid vector comprising:

(a) a nucleic acid sequence encoding a Cas nuclease and

(b) a nucleic acid sequence encoding a guide RNA or a crRNA to selectively target the genome of the host bacterial cells in the gut microbiota, wherein the Cas nuclease cuts one or more target nucleotide sequences comprised by the host bacterial cells, thereby selectively killing host bacterial cells or reducing the growth thereof, or

(ii) the antibacterial agent comprises a nucleic acid vector comprising a nucleic acid sequence encoding a guide RNA or a crRNA to selectively target the genome of the host bacterial cells in the gut microbiota, wherein the guide RNA or crRNA comprises a sequence that is capable of hybridizing to a target sequence of the host bacterial cell to guide a Cas nuclease in the host bacterial cell to the target sequence in the host bacterial cell, whereby the target sequence is cut and the host bacterial cell is killed or growth of host bacterial cells is reduced,

[and] wherein said selective killing of host bacterial cells or reducing the growth **[thereof modulates]** *of the host bacterial cells upregulates or expands* immune cells in the human or animal subject, thereby enhancing efficacy of the immunotherapy for the colon cancer in the human or animal subject, *and wherein the immune cells comprise CD8+ cells.*

5. A method of enhancing efficacy of **[a]** *an* immunotherapy for a colon cancer in a human or animal subject, wherein the subject comprises a gut microbiota that comprises host bacterial cells, the method comprising administering *a* phage to the subject, wherein the phage infects host bacterial cells comprised by the gut microbiota, wherein the host bacterial cells are *Fusobacterium* cells, wherein the phage comprises or encodes an antibacterial agent,

and wherein:

(i) the antibacterial agent comprises:

(a) a nucleic acid sequence encoding a Cas nuclease and

(b) a nucleic acid sequence encoding a guide RNA or a crRNA to selectively target the genome of the host bacterial cells in the gut microbiota, wherein the Cas nuclease cuts one or more target nucleotide sequences comprised by the host bacterial cells, thereby selectively killing host bacterial cells or reducing the growth thereof, or

(ii) the antibacterial agent comprises a nucleic acid sequence encoding a guide RNA or a crRNA to selectively target the genome of the host bacterial cells in the gut microbiota, wherein the guide RNA or crRNA comprises a sequence that is capable of hybridizing to a target sequence of the host bacterial cell to guide a Cas nuclease in the host bacterial cell to the target sequence in the host bacterial cell, whereby the target sequence is cut and the host bacterial cell is killed or growth of host bacterial cells is reduced,

[and] wherein said selective killing of host bacterial cells or reducing the growth **[thereof modulates]** *of the host bacterial cells upregulates or expands* immune cells in the human or animal subject, thereby enhancing efficacy of the immunotherapy for the colon cancer in the human or animal subject, *and wherein the immune cells comprise CD8+ cells.*

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