IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MICROBIOTICA, LIMITED
Petitioner,

v.

BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM
Patent Owner.

U.S. Patent No. 11,395,838
Issue Date: July 26, 2022
Title: Methods for Enhancing Immune Checkpoint Blockade Therapy by Modulating the Microbiome

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Post Grant Review No.: Unassigned

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# DECLARATION OF MATTHEW ROBINSON IN SUPPORT OF PETITION FOR POST GRANT REVIEW OF U.S. PATENT NO. 11,395,838

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# I. INTRODUCTION

1. I am over the age of eighteen (18) and otherwise competent to make this declaration.

2. I have been asked to serve as an expert witness on behalf of Petitioner Microbiotica Limited ("Petitioner" or "Microbiotica") in the above-captioned Petition for post grant review. I am employed by Microbiotica, and I am not being paid for my time in connection with this matter apart from my standard annual compensation. My compensation or employment is in no way dependent on the outcome of this post grant review.

3. Petitioner's Petition for post grant review involves U.S. Patent No. 11,395,838 ("the '838 Patent") (EX-1001). The '838 Patent is entitled "Methods for Enhancing Immune Checkpoint Blockade Therapy by Modulating the Microbiome," and lists Jennifer Wargo and Vancheswaran Gopalakrishnan as the inventors.

4. The '838 Patent issued on July 26, 2022 and claims priority to three provisional applications: provisional application No. 62/400,372, filed on September 27, 2016, provisional application No. 62/508,885, filed on May 19, 2017, and provisional application No. 62/557,566, filed on September 12, 2017.

5. For the purposes of this post grant review, I have been instructed to assume that the effective filing date of the Claims of the '838 Patent challenged by

the Petitioner in this post grant review is the earliest possible priority date, *i.e.,* the September 27, 2016, filing date of U.S. provisional application No. 62/400,372.

6. I understand that according to USPTO records, the ’838 Patent is currently assigned to Board of Reagents at The University of Texas System (“Patent Owner” or
“PO”).

7. The ’838 Patent is related generally to “methods and compositions for treatment of cancer by modulating the microbiome to enhance the efficacy of immune checkpoint blockade.” EX-1001, ABSTRACT. I am familiar with the technology described in the ’838 Patent as of the earliest possible priority date of September 27, 2016.

8. In preparing this Declaration, I have reviewed the ’838 Patent (EX-1001), the file history of the ’838 Patent (EX-1002), and each of the documents cited herein, and I have considered these documents in light of the general knowledge in the art as of September 7, 2016. In formulating my opinions, I have relied upon my experience in the relevant art. I have also considered the viewpoint of a person of ordinary skill in the art (“POSA”) in the field of microbiome science and/or microbiome-derived cancer treatment, as of September 27, 2016.

9. I have been asked to provide my technical expertise, analysis, insights and opinions regarding the ’838 Patent and relevant references that form the basis



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of the grounds of rejection set forth in the accompanying Petition for post grant review of the ’838 Patent. As described in detail below, I offer the following opinions in this Declaration:

- A POSA would have found Claims 1-19 of the ’838 Patent to be unpatentable for lack of a written description that is sufficiently detailed so that a POSA can reasonably conclude that the inventors had possession of the full scope of Claims 1-19 at the time of filing the application leading to the ’838 Patent (*i.e.*, September 27, 2016).
- A POSA would have found Claims 1-19 of the ’838 Patent to be unpatentable for lack of enablement because the ’838 Patent specification does not teach a POSA how to make and use the full scope of Claims 1-19 without undue experimentation.
- A POSA would have found Claims 1-19 of the ’838 Patent to be unpatentable for indefiniteness because the Claims 1-19 of the ’838 Patent fails to inform a POSA of the scope of the invention.
- A POSA would have found the invention of Claims 1-3, 5-19 of the ’838 Patent to be obvious by the Honda (EX-1011) in view of Gajewski (EX-1012) references.



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- Honda in view of Gajewski teaches each element of Claims 1-3, 5-19, and a POSA would have been motivated to modify the teachings of this references.
- A POSA would have found the invention of Claim 4 of the '838 Patent to be obvious over Honda in view of Gajewski and Miquel (EX-1014) references.
- Honda in view of Gajewski and Miquel teaches each element of Claim 4 and a POSA would have been motivated to combine the teachings of these references.

## II. LIST OF DOCUMENTS I CONSIDERED IN FORMING MY OPINIONS

10. In formulating my opinions, I have considered the following documents:

| ***ML Exhibit #*** | ***Description*** |
|---|---|
| **1001** | U.S. Patent No. 11,395,838 ("the '838 Patent") |
| **1002** | U.S. Patent No. 11,395,838 File History |
| **1005** | Patyar et al. "Bacteria in cancer therapy: a novel experimental Strategy", Journal of Biomedical Science 17:21 http://www.jbiomedsci.com/content/17/1/21 (2010) (Patyar) |
| **1006** | Wei et al., "Bacterial targeted tumour therapy-dawn of a new era", Cancer Letters 259 16–27 (2008) (Wei) |
| **1007** | Pitt et al., "Resistance Mechanisms to Immune-Checkpoint Blockade in Cancer: Tumor-Intrinsic and -Extrinsic Factors", Immunity 44:1255-1269 (June 21, 2016) (Pitt) |



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| *ML Exhibit #* | ***Description*** |
|---|---|
| **1008** | Viaud et al., "Gut microbiome and anticancer immune response: really hot Sh*t!", Cell Death and Differentiation 22:199–214 (2015) (Viaud) |
| **1009** | Lopez-Siles et al., "Changes in the Abundance of *Faecalibacterium prausnitzii* Phylogroups I and II in the Intestinal Mucosa of Inflammatory Bowel Disease and Patients with Colorectal Cancer", Inflamm Bowel Dis 22(1): 28-41 (20 November 2015) (Lopez-Siles) |
| **1010** | Martin-Orozco et al., T Helper 17 Cells Promote Cytotoxic T Cell Activation in Tumor Immunity", Immunity 31:787–798 (2009) (Martin-Orozco) |
| **1011** | Honda et al. / Riken et al., WO2015/156419, published October 15, 2015 (Honda) |
| **1012** | Gajewski et al. / The University of Chicago, WO2016196605A1, published December 8, 2016 from PCT/US2016/035228, filed June 1, 2016 (Gajewski) |
| **1013** | Gajewski et al. / The University of Chicago, PCT/US2016/035228, filed June 1, 2016 (from WIPO public database for Gajewski, showing that content of Gajewski is the same as the content of PCT/US2016/035228 as filed June 1, 2016) |
| **1014** | Miquel et al., "Faecalibacterium prausnitzii and human intestinal health", Current Opinion in Microbiology, 16:255–261 (2013) (Miquel) |
| **1015** | Volume 3 of Bergey's Manual of Systemic Baceriology (2nd Ed. 2009) |
| **1016** | Tindall, Int J Syst Evol Microbiol 69:3927–3932 (2019) |
| **1017** | Louis et al., "Diversity, metabolism and microbial ecology of butyrate-producing bacteria from the human large intestine" FEMS Microbiol Lett. 294:1–8 (2009) |
| **1018** | Barcenilla et al., "Phylogenetic relationships of butyrate-producing bacteria from the human gut", Appl Environ Microbiol. 66:1654–1661 (2000) |
| **1019** | Duncan SH, Hold GL, Harmsen HJ, Stewart CS, Flint HJ, "Growth requirements and fermentation products of Fusobacterium prausnitzii, and a proposal to reclassify it as Faecalibacterium prausnitzii gen. nov., comb. nov.", Int J Syst Evol Microbiol 2002, 52:2141-2146 |



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| *ML Exhibit #* | *Description* |
|---|---|
| **1020** | Walker AW, Duncan SH, Harmsen H, Holtrop G, Welling GW, Flint HJ, "The species composition of the human intestinal microbiota differs between particle-associated and liquid phase communities", Environmental Microbiology (2008) 10(12), 3275–3283. |
| **1021** | Gopalakrishnan, P. et al., "Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients", Science (2018) 359, 97-103. |
| **1022** | Definition of "bacterial isolate", Collin English Language Dictionary: https://www.collinsdictionary.com/dictionary/english/bacterial-isolate |
| **1023** | Definition of "purify", Collin English Language Dictionary: https://www.collinsdictionary.com/dictionary/english/purify |
| **1024** | Pardon, "The blockade of immune checkpoints in cancer immunotherapy", Nat Rev Cancer 12(4): 252-264 (2012), Author Manuscript, published May 4, 2016 |
| **1025** | Ma et al., "Current status and perspectives in translational biomarker research for PD-1/PD-L1 immune checkpoint blockade therapy", Journal of Hematology & Oncology" (2016) 9:47 |

## III. MY BACKGROUND AND QUALIFICATIONS

11. My expertise qualifies me to do the type of analysis required in this case in the field of microbiome science and/or microbiome-derived cancer treatment.

12. Of particular relevance, I have more than 25 years' research experience across academia and industry in the field of microbiome science and/or microbiome-derived cancer treatment. I received a BSc in Biochemistry from the University of Bath in 1996, and a PhD in Immunology from University College London in 2000. I continued academic research for a further seven years with postdoctoral research positions at National Institute of Medical Research and

Cancer Research UK (both London UK). During this time, my research focused on how microbes interact with innate immune cells to trigger inflammation and instruct the adaptive immune response.

13. For example, during my time as a post-graduate student and research fellow, I was focused on cloning and characterizing a series of Neutrophil S100 proteins associated with inflammation. This research led to my postdoctoral research fellowship focused on macrophage cell signaling in response to microbial stimuli. Specifically, I worked to elucidate two mechanisms by which lipopolysaccharides (LPS) activate the MAP3-kinase TPL-2, namely degradation of an inhibitor and identification of a regulatory phosphorylation site. My work studied how this regulation contributes to macrophage activation and induction of TNF.

14. In 2005, I joined Cancer Research UK LRI (now part of Francis Crick Institute) in London, UK, as a postdoctoral research fellow. My work there was focused on innate immune receptors that recognize fungi, including identification of novel pattern recognition receptors expressed by dendritic cells that engage fungi, and signaling pathways triggered by these fungal receptors. This work included extensive analysis of the resultant cell activation, cytokine release and adaptive immune response by assessment of T lymphocyte differentiation.



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15. In 2008, I joined MedImmune/AstraZeneca where I worked for over ten years holding various scientific roles with increasing responsibility and strategic influence in the Oncology, Respiratory, Inflammation and Autoimmunity fields. I led multiple research projects, pre-clinical teams and strategic initiatives in the biology of disease, including from target identification to discovery and clinical development on a series of preclinical immuno-oncology projects.

16. For example, as a Scientist II and Senior Scientist at MedImmune/AstraZeneca, I was a Team Leader in Preclinical Research on projects involving treatment of chronic obstructive pulmonary disease (COPD), asthma and autoimmunity, as well as co-chair of a cross-functional strategy team focused on treatment of inflammatory bowel disease (IBD).

17. I was also a member of the clinical development teams focused on the development of several monoclonal antibodies, including Brazikumab and Abrilumab. Brazikumab (formerly MEDI2070) is a monoclonal antibody that selectively blocks the IL23 immune signal, preventing intestinal inflammation in the human gut. I was involved in Phase 2a to Phase 2b clinical trials related to Brazikumab for treatment of Crohn's disease.

18. Abrilumab is an anti-α4β7 antibody for treatment of patients with moderate-to-severe ulcerative colitis. I worked on the in Phase 2b clinical trials related to Abrilumab.



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19. In 2017, I was promoted to Associate Director of Research at MedImmune/AstraZeneca. I was also the Chair of a strategic team focused on novel T cell targeted therapies in oncology, and lead a team of 9 preclinical research scientists.

20. I was the research representative for the Oleclumab (MEDI-9447) clinical development team. Oleclumab is a new molecular entity (NME) under development for the treatment of refractory solid tumors such as non-small cell lung cancer, pancreatic cancer, prostate cancer, breast cancer, angiosarcoma, dedifferentiated liposarcoma and osteosarcoma. Oleclumab is a human monoclonal antibody targeting the ectonucleotidase CD73. It is administered intravenously as a powder for solution. Oleclumab has now entered into Phase III clinical development for Non-Small Cell Lung Cancer.

21. I joined Microbiotica (Cambridge, UK) in 2019 as the Vice President of Translational Biology. In 2022, I was promoted to Senior Vice President of Research. While at Microbiotica, I helped establish and continue to lead the Translational Biology Group which studies how microbiome-derived bacteria interact with the host. I have taken on responsibility for the discovery research across the company from overall strategy to developing the microbiome analysis platform and discovery projects. This includes directing approximately 16



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microbiome scientists across different disciplines including the Discovery Microbiology and Bioinformatics teams.

22. Throughout a career spanning over two decades, I have published numerous peer-reviewed articles devoted to microbiome science and the use of microbiome as immunotherapy. A copy of my current curriculum vitae is provided as EX-1004, and it provides a comprehensive description of my academic and employment history, including a list of relevant art publications for at least the last 10 years, and a list of all other cases in which I have testified as an expert at trial or by deposition.

23. Throughout the remainder of this Declaration, I will refer to the field of microbiome science and/or microbiome-derived cancer treatment, as the "relevant field" or the "relevant art." In formulating my opinions, I have relied upon my training, knowledge, and experience in the relevant art.

## IV. PERSON OF ORDINARY SKILL IN THE ART (POSA)

24. I am familiar with the knowledge and capabilities of one of ordinary skill in the art. For example, my work as a microbiome scientist with doctoral level studies in immunology, including the importance of the microbiome in cancer immunotherapy, allowed me to become personally familiar with the level of skill of individuals and the general state of the art. Unless otherwise stated, my



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testimony below refers to the knowledge of one of ordinary skill in the art as of September 27, 2016, the earliest possible effective filing date of the '838 Patent.

25. I have been informed and understand that a Person of Ordinary Skill in the Art ("POSA") is a hypothetical person who is presumed to be aware of all pertinent prior art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. With respect to the '838 Patent, in my opinion, a POSA in September 2016 would have had education and/or experience in the field of microbiology, and/or oncology, and knowledge of the scientific literature concerning the same. The experience and education levels may vary between persons of ordinary skill, with some persons holding a basic Bachelor's degree with four to five years of relevant work experience, and others holding a Masters or Ph.D. but having fewer years of experience.

## V. RELEVANT LEGAL STANDARDS

26. I am not a lawyer and will not provide any legal opinions. Although I am not a lawyer, I have been informed and understand that certain legal standards are to be applied by technical experts in forming opinions regarding the meaning and validity of patent claims. I have been asked to provide my opinions regarding whether the claims of the '838 Patent would have been obvious to a person having ordinary skill in the art at the time of the alleged invention, in light of the prior art.



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27. I have been instructed that Petitioner must demonstrate the unpatentability of the challenged claims by a preponderance of the evidence. I have been instructed to apply, and I have applied, the below-referenced standards provided by counsel in drafting this Declaration.

28. I understand that the use of "comprising" transition in a claim is understood to mean "including but not limited to."

**A. Written Description**

29. I have been instructed that a patent claim is invalid if the patent does not contain an adequate written description of the claimed invention. The purpose of this written description requirement is to demonstrate that the inventor was in possession of the full scope of the claimed invention at the time the application for the patent was filed, even though the claim may have changed or new claims added since that time. Put another way, the purpose of the written description requirement is to ensure that the scope of the right to exclude, as set forth in the claims, does not exceed the scope of the inventors' contribution to the field.

30. I have been instructed that the written description requirement is satisfied if a person of ordinary skill in the art reading the original patent application at the time it was filed would have recognized that the patent application described the invention as claimed, even though the description may not use the exact words founds in the claim. I have been instructed that a



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requirement in a claim need not be specifically disclosed in the patent application as originally filed if a person of ordinary skill in the art would understand that the missing requirement is necessarily implied in the patent application as originally filed. I have been instructed that it is insufficient to consider whether one skilled in the art might be able to construct the claimed subject matter from the teachings of the disclosure. I have been instructed that it is not sufficient for purposes of the written description requirement that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose.

31. I have been instructed that the description must do more than merely disclose that which would render the claimed invention obvious. In other words, the knowledge of ordinary artisans may not be used to teach limitations that are not described in the specification, even if those limitations would be rendered obvious by the specification.

32. In evaluating whether the specification has provided an adequate written description, I have been instructed that I may consider such factors as: the nature and scope of the patent claims; the complexity, predictability, and maturity of the technology at issue; the existing knowledge in the relevant field; and the scope and content of the prior art. I further have been instructed that the issue of written description is decided on a claim-by-claim basis, not as to the entire patent



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or groups of claims. When determining whether the specification discloses the claimed invention of a claim, the claim must be viewed as a whole.

33. I have been instructed that during prosecution of a patent application, an applicant is allowed to amend its claims so long as the original application as filed demonstrates that the inventors were in possession of the full scope of the subject matter as claimed in the new claims.

**B. Enablement**

34. I have been instructed that a patent claim is invalid if the patent at the time it was filed did not contain a description of the claimed invention that is sufficiently full and clear to enable a person of ordinary skill in the art at the time to make and use the full scope of the invention. This is known as the "enablement" requirement. The purpose of this requirement is to ensure that the public, in exchange for the patent rights given to the inventor, obtains from the inventor a full disclosure of how to make and use the invention.

35. I have been instructed that the patent is not required to disclose information that would be known to persons of skill in the art. The patent may be enabling even though it does not expressly state some information if a person of ordinary skill in the art could make and use the invention without having to do excessive experimentation. In determining whether excessive experimentation is required, the following factors may be considered:



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(a) the scope of the claimed invention;

(b) the amount of guidance presented in the patent;

(c) the amount of experimentation necessary;

(d) the time and cost of any necessary experimentation;

(e) how routine any necessary experimentation is in the field;

(f) whether the patent discloses specific working examples of the claimed invention;

(g) the nature and predictability of the field; and

(h) the level of ordinary skill in the field.

36. I have been instructed that the enablement requirement is met if the specification enables any mode of making and using the invention, provided that the full scope of the invention is enabled. The patent need not enable an optimized or commercially viable process or method of practicing the invention unless the claims specify that the invention is directed at an optimized or commercially viable process.

37. I have been instructed that the "how to use" prong of the enablement requirement further requires that the specification disclose a practical utility for the invention. In other words, the specification must disclose a practical use for the invention.



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38. Finally, I have been instructed that the question of whether a patent is enabling is judged as of the date the application for the patent was first filed.

**C. Indefiniteness**

39. I understand that the claims define the invention that an applicant believes is patentable and that the claims must particularly point out and distinctly claim the subject matter that the patent applicant regards as his or her invention.

40. I understand that a patent must be precise enough to afford clear notice of what is claimed, thereby apprising the public of what is still open to them.

41. I understand that a claim is indefinite if its claims, read in light of the specification delineating the patent, and the prosecution history fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.

42. I further understand that when terms of degree are used in a claim, the specification must provide some standard for measuring that degree.

**D. Obviousness**

43. I have been instructed that not all innovations are patentable. A patent claim is invalid if the claimed invention would have been obvious to a person of ordinary skill in the art as of its effective filing date. This means that even if all of the requirements of the claim cannot be found in a single prior art reference that would anticipate the claim or constitute a statutory bar to that claim, a person of



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ordinary skill in the art who knew about all this prior art would have come up with the claimed invention.

44. I have been instructed that the ultimate conclusion of whether a claim is obvious should be based upon a determination of several factual decisions.

45. First, the level of ordinary skill in the field that someone would have had as of the effective filing date of the claimed invention must be determined.

46. Second, the scope and content of the prior art must be determined. In order to be considered as prior art to an asserted patent, these references must be reasonably related or pertinent to the claimed invention of that patent. A reference is reasonably related if it is in the same field as the claimed invention or is from another field to which a person of ordinary skill in the art would look to solve a known problem. In order for a reference to be "reasonably pertinent" to the problem, it must logically have commended itself to an inventor's attention in considering his problem. In determining whether a reference is reasonably pertinent, one should consider the problem faced by the inventor, as reflected - either explicitly or implicitly - in the specification.

47. Third, what difference, if any, existed between the claimed invention and the prior art must be determined.

48. Finally, I have been instructed that I should consider any objective evidence offered by the patent owner (sometimes called "secondary



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considerations" or "objective indicia" of non-obviousness) that may have existed at the time of the purported invention and afterwards that may shed light on the obviousness or not of the claimed invention, such as:

(a) Whether the invention was commercially successful as a result of the merits of the claimed invention (rather than the result of design needs or market-pressure advertising or similar activities);

(b) Whether the invention satisfied a long-felt but unresolved need;

(c) Whether others had tried and failed to make the invention;

(d) Whether others having ordinary skill in the field independently made the claimed invention at about the same time the inventor made the invention;

(e) Whether others copied the invention;

(f) Whether there were changes or related technologies or market needs contemporaneous with the invention;

(g) Whether the invention achieved unexpected results;

(h) Whether others in the field praised the invention;

(i) Whether persons having ordinary skill in the art of the invention expressed surprise or disbelief regarding the invention;

(j) Whether others sought or obtained rights to the patent from the patent holder (e.g., whether others have taken licenses to use the invention); and



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(k) Whether the inventor proceeded contrary to accepted wisdom in the field.

49. I have been instructed that these "secondary considerations" are relevant to obviousness only, and not anticipation.

50. I have been instructed that any assertion of the above indicia must be accompanied by a "nexus" between the merits of the invention and the evidence offered. The patent owner bears the burden of showing that a nexus exists. For example, commercial success of a product is relevant to obviousness only if the patent owner can show that the success of the product is attributable to the patented features of the claimed invention. If, on the other hand, commercial success is due to features of the product not claimed in the patent, due to claimed features that existed in the prior art, and/or due to advertising, promotion, salesmanship or the like, then any commercial success should not be considered an indication of non-obviousness.

51. I have further been instructed that none of the indicia listed above is by itself dispositive, and that I should consider the obviousness or non-obviousness of the subject matter as a whole. If some or all of the secondary indicia are established, that may suggest that the claim was not obvious. However, even if some of the indicia are established, that indicia should be considered along with all



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the other evidence in the case in determining whether the claimed subject matter would have been obvious.

52. I have been instructed that a reference may be combined with other references to disclose each element of the purported invention. I have been instructed that a reference may also be combined with the knowledge of a skilled artisan, and that this knowledge may be used to combine multiple references. I further have been instructed that a skilled artisan is presumed to know the relevant prior art. I have been instructed that the obviousness analysis may take into account the inferences and creative steps that a skilled artisan would employ.

53. I have been instructed that a patent claim composed of several elements is not proved obvious merely by demonstrating that each of its elements was independently known in the prior art. In evaluating whether such a claim would have been obvious, I have been instructed that I should consider whether the there is a reason that would have prompted a person of ordinary skill in the art to combine the elements or concepts from the prior art in the same way as in the claimed invention. There is no single way to define the line between true inventiveness on the one hand (which is patentable) and the application of common sense and ordinary skill to solve a problem on the other hand (which is not patentable). For example, market forces or other design incentives may be what produced a change, rather than true inventiveness. I may consider whether the



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change was merely the predictable result of using prior art elements according to their known functions, or whether it was the result of true inventiveness. I may also consider whether there is some teaching or suggestion in the prior art to make the modification or combination of elements claimed in the patent. Also, I may consider whether the innovation applies a known technique that had been used to improve a similar device or method in a similar way. I may also consider whether the claimed invention would have been obvious to try, meaning that the claimed innovation was one of a relatively small number of possible approaches to the problem with a reasonable expectation of success by those skilled in the art.

54. However, I have been instructed that I must be careful not to determine obviousness using the benefit of hindsight; many true inventions might seem obvious after the fact. I should put myself in the position of a person of ordinary skill in the art at the time of the effective filing date of the Asserted Claim and I should not consider what is known today or what is learned from the teaching of the patent. Finally, I should consider whether a proposed combination of references would be expected to work.

55. I have also been have been instructed that determining whether there are any material differences between the scope and content of the prior art and each asserted claim of the patent-in-suit requires consideration of the claimed invention as a whole to determine whether or not it would have been obvious in light of the



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prior art. If the prior art discloses all the steps or elements in separate references, consideration should be given to whether it would have been obvious to combine those references.

56. I have been instructed that obviousness may also be shown by demonstrating that a single piece of prior art could be modified to create the patented invention. I have been instructed that in order for a claim to be rendered obvious based on a single piece of prior art, it is important to identify a reason that would have prompted a person of ordinary skill in the art to modify that prior art to create the claimed invention.

## VI. OVERVIEW

57. The Challenged Claims are unpatentable under Section 112(a) and (b) as they are not supported by, nor enabled by, the specification of the '838 Patent and they fail to inform, with reasonable certainty, to persons of ordinary skill in the art ("POSA") about the scope of the invention. The Challenged Claims purport to cover the unbounded concept of delaying or reducing growth of all types of skin cancer tumors by administering, through any means known to man, an undefined "composition" of unidentified bacteria belonging to the family Ruminococcaceae. There are no limits on the type of skin cancer tumors that can be treated. There are no list of ingredients or limits on the type(s) of composition to be administered, how the composition can be administered, or even where the composition should



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be administered. There is no identification of the species of Ruminococcaceae bacteria that must be used, the concentration of such bacteria, or the purity of such bacteria. And the only "working examples" of a "composition" administered to a "subject" was that of an aliquot of unprocessed human feces (uncharacterized as to bacteria present and amounts thereof supernatant from 0.1 g/µ1 human fecal suspension) orally gavaged into a. Simply put, the Challenged Claims present a vague and ambiguous wish list of ideas to be invented, while the specification is devoid of any experimental data showing how this theoretical end result was, or could be, achieved by the inventors.

58. Compounding the over-breadth of Challenged Claims, PO injected ambiguity when it chose to define the metes and bounds of its purported invention with claim limitations that have contradictory and, at times, incoherent definitions that lie far outside the understanding of the skilled artesian. When viewed in the context of the claim language, the specification and the prosecution history, the "isolated or purified" claim limitations simply defy construction, leaving a POSA to guess as to what is claimed and what is still open to the public, while the claimed "family of Ruminococcaceae" bacteria is a moving target that is not consistently applied in the relevant field. Thus, the Challenged Claims are unpatentable under 35 U.S.C. § 112(a) and (b).



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59. Worse yet, the conceptual technological problems or solutions theorized by the ’838 Patent are not new. PO’s efforts to ensnare virtually any and all uses of this family of bacteria to treat virtually any and all types of skin cancer, requires a wide berth to navigate the prior art. However, the use of certain bacteria as an anti-cancer agent, including bacteria in the Ruminococcaceae family, was recognized well before the priority date of the ’838 Patent, as shown by the herein-cited Gajewski and Honda references.

60. The sole independent claim of the ’838 Patent recites a single step—“*administering*… a composition comprising [any] isolated or purified population of bacteria belonging to the family Ruminococcaceae”—which was conventional activity as established by Gajewski and Honda. Claim 3 recites further “administering an additional anticancer treatment”, but its breadth does little to distinguish over the well-developed field of prior art. Combination cancer therapies (including combining bacterial agents with a myriad of “other” anticancer treatments) was state of the art. And the “wherein” recitations in dependent claims 8-18 merely recite the intended results of administering a bacterial composition that require no further step or act. As a result, these claims recite only non-limiting statements of intended results; they do not limit the scope of the claims from which they depend.



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## VII. SUMMARY OF THE '838 PATENT

61. The '838 Patent generally relates to methods and compositions for modulating the body's microbiome in order to enhance an immune checkpoint response for the treatment of cancer. A microbiome is a community of microorganisms (*i.e.,* bacteria) that can usually be found living together in any given habitat, such as in the mouth or gut. Immune checkpoints are a normal part of the immune system. Their role is to regulate (either turn up or turn down) an immune response to foreign bodies (including tumor cells) in the body. EX-1023, Abstract, pp.5,6; EX-1024, p. 3.

62. Immune checkpoint inhibitors inhibit the activity of checkpoint proteins (such as PD-1) to up-regulate the activity of the immune cells. EX-1023, Abstract, pp.5,6; EX-1024, p. 3. The '838 Patent acknowledges that "[i]n the context of cancer treatment, immunotherapeutics generally rely on the use of immune effector cells and molecules to target and destroy cancer cells." EX-1001 149:47-63. "Immune checkpoint inhibitors may be drugs such as small molecules, recombinant forms of ligand or receptors, or human antibodies. EX-1001 140:27-30. PD-1 is one example of a known checkpoint protein on the surface of immune cells, called T cells, discussed in the patent. It normally acts as a type of "off switch" that helps keep the T cells from attacking other cells in the body." EX-1023, Abstract, pp.5,6; EX-1024, p. 3.



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63. The ’838 Patent acknowledges that immunotherapy drugs were commercialized decades prior to the filing date of the ’838 Patent. For example, the patent references RITUXAN® (Rituximabz) as a commercially available immunotherapy prior to the effective date of the ’838 Patent. EX-1001 149:46-150:19 (further identifying ADCETRIS®, and KADCYLA® as commercially available antibody drug conjugates).

64. The ’838 Patent acknowledges that numerous prior art “studies suggest that bacteria present in the tumor and the gut may impact therapeutic responses” to cancer therapy. EX-1001 1:44-49. For example, studies conducted between 2008 and 2016 had already shown that a “loss of diversity (dysbiosis)” in the microbiome “is associated with chronic health conditions, cancer and is also associated with poor outcomes to certain forms of cancer therapy….” EX-1001 152:63-153:1. The ’838 Patent further acknowledges that other studies from the same time period had taught that “[c]ompositional differences in the microbiome may also influence cancer development and response to therapy….” EX-1001 153:15-20.

65. The specification describes studies showing that patients with a high abundance of certain gut bacteria presented with a greater immune response compared to other microbiome compositions. EX-1001 157:12-20.One such study, completed in 2015, showed that “patients with a high abundance



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of *Faecalibacterium* in the gut microbiome had a higher density of immune cells and markers of antigen processing and presentation compared to those with a high abundance of Bacteroidales… suggesting a possible mechanism through which the gut microbiome may modulate anti-tumor immune responses." EX-1001 157:12-20; 154:23-28 ("This is in line with recently published data in a small cohort of patients on CTLA-4 blockade, where patients with a higher abundance of *Faecalibacterium* had a prolonged [progression-free survival] compared to those with a higher abundance of *Bacteroides* in the gut microbiome.").

66. In view of this known body of art, PO set out to confirm "if differences existed in component microbiota in the oral or gut microbiomes" of patients showing a response to treatment with anti-PD-1 therapy ("responders" or "R") compared to those who did not show a response ("non-responders" or "NR"). But in answering this question, PO was not starting from scratch. The specification acknowledges that, as of 2015, there already existed "*clear evidence* in pre-clinical models that differential composition of the gut microbiome may influence therapeutic responses to PD-1 blockade at the level of the tumor microenvironment." EX-1001 156:8-12 (emphasis added). PO's "hypothesis," that "patients with a 'favorable' gut microbiome (with high diversity and abundance of Ruminococcaceae/*Faecalibacterium*) have enhanced systemic and anti-tumor immune responses" compared to "patients with an 'unfavorable' gut



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microbiome (with low diversity and high relative abundance of Bacteroidales…") was already suggested in the art. *Id*. 158:1-19.

67. Nonetheless, to test this "hypothesis," PO constructed several "experiments." In the first two experiments, oral (buccal) and gut (fecal) microbiome samples were collected from human patients with metastatic melanoma. EX-1001 151:60-152:17; 175:55-177:12. Patients were grouped into two cohorts characterized as either "responders" or "non-responders" to anti-PD-1 therapy. *Id.* Patients with certain types of melanoma, *e.g.,* uveal melanoma, were excluded from the analysis. EX-1001 175:63-67. Compositional differences in the microbiomes from the two groups were analyzed and characterized. *Id.* Analysis was also performed to determine whether sampled bacterial composition and abundances could serve as a predictor of response to PD-1 blockade, and to determine the potential mechanism for influencing such a response. EX-1001 153:50-154:36; 155:55-156:7; 177:25-181:21. In the second human experiment, immunohistochemistry was also performed on tumor and blood samples obtained from the patients. EX-1001 184:46-187:11.

68. Notably, neither human experiment involved "administering" a "composition" of any kind to a human patient; the only testing was performed on buccal and fecal microbiome samples. EX-1001 156:60-187:11. Instead, consistent with the literature, PO's experiments confirmed what was already



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known: patients that responded to checkpoint inhibitors had higher biodiversity and abundance of *Faecalibacterium* (a member of the Ruminococcaceae family) compared to patients with low diversity and high relative abundance of Bacteroidales. *Id*. 158:1-19.

69. PO's remaining experiments were performed on healthy mice that were subsequently injected with a murine melanoma tumor model. EX-1001 181:23-187:10. The first mouse experiment (Example 3) sought to determine whether butyrate (a short chain fatty acid) could enhance anti-tumor responses by providing a substrate to facilitate a favorable gut microbiome. EX-1001 181:23-182:5. Butyrate was orally administered to two mice cohorts with distinct commensal microbiota purchased from different vendors (*i.e.,* Jackson Laboratory (JAX) and Taconic Farms (TAC)). EX-1001, 181:23-182:5. The TAC cohort had a microbiome enriched with short chain fatty acid producing bacteria, the JAX cohort was not enriched. *Id*. PO reported that butyrate was associated with an enhanced anti-tumor response. *Id.*

70. The next set of mouse experiments (Examples 4 and 5) involved transplants of human fecal matter. EX-1001 182:6-187:10. Germ free mice were transplanted by oral gavage (a small tube inserted directly into the stomach or intestine of the mouse) with human feces from responder or non-responder patients. EX-1001 182:6-27; 184:50-185:8. Two weeks after the fecal matter



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transplant (FMT), the mice were injected with cells containing a murine melanoma tumor model. In one experiment (FMT2), mice were also treated with anti-PD-L1 monoclonal antibody once the tumors reached a designated size. *Id.*

71. Example 4 does not disclose what steps were taken, if any, to prepare the fecal samples. EX-1001 182:6-184:44. Nor does the specification disclose any steps that were taken to characterize the specific bacteria, or the concentration of such bacteria, present in the human fecal samples. *Id*.

72. Similarly, Example 5 (entitled "Fecal Microbiota Transplantation Methods") fails to disclose any steps taken to characterize the specific bacteria present in the transplanted human fecal samples. *Id.* Indeed, despite containing the only description in the specification of *any* composition "administered" to a "subject" (*i.e.,* mice), Example 5 states only that "a 200 µl cleared supernatant from 0.1 g/µl human fecal suspension was obtained using a 100 µm strainer and gavaged into mice for 3 doses over 1 week, followed by a break of 1-week to allow microbiome establishment." EX-1001 184:61-185:2. Neither the concentration nor the composition of bacteria in the FMT were measured so it is unknown if anything was isolated or purified.[1] EX-1001 184:50-186:18.

[1] And, thus, to the extent that the purported "methods" disclosed in Example 5 can (generously) be read to have been applied to the FMT's disclosed in Example 4



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### A. Prosecution History

73. On March 28, 2019, PO filed the application leading to the '838 Patent containing 161 claims. Following a restriction requirement, PO elected to prosecute group III (method claims) and made a species election (class Clostridia). EX-1002, 132 and 135. The election included the following original independent claim 44:

> A method of treating or preventing cancer in a subject comprising administering to the subject a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus *Faecalibacterium*.

EX-1002, 620.

74. Examiner issued the first substantive Office Action on April 9, 2021. Examiner rejected all pending claims because the grouping of bacteria set forth in Claim 44 did not share both a single structural similarity and a common use and, thus, contained an improper Markush group. Examiner also rejected claim 44, the only independent claim, as anticipated by both *Miquel*, et al. (EX-1014) and

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(there is no such indication in the specification), Example 5 fails to provide any additional detail.



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*Patyar*, et al., (EX-1005), and claim 44 as obvious over *Patyar,* et al. (EX-1005) in view of *Wei*, et al. (EX-1006). Ex-1002, 115-120.

75. In response, PO amended claim 44 to recite only bacteria in "the family Ruminococcaceae," thereby withdrawing claim scope directed at bacteria in the "class Clostridia", "class Mollicutes," and "order Clostridiales." Ex-1002, 100-110. PO also deleted reference to a method of "preventing cancer," focusing instead on a method of "treating cancer or reducing or delaying tumor growth." *Id.* PO argued that these claim amendments overcame Examiner's rejections. *Id.*

76. In response, Examiner issued a final Office Action rejecting the pending claims under 35 U.S.C. 112(a) because the specification failed to demonstrate possession of the full scope of amended claim 44. EX-1002, 85-91. PO responded by again amending claim 44 and submitting remarks purportedly identifying written description support for the scope of pending claims. Specifically, PO deleted reference to "*one or more*" isolated or purified population of bacteria belonging to the family Ruminococcaceae from claim 44. *See* EX-1002, 38-49. Moreover, relying heavily on Example 4, PO argued that its disclosure "is not limited to 'direct injection of a fecal microbiota sample (FMT) to said tumor'" but more broadly to administration of a composition of such bacteria by any means possible. *Id.*



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77. Nowhere, however, did PO identify any composition – other than uncharacterized human feces – that was administered to a subject to cause the claimed "reduction or delayed growth" of tumor cells. *Id.* Moreover, PO failed to identify any steps taken to "isolate or purify" the fecal samples, to determine the actual composition or concentration of bacteria contained in the fecal samples, or to formulate or administer a pharmaceutically acceptable dosage of such bacteria that was safe or effective in all subjects. *Id.*

78. Following a telephonic interview, Examiner proposed claim amendments, authorized by PO, deleting reference to, *inter alia*, "treating cancer" from the claim scope. EX-1002, 19. On March 18, 2022, Examiner allowed the application without providing any explicit Reasons for Allowance. EX-1002, 11-19.

### B. Claim Construction

79. I understand that Petitioner proposes that each claim term in the Challenged Claims not identified below be given its plain and ordinary meaning in this proceeding. For the terms "isolated or purified" the specification sets forth a definition that deviates from the plain and ordinary meaning.

#### 1. "subject in need thereof"

80. This phrase is expressly recited in independent Claim 1, which refers to a "method of reducing or delaying growth of a skin cancer tumor 'in subject in



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need thereof.'" EX-1001 189:1-6. As set forth below, a POSA understood this phrase to mean "a human or non-human, such as primates, mammals, and vertebrates."

81. Indeed, the language in the specification and the working examples are instructive. As an initial matter, the specification contains a "definition" section which expressly provides that the terms:

> 'Subject' and 'patient' refer to either a human or non-human, such as primates, mammals, and vertebrates. In particular embodiments, the subject is a human.
>
> EX-1001, 27:50-52.

82. PO's express definition is confirmed by their use of the term "subject" to refer to both human and non-human species throughout the specification, wherein the term "subject" was used to refer to both human patients and non-human mice. EX-1001 18:28-34; FIG. 9A-B (describing "subject" data relating to a human "patient"); 25:64-26:23 (using the term "subject" and "patient" interchangeably); 139:25-33 ("the present disclosure concerns… obtaining a sample obtained from a subject (*e.g., a human subject*)…")(emphasis added).



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### 2. Wherein Clauses Reciting Intended Results Are Not Limiting

83. The following claim phrases found each purport to add a feature to the claims from which they depend, but in fact are only non-limiting statements of intended results:

| Claim No.: | Non-limiting statement of intended effect: |
|---|---|
| 8 | ***wherein*** administration of the composition ***results in*** an increase of $CD8^+$ T lymphocytes in the tumor. |
| 9 | ***wherein*** the [administration of the composition ***results in*** an increase of]… cytotoxic T lymphocytes. |
| 10 | ***wherein*** administration of the composition ***results in*** an increase of effector $CD4^+$, $CD8^+$ T lymphocytes, monocytes and/or myeloid dendritic cells in the systemic circulation or the peripheral blood of the subject. |
| 11 | ***wherein*** administration of the composition ***results in*** a decrease of B cells, regulatory T cells and/or myeloid derived suppressor cells in the systemic circulation or the peripheral blood of the subject. |
| 12 | ***wherein*** administration of the composition to the subject ***results in*** an increase in CD3, CD8, PD1, FoxP3, Granzyme B and/or PD-L1 expression in a tumor immune infiltrate. |
| 13 | ***wherein*** administration of the composition to the subject ***results in*** a decrease in RORγT expression in a tumor immune infiltrate. |
| 14 | ***wherein*** administration of the composition to the subject ***results in*** an increase in $CD45^+$, $CD3^+/CD20^+/CD56^+$, $CD68^+$ and/or HLA-$DR^+$ cells in the tumor. |
| 15 | ***wherein*** administration of the composition to the subject ***results in*** an increase in the level of innate effector cells in the subject. |



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| | |
|---|---|
| 16 | ***wherein*** the [administration of the composition to the subject ***results in*** an increase in the level of]… $D45^+CD11b^+Ly6G^+$ [innate effector] cells. |
| 17 | ***wherein*** administration of the composition to the subject ***results in*** a decrease of the level of suppressive myeloid cells in the subject. |
| 18 | ***wherein*** [administration of the composition to the subject ***results in*** a decrease of the level of]… $CD45^+CD11b^+CD11c^+$ [suppressive myeloid] cells. |

84. I understand that claim language that merely recites an intended result of a claimed method and does not alter the steps of the method does not limit the scope of the claim. This is particularly true of "wherein" clauses, which often signal recitations of intended results that do not limit claim scope. I understand that although a wherein clause may be limiting when it states a condition that is material to patentability, that is true only when the clause is *more than* the intended result of a process step and is part of the process itself or an integral part of the invention.

85. I further understand that, while the doctrine of claim differentiation creates presumption that each claim in a patent has a different scope; it is not a hard and fast rule of construction.

86. In this case, Claim 1 of '838 Patent is drawn to the straightforward method of "administering" to a subject "a composition comprising an isolated or purified population of bacteria…." Thus, the only action, or manipulative step,



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required by the claimed method is "administering" a composition to the subject. EX-1001 189:1-6. This step defines a complete treatment method. Dependent claims 8-18, by contrast, do nothing more than identify the purpose and intended results of the recited administration. They do not alter the method at all. They do not suggest any adjustments to the amount of bacteria to be administered, the route of administration, the frequency or timing of administration, or the subjects to whom the composition is administered.

87. Rather Claims 8-18 include "wherein" clauses that recite various known measures used to determine the efficacy of skin cancer treatments, including both therapeutic and systemic immune responses. The specification characterizes these features as natural results of the body's systemic "anti-tumoral response," including cell-mediated immune responses such as regulation of cytokines, regulatory T cells (*e.g.,* lymphocytes, and monocytes) and myeloid derived suppressor cells in the systemic circulation. EX-1001, 183:17-31. The specification never suggests that these measures of efficacy have any impact on what steps are performed or how they are performed.

88. Similarly, PO characterized these "indicators" of the biological response as resulting from the administering Ruminococcaceae bacteria during prosecution. EX-1002 pg. 46 (stating that stool administration from responder patients "***resulted in*** stable transplantation… and a higher percentage of innate



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effector cells (expressing CD45+CD1lb+Ly6G+) and lower frequency of suppressive myeloid cells (expressing CD11b+CD11c+)"). As such, a POSA understood that these are the "outcome measures" and "results" of administering a bacterial composition; they are not steps.

89. Because the wherein clauses of claims 8-18 of the '838 Patent recite only intended results that in no way limit, qualify, or change the steps of the claimed method, they are not limitations. *Id.*

**3. "isolated or purified"**

90. This phrase is expressly recited in Claim 1, which refers to an "isolated or purified" population of bacteria belonging to the family Ruminococcaceae." EX-1001, 189:1-6. As set forth below, these terms, when read in view of the claims, the specification and the prosecution history, fail reasonably inform a POSA as to the scope of the claimed invention. Neither the "plain and ordinary" meaning of these terms, nor the meaning PO chose to ascribe these terms in the "definitions" section of the specification, afford a POSA clear notice of what is claimed and what is not.

91. If, however, the Board were to find this term not indefinite, a POSA understood that the plain and ordinary meaning of the term "isolated" would at least include "a single species of a bacterium obtained in a pure culture." EX-1022. Similarly, a POSA might reasonably construe a "purified" bacterial



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population to refer to one that has been made "pure by removing any harmful, dirty, or inferior substances from it." EX-1023.

### C. Priority Date of the Challenged Claims

92. I understand that the '838 Patent claims priority to three provisional applications, provisional application No. 62/400,372, filed on September 27, 2016, provisional application No. 62/508,885, filed on May 19, 2017, and provisional application No. 62/557,566, filed on September 12, 2017. I have been instructed to assume for purposes of this Petition, the filing date of the earliest provisional application leading to the '838 Patent, September 27, 2016, is the priority date of the Challenged Claims.

### D. State of the Art

93. The following section describes the state of the art concerning the effects of the microbiome on skin cancer growth as of the effective filing date, September 27, 2016 (*see* § VI(D), *supra*). The prior art references discussed in this section, and discussions of what was known to a POSA, provide a general description of the state of the art at the time of the invention, provide additional background as to why it was necessary for the specification to identify and describe various conditions and parameters impacted by such conditions to show how the theoretical end result described in the '838 Patent was or could have been achieved by the inventors and/or a POSA, provide additional motivation to



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combine the primary reference Honda with the other references cited herein (Gajewski and Miquel), and provide support for why a POSA would have had a reasonable expectation of success in combining the teachings of these references. The additional prior art references identified in this section are exemplary in nature, and provide factual support for my opinions, and considered to show the general state of the art, to identify an absence of written description support or enablement in the specification, to identify motivation to combine the teachings of the primary references, to support reasonable expectation of success, to rebut any assertions of unpredictability in the art or unexpected results, and to rebut any assertions that the claims are directed patentable subject matter.

### 1. The Human Gut Microbiome

94. It is estimated that the distal intestine of humans contains tens of trillions of microbes (of thousands different species potentially outnumbering the number of human cells in our bodies). EX-1008 p.1; EX-1007 p.260. It has long been known that microorganisms in the gut (*i.e.,* "commensals" or "commensal microorganisms") exert a battery of functions for the optimal health of an organism, including the processing of nutrients, degradation of xenobiotics, protection from pathogenic microbes, regulation of intestinal barrier homeostasis, and maturation of the immune and enteric nervous systems. EX-1007 p.261; EX-1008 pp.200-201. Although the microbiome is generally stable within each



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individual, there exists a vast level of inter-individual heterogeneity that is largely determined by the host's diet and environment as well as by other factors such as medications (*e.g.*, antibiotics) and smoking. EX-1007 p.261.

95. Among the Bacteria colonizing the human gut, Bacteria in the genus *Ruminococcus* is known to be among the most dominant, and Bacteria of the genus and species "*Faecalibacterium prausnitzii"* is one of the three most abundant species found in the gut. EX-1008 p.200; EX-1009 p.28 (reporting that *Faecalibacterium prausnitzii* represents "between 2% and 20% of the fecal microbiota in healthy individuals"). Hence, Bacteria of the purported Ruminococcaceae family are known to be dominant Bacteria colonizing the human gut (since *Ruminococcus* and *Faecalibacterium prausnitzii* are in the purported family Ruminococcaceae). EX-1015 p.1016.

96. Scientists and clinicians have had particular interest in *F. prausnitzii* given its role in promoting gut health through the formation of anti-inflammatory compounds, including butyrate, and enhancement of intestinal function. *See e.g.,* EX-1009 pp.28-29, EX-1017 and EX-1018. Since at least the mid-2000's, POSAs conducted an increasing number of studies describing the importance of this highly metabolically active commensal bacterium. POSAs recognized that changes in the abundance of *F. prausnitzii* – namely, lower levels than that found in normal, healthy individuals – were associated with patients with cancer, and that levels of



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*F. prausnitzii* could be a useful indicator of healthy gut status and hence a patient's health. EX-1009 p.28 (lower levels of… *F. prausnitzii*… were found in subjects with… colorectal cancer (P<0.001) compared with [healthy] subjects.").

97. But the use of bacteria as therapeutic agents can also present certain challenges when administered outside of the intestinal tract as permitted by the Challenged Claims. EX-1005 pp.2, 6. For example, one major problem with using bacteria as therapeutic agents administered outside of the intestinal tract is their toxicity at the dose required for therapeutic efficacy, while reducing the dose can result in diminished efficacy. EX-1005 p.2. Moreover, a systemic infection of bacteria carries higher risk of obvious toxicity. EX-1005 p.6.

98. Cultivating and formulating bacteria into pharmaceutically acceptable compositions can also present myriad issues. *Id*. It was well-known that many gut bacteria are anaerobic, and will die when they come in contact with oxygen. EX-1005 p.2; EX-1019 pp.2142-44. For example, *F. prausnitzii* is an extremely oxygen sensitive bacterium and is difficult to cultivate even in anaerobic conditions. EX-1019 pp.2142-44.

99. Nonetheless, in view of Bacteria of the Ruminococcaceae family, the *Ruminococcus* genus and the genus and species *Faecalibacterium prausnitzii* being butyrate producers, and the recognized importance of the gut microbiome to overall health and disease, POSAs remained focused on the use of Bacteria of the



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Ruminococcaceae family, the *Ruminococcus* genus and the genus and species *Faecalibacterium prausnitzii* for therapeutic treatments.

### 2. Bacterial Treatment Was a Well-Recognized Strategy for Cancer Treatment

100. The role of bacteria as anticancer agent was recognized almost one hundred years back. EX-1005 pp.2-3. For example, German physicians W. Busch and F. Fehleisen separately observed that certain cancers regressed following accidental infections with certain bacteria (*Streptococcus pyogenes*). *Id*. Independently, an American physician, William Coley, made a similar observation. *Id*. As a result, Coley began the first well-documented use of bacteria and their toxins to treat end stage cancers. *Id*. By the late 1800's, he had developed a widely used bacterial vaccine to successfully treat sarcomas, carcinomas, lymphomas, melanomas and myelomas. *Id*.

101. Soon, the use of live, attenuated or genetically-modified, non-pathogenic bacteria began to emerge as antitumor agents, either to provide direct tumoricidal effects or to deliver tumoricidal molecules. *Id*. POSAs recognized that bacteria could be used as anti-cancer agents either alone or in combination with conventional chemotherapeutic agents. *Id.*; EX-1007 p.202 ("gut microbiota is indispensable for the immunomodulatory and antitumor effects of certain anticancer therapeutics"). POSAs understood that gut microbiota could influence



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both therapeutic and adverse effects of anti-cancer interventions either through pharmacodynamic or immunological mechanisms. EX-1007 p.1261.

102. With respect to the immunological mechanisms, POSAs understood that immunotherapy for treating cancer included inhibition of immune regulatory checkpoints, such as such as CTLA-4 and the PD-1-PD-L1 axis–immune-checkpoint blockers. EX-1007 Abstract, 1255. T-helper 17 (Th17) cells were also known to play a protective role against tumors. EX-1010 Abstract, 787. Th17 cells, found in tumor tissues, were known to elicit a protective inflammation that promotes the activation of tumor-specific CD8+ T cells. EX-1010 Abstract, 787.

103. By 2015, POSAs were aware of a cause-effect relationship between lack of Th17 cells elicited by commensals (gut microbiome) and loss of chemotherapeutic efficacy in a transplantable tumor model. EX-1008 p.205.

104. Another chemical known to POSAs to play a major role in modulation of immune system and reduction of cancer progression is butyrate. EX-1008 p.209. For example, "butyrate, one of the most abundant short-chain fatty acids resulting from the bacterial fermentation of fibers" within the gut, was known to be "the most compelling tumor-suppressing molecule". EX-1008 p.209 ("Butyrate acts within T cells to enhance acetylation of the Foxp3 locus and protein … [g]ut microbiota also controls the systemic TH17 pool.").



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105. These initial breakthroughs linking the gut microbiota to the immune-mediated efficacies of anti-cancer therapies highlighted the importance of an intact commensal microbiota in cancer therapy and suggested the possibility of (re)establishing a favorable microbiota in patients with ineffective pre-existing enteric microbial microflora. EX-1007 pp.1261-1262. By 2015, "[t]he impact of gut microbiota in eliciting innate and adaptive immune responses beneficial for the host in the context of effective therapies against cancer" was well recognized in the art. EX-1008 Abstract. POSAs had concluded that "restoring an 'ideal' microbial composition could theoretically be a more suitable option" to reduce inflammation-induced cancers, and that "[p]robiotics and prebiotics represent more common ways to establish/maintain healthy microbiomes." EX-1008 p.209.

106. Indeed, as shown in the illustration below, POSAs had concluded that "better management of cancer patients" should be directed at

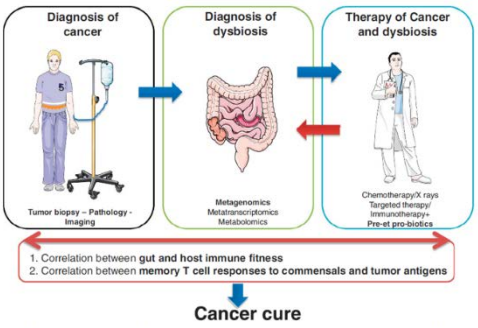
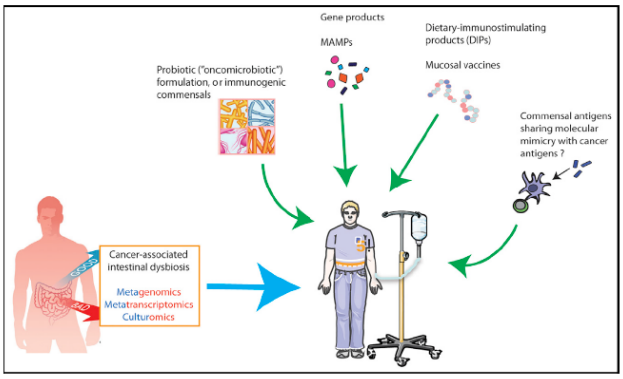



**Figure 3** Future prospects and clinical implementations of this work. To date, patients who are being diagnosed with cancer undergo a pathological biopsy and imaging tomography/magnetic resonance to analyze spreading of the malignant process. In the near future, we will need to investigate their intestinal microbiota and their systemic anticancer and antimicrobial immunity to be able to adapt/personalize the oncological therapy according to their microbial dysbiosis or immune dysfunctions. Specific food intake as well as probiotics composed of immunogenic (and safe) commensal/pathobionts could precede chemotherapeutics to facilitate their tumoricidal activity through bacterial adjuvantization

"(i) diagnosing patients dysbiosis…, (ii) compensating dysbiosis by appropriate 'immunogenic probiotics'…, and (iii) prebiotics synergizing with probiotics to set the stage for a healthy intestine…." EX-1008 pp.209-210. Moreover, this view was shared by others in the field. For instance, Pitt's Figure 3 (reproduced below) also




emphasized the use of probiotic formulations as effective immunotherapy, concluding that:

> Determining the precise microbiome of a given patient is becoming possible with the development of metagenomics, metatranscriptomics, and culturomics platforms. The gathered information from these techniques can be used for selecting an approach that will facilitate a particular cancer immunotherapy. ***Ancillary therapeutic approaches that can be selected to achieve this might include probiotic formulations….***



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EX-1007 p.1264 (emphasis added).

## VIII. IDENTIFICATION OF CHALLENGES

### A. Challenged Claims

107. All 19 claims of the ’838 Patent are challenged in this Petition.

### B. Statutory Grounds for Challenges

108. The Challenges are set forth in detail below:

| GROUND | CLAIMS | BASIS | PRIOR ART |
|---|---|---|---|
| 1 | 1-19 | 35 U.S.C. § 112(a) (possession of invention) | |
| 2 | 1-19 | 35 U.S.C. § 112(a) (lack of enablement) | |
| 3 | 1-19 | 35 U.S.C. § 112(b) (indefiniteness) | |
| 4 | 1-3, 5-19 | 35 U.S.C. § 103 | Honda in view Gajewski |
| 5 | 4 | 35 U.S.C. § 103 | Honda in view of Gajewski and Miquel |

109. I have been informed that International Publication No. WO2015/156419 (Honda), International Publication No. WO2016196605A1 (Gajewski), and printed article “*Faecalibacterium prausnitzii* and human intestinal health” (Miquel) each qualify as prior art under 35 U.S.C. § 103 for purposes of this IPR.



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## IX. IDENTIFICATION OF HOW THE CHALLENGED CLAIMS ARE UNPATENTABLE

### A. Ground 1: Claims 1-19 are Unpatentable Under 35 U.S.C. § 112 for Lack of Adequate Written Description Support

110. In this case, the specification simply cannot support the broad breadth of the Challenged Claims. Several claim limitations, including "administering", "subject", "composition", and "skin cancer tumor" have such limitless range that the scope of the Challenged Claims are entirely untethered from any reasonable construction of PO's purported "invention" described in the specification. The sheer breadth of these terms – when construed consistent with the specification and PO's own definitions – expands the scope of these claims far outside the bounds of any written description support in the specification.

111. Indeed, the '838 Patent specification merely theorizes that a population of bacteria arising under the *entire* taxonomic family of Ruminococcaceae may be formulated, *in any way imaginable*, to be administered, *using any technique imaginable*, to *every vertebrate subject imaginable*, to reduce or delay the growth of skin cancer of *any type imaginable*. PO claims this unbounded technological breakthrough even though they did not create *a single* composition, administered in *any way*, to reduce or delay growth of *any type* of skin tumor in a human – or across the breadth of every vertebrate.



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112. The Petition provides three examples that demonstrate that the '838 Patent specification contains no disclosure whatsoever that can be said to reasonably convey to a POSA that the inventors had possession of a composition for reducing or delaying growth of all skin cancer tumors in all subjects as of September 27, 2016.

### 1. PO Did Not Administer Any "Composition" To An Animal Model Across the Breadth of "Subject"

113. As described above, the '838 Patent specification discloses two types of experiments: the first involved *characterizing* the microbiome of human patients with metastatic melanoma; while the second investigated the effects of altering the microbiome on tumor growth in mice. Critically, the patent contains no disclosure of a single "composition" comprising "isolated or purified" Ruminococcaceae bacteria administered to a human, yet such a composition falls squarely within the scope of the Challenged Claims.

114. Instead, the only experiments conducted with human patients involved the *characterization* of gut and buccal microbiome of metastatic melanoma patients. Specifically, buccal (oral) and gut (fecal) microbiota samples were collected from patients undergoing treatment with an immune checkpoint blockade therapy for metastatic melanoma. EX-1001 151:60-152:62. Genomic sequencing was then used to compare the microbiome samples from patients who were deemed "responders" to those deemed "non-responders" to the therapy, in order to



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identify potential differences in the respective bacterial composition of the microbiome. *Id.* Among the many types of bacteria found in the responder samples, included some bacteria from the family Ruminococcaceae. EX-1001 153:15-49.

115. Notably, only genomic analysis of the oral and fecal samples was performed; no "composition" of any kind was "administered" to any subject. EX-1001 151:60-181:21. Nor can any results of the experimentation reported in the '838 Patent be ascribed to bacteria particularly from the family Ruminococcaceae. *Id.* To the contrary, as discussed below, and as shown in Tables 1 and 2 of the '838 Patent, bacteria from the family Ruminococcaceae were found in ***both*** the "responder" and "non-responder" fecal samples. EX-1001, Table 1 and 2.

116. The second type of experiments were conducted on a mouse melanoma model system. In the first mouse experiment, a cohort of mice were orally administered butyrate (a short chain fatty acid) in order to explore its impact on the mouse gut microbiome. EX-1001 181:21-182:5. While in the second set of mice experiments, mice received a "fecal microbiota transplantation" (FMT) (*i.e.,* a sample of human feces) taken from either a human "responder" patient or a human "non-responder" patient, in order to establish an altered version of these microbiomes in the mice. EX-1001 182:6-184:44. Uncharacterized non-sterile human feces was gavaged directly into the stomachs or small intestines of the



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mice. EX-1001 181:21-184:44. Tumor growth was then measured and compared between the mice gavaged with responder stool versus mice gavaged with non-responder stool. *Id.* PO then invited more research to determine the potential value in humans, concluding that "[t]hese findings highlight the potential for parallel modulation of the gut microbiome to significantly enhance checkpoint blockade efficacy, ***warranting prompt evaluation in clinical trials***." EX-1001 23:49-52 (emphasis added). Again, no clinical trials were performed and no human was administered either butyrate or a fecal matter transplant. EX-1001 181:21-184:44. Nor were any steps taken to characterize the composition or concentration of bacteria in the FMT. EX-1001 182:6-184:44.

117. Despite this limited disclosure, the Challenged Claims nonetheless claim any and all "compositions" comprising an isolated or purified population of bacteria belonging to the family Ruminococcaceae, that can be "administered" in any way, to any type of "subject," to reduce or delay growth of any type of "skin cancer tumor." Yet, the only "composition" of such bacteria taught in the specification, was an uncharacterized sample of human feces; the only route of "administration" taught in the specification, was "oral gavage"; the only type of "subject" taught in the specification, were mice; and the only type of "skin cancer tumor" taught in the specification, was non-naturally occurring melanoma that was artificially implanted on mice.



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### 2. PO Did Not Possess Any "Composition" For "Administration" To a Human

#### a. PO Did Not Formulate Any "Compositions" For Administration

118. PO never formulated any "composition" suitable for administration to a human, much less a composition suitable for administration by any means imaginable. To be sure, the specification does theorize as to the host of different compositions that *could* potentially be formulated (*e.g.,* "tablet or powder form… chewable formulation, a dissolving formulation, an encapsulated/coated formulation, a multi-layered lozenge... or other suitable formulations…"). And the specification theorizes about a near limitless list of ingredients that *could* potentially be used to create such formulations. EX-1001, 137:42-45 (*e.g.,* "various substances, such as gelatin, cellulose, carbohydrate or the like"); 137:47-55 (identifying over 25 compounds or classes of compounds); 137:56-139:25 (identifying countless additional active and inactive ingredients that could be used to formulate the claimed composition).

119. However, the specification fails to disclose a *single* such composition that was *actually* created. And the specification is silent as to any experimental conditions necessary to formulate any of these theoretical, and assumed, compositions.



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120. A POSA understood that determining which excipients or combinations of excipients are best suited for a robust formulation requires a comprehensive pre-formulation strategy that includes a host of experimentation and testing. This includes analysis of the physicochemical, biopharmaceutical, and pharmacokinetic properties of the dosage form, as well as stability, bioavailability, and toxicology considerations of the bacteria.

121. Moreover, because bacteria are living microorganisms, a POSA understood that many biological and biopharmaceutical barriers limit their clinical application. For example, they are easily destabilized during their preparation, storage, and in vivo application. They easily lose their viability under thermal, compressive or oxidative stress during their preparation, manufacture and storage. Bacteria may lose their activity in the harsh gastric conditions of the stomach, in aerobic (or anaerobic) conditions, or in the presence of bile salts. Therefore, stable formulations of bacteria are required to overcome the various physicochemical, biopharmaceutical, and biological barriers and to maximize their therapeutic effectiveness and clinical applicability.

122. Nothing in the specification demonstrates that PO was in possession of any "composition" comprising Ruminococcaceae bacteria suitable for administration to a human. Similarly, nothing in the specification enables a POSA



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to make and use a composition safe and effective for administration, by every means possible.

### b. Formulation Strategies Change Depending on the Route of Administration

123. POSAs recognized that formulation strategies will vary depending on the route of administration, and that each route of administration has its own biological barriers and limitations. For example, POSAs recognized that the route of administration is impacted by the anatomical properties, microclimate, and specific physiological conditions of the administration site. Therefore, formulation strategies can vary with routes of administration, bacteria strains, and therapeutic areas.

124. The specification of the ’838 Patent, however, does not provide any teaching as to how the route of administration may alter the theoretical, and assumed, compositions recited in the Challenged Claims. EX-1001, 137:30-37 (stating only that “[w]hile the compositions of the present disclosure are preferably formulated for oral administration, other routes of administration can be employed, however, including, but not limited to, subcutaneous, intramuscular, intradermal, transdermal, intraocular, intraperitoneal, mucosal, vaginal, rectal, and intravenous.”). The near limitless breath of the Challenged Claims is unsupported in view of the fact that the only composition “administered” in the specification was an aliquot of human feces orally gavaged into mice. No human was orally



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"administered" any unprocessed fecal composition (and, no doubt, for good reason!).

125. Nonetheless, having failed to administer *any* composition of Ruminococcaceae bacteria to a human, PO cannot be found to be in possession of a claim to administering such a composition, and by *every means possible*.

### c. PO Does Not Teach What Bacterial Concentrations Were Used

126. Perhaps even more critically, the specification fails to disclose the concentration of bacteria that was used in the mouse experiments, much less what concentration may be necessary to create a safe and effective dose in any subject (or how that concentration may be required to change depending on the route of administration or the type of subject being treated). For example, the specification discloses that "200 µl cleared supernatant from 0.1 g/µ1 human fecal suspension was obtained using a 100 µm strainer and gavaged into mice for 3 doses over 1 week". EX-1001 184:65-185:2. But that does nothing to inform a POSA of the concentration of bacteria found in the "200 µl cleared supernatant" repeatedly gavaged into the mice.

127. Nor does PO's experiments inform a POSA of what concentration is required for an effective dose across all claimed subjects. Instead, a POSA readily understood, and the specification itself acknowledges, that "[t]he actual dosage amount of a composition of the present embodiments administered to a patient or



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subject" can only be determined by a host of "physical and physiological factors, such as body weight, the age, health, and sex of the subject, the type of disease being treated, the extent of disease penetration, previous or concurrent therapeutic interventions, idiopathy of the patient, the route of administration, and the potency, stability, and toxicity of the particular therapeutic substance." EX-1001 25:64-26:23. Nothing in the specification teaches a POSA how to adjust the bacterial concentration in the composition based on any of the numerous physical and physiological factors that impact this amount.

128. Instead, the specification then provides a broad range "from about 1 μg/kg/body weight to about 1000 mg/kg/body weight" – a difference of $1x10^6$ – which is also intended to "include[ ] intervening doses… or more per administration, and any particular dose derivable therein" and be effective across all species. EX-1001, 26:12-16. For human administration, the specification speculates that a "therapeutically effective or sufficient amount" will be "at least about $1\times10^3$ to… $1\times10^{15}$ *or greater*" colony forming units (CFU) of bacteria. EX-1001, 146:48-65. However, an adequate written description requires more than a mere wish or plan for obtaining the claimed chemical invention.

129. Having failed to administer *any* concentration of bacteria to a human to reduce or delay growth of a skin cancer tumor, PO simply could not have been



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in possession of a method of administering the *every* conceivable concentration of such bacteria.

### d. Bacteria from the "Family of Ruminococcaceae" Lacks Written Description Support

130. Further compounding the lack of written description or supporting disclosure for a method of administering "all" concentrations of Ruminococcaceae bacteria, is the fact that: (i) certain species of bacteria from the claimed "Ruminococcaceae" family were found only in stool of "non-responder" patients; and (ii) in any event, the claims are not limited to bacteria from this taxonomic family. EX-1001 Table 2; 189:1-190:34.

131. For example, Table 2 of the '838 Patent identifies several species of Ruminococcaceae that PO found to be more abundant in "non-responders", including "Anaerotruncus colihominis," "Ruminococcaceae bacterium D16" and "*Ruminococcus* gnavus." EX-1001, Table 2. The specification reports that these "non-responder" (NR) bacterial species are "predicted to not have a favorable response to the immune checkpoint inhibitors." EX-1001, 15:35-55. Moreover, "if the microbial profile comprises one or more of the bacteria species in Table 2 designated with a response status of non-responder (NR)… then the patient is predicted to not have a favorable response to the immune checkpoint inhibitor." EX-1001, 16:21-32. Thus, a POSA would understand that at least several species



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of Ruminococcaceae would *not* result in the claimed "reduction" or "delay" in skin cancer tumor growth.

132. This understanding is further supported by PO's manuscript (published after the filing date of the '838 Patent), as well as data in Table 1. For example, the subsequently published manuscript contains additional data on the bacterial species reported in Table 2. EX-1021, Table S4. This data show that the majority of species in the Ruminococcaceae family were not significantly associated with either "responder" or "non-responder" samples. *Id.*

133. Moreover, Table 1 of the '838 Patent identifies fifteen different Ruminococcaceae bacteria were found *only* in fecal samples of *non-responder* patients. EX-1001, Table 1; 178:22-27 (explaining that bacteria in Table 1 having an "enrichment index" (ei) of "-1" indicates that the identified species is present in *all* non-responder samples *but not* in responder samples). And an additional four different Ruminococcaceae bacteria were found *more often* in fecal samples of *non-responder* patients than in responder samples. EX-1001, Table 1; 178:22-27 (*i.e.,* bacteria in Table 1 having an ei of <-0.5). As a result, a POSA understood that PO was not in possession of a method of reducing or delaying growth of a skin cancer tumor by administered a composition comprising bacteria from the entire family of Ruminococcaceae, because the specification teaches numerous species of



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Ruminococcaceae that would *not* result in the claimed "reduction" or "delay" and are found *only* in non-responder feces.

### e. The "Comprising" Transition Creates Additional Written Description Problems

134. The over breadth of Claim 1 is further compounded by PO's use of the "comprising" transition. EX-1001 at 189:1-190:34 (*i.e.,* "a composition *comprising* an isolated or purified population of bacteria from the family Ruminococcaceae"). Given the plain meaning of the "comprising" transition, a POSA understood that the administered composition can include bacteria arising from other taxonomic families, so long as it also includes bacteria from the Ruminococcaceae family. Not only does this open transition render the "isolated or purified" claim language nonsensical (as discussed further below), but the resulting claim scope lacks support in the specification.

135. For example, the specification identifies numerous bacterial species, including bacteria of the class Bacteroidia or family Prevotellaceease, that demonstrated "a strong negative correlation" or detrimental effect on the "anti-tumor immune responses". EX-1001, 156:8-157:8; FIGS. 4D and 21-22. Yet, the "comprising" claim transition expressly permits such undesirable bacterial species to be present in the administered composition.

136. As a result, the specification lacks written description support demonstrating that PO was in possession of a composition comprising bacteria



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from both (i) the family of Ruminococcaceae, and (ii) the class Bacteroidia or family Prevotellaceease (or any other non-desired species), which can reduce or delay growth of skin cancer tumors. To the contrary, there is no disclosure in the specification of the anti-tumor characteristics or therapeutic impact of any such combination (or combinations) of responder and non-responder bacteria.

### 3. PO Did Not Possess A "Composition" Capable of "Reducing or Delaying Growth" of All Skin Cancer Tumors

137. Finally, the '838 Patent acknowledges that efficacy of claimed method, will vary depending on the type, location, and disease progression of the "skin cancer tumor" being treated, as well as the health and age of the patient. EX-1001, 147:9-17. The specification teaches that "[o]bviously, certain types of tumors will require more aggressive treatment, while at the same time, certain patients cannot tolerate more taxing protocols." EX-1001 147:11-16. Ultimately, the specification leaves the "clinician… to make such decisions based on the known efficacy and toxicity (if any) of the therapeutic formulations." *Id*. The specification, however, contains results from a single "syngeneic model of injectable murine melanoma" induced in mice. EX-1001 181:34-185:8. Given that the specification identifies dozens of different types of "skin cancer tumors", and PO did not conduct any experiments – and the specification contains no data or results – demonstrating the claimed method of administration would be effective for anything other than the mice model experiments, a POSA would not have



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understood PO to be in possession of a method of treating every type of "skin cancer tumor" in every type of subject. EX-1001 13:12-24.

138. And much of the data presented in the specification is unreliable. For example, while the tumor size in mice receiving FMT2 in Example 4 were significantly different at day 14 (before anti-PD1 treatment), no such statistical significance was observed at the end of the experiment (day 28 p=0.2). EX-1001 FIG. 28A-C. As a result, PO's data do not provide evidence of enhancing anti-PD(L)1.[2] *Id.* Similarly, with respect to mice receiving FMT3, a POSA understood that it is not even possible to show a "statistically significant difference" because the specification teaches that only 1 mouse in each group received the FMT. EX-1001 184:27-45. A POSA understood that a sample size of 1 is simply too small to show "significance".

139. PO also took steps to actively *exclude* from its experiments certain types of melanoma including, for example, uveal melanoma. EX-1001 175:63-67 ("Patients who were diagnosed with uveal melanoma (n=10)… *were excluded* from this analysis.") (emphasis added). Having deliberately excluded certain types

[2] Moreover, a POSA would be unable to determine, based on a single time point, whether the observed difference is a purported "delay" in tumor growth or a "reduction" in tumor growth.



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of melanoma from its experiments, a POSA understood that PO was not in possession of a method of treating across the breath of all types of skin cancer.

140. Yet not only is claim 1 broad enough to claim all types of skin cancer tumors, but claim 2 purports to expand the "skin cancer" limitation to include other forms of cancer that are not always found in the skin. EX-1001, 181:7-13 (including "Paget's disease" (a type of breast cancer), "Leiomyosarcoma" (a type of smooth muscle cancer), and "Angiosarcoma" (a rare type of cancer capable of forming throughout the entire body). EX-1001 at 181:7-13. Having failed to demonstrate possession of a method of treating every type of skin cancer tumor, a POSA surely would not have understood PO to be in possession of a method of treating other forms of cancer as well.

141. Simply put, PO's attempt to extrapolate its results pertaining to a single type of melanoma skin cancer tumor implanted in mice to cover *all forms* of skin cancer in *all types* of subjects (including all vertebrates, including humans), as well as other forms of cancer in general, is unsupported by the specification. The specification is silent as to any data supporting such an "extrapolation" or any known efficacy and toxicity of the claimed compositions on other types of skin cancer tumors.

142. Accordingly, a POSA considering the specification as a whole, would conclude that it fails to describe a method of reducing and delaying growth of any



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type of skin cancer tumor, in any type of subject, by administering, through any means possible, a composition comprising any formulation of ingredients mixed with any concentration of an open-ended flora of bacteria. Whether or not the administration of all such compositions is effective is entirely dependent on numerous interrelated and co-dependent variables that are described no where in the specification. In view of the foregoing, a POSA would conclude that PO did not have possession of the full scope of the invention claimed in the Challenged Claims.

### B. Ground 2: Claims 1-19 are Unpatentable for Lack of Enablement

143. As set forth in §VII.A of the Petition, a POSA would conclude that the specification, considered as a whole, fails to enable a POSA to formulate any composition of bacteria belonging to the Ruminococcaceae family, that can be administered through any means possible, at any concentration, in any type of subject, and is safe and effective at treating any type of skin cancer tumor. §VII.A. Thus, in view of the foregoing, a POSA would conclude that the '838 Patent specification fails to teach a POSA how to make and use the full scope of the claimed invention without considerable experimentation. The Challenged Claims are therefore unpatentable for failure to comply with AIA §112(a).



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### C. Ground 3: Claims 1-19 are Unpatentable for Indefiniteness

144. In this case, at least several claim limitations in the Challenged Claims are indefinite. For example, the "isolated" and "purified" claim limitations, when read in view of the patent record—the claims, specification, and prosecution history—fail to reasonably inform a POSA about the scope of the claimed invention. As set forth below, the phrase "isolated" and "purified" – whether read individually or in combination – are subject to at least two potential constructions; neither of which resolve the definiteness problem. EX-1001 189:1-6; 28:40-29:11.

145. Moreover, the claimed "bacteria belonging to the family Ruminococcaceae" is a moving target; the metes and bounds of which is unclear. A POSA understood that both the validity and the scope of this claimed "taxonomic family" is inconsistent in the scientific literature. *Compare* EX-1015 p.10 *with* EX-1015 p.1016 (11 genera vs. 12 genera) *with* EX-1016 p.3932 (family name Ruminococcaceae is "illegitimate" and "replaced by … *Oscillospiraceae*" that contains 27 genera). As a result, the bacteria falling under this ever-changing umbrella and, thus the claim scope, are subject to change over time. And nothing in the specification clarifies this claim scope. This fits the definition of indefiniteness, and, in addition, gives rise to lack of enablement across the breadth of the claims.



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146. As set forth below, any attempt at construing the '838 Patent claim limitations leads to the same result: the Challenged Claims, read in view of the '838 Patent as a whole, fail to inform, with reasonable certainty, the degree of "isolation" or "purity" required by the claims, and which types of bacteria are covered by the claims.

### 1. The Meanings of "Isolated" and "Purified" Are Ambiguous to a POSA:

#### a. The "Plain and Ordinary" Meanings of "Isolated" and "Purified" Are Inconsistent with the Patent Record

147. The plain and ordinary meaning of the terms "isolated" and "purified" does not comport with the patent record and, thus, cannot reasonably inform a POSA about the scope of the claimed invention. The relevant language of claim 1 recites "a composition comprising an isolated or purified population of bacteria belonging to the family Ruminococcaceae." EX-1001 189:2-190:34. As such, the claim limitations "isolated or purified" modify the claimed "population of bacteria." *Id.* When viewed in isolation, a POSA might reasonably construe the "isolated" limitation to reference a bacterial population that contains "a single species of a bacterium obtained in a pure culture." EX-1022. Similarly, a POSA might reasonably construe a "purified" bacterial population to refer to one that has been made "pure by removing any harmful, dirty, or inferior substances from it."



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EX-1023. But the remaining evidence contained within the patent record negates those inferences.

148. As an initial matter, the "plain and ordinary" meanings of the "isolated or purified" limitations is belied by the surrounding claim language. Claim 1 employs the open-ended "comprising" transition, which I understand means "including but not limited to." EX-1001 189:2-190:34. However, the use of the open-ended comprising transition – which permits additional bacteria to be present in the composition – is inconsistent with the plain and ordinary meaning of an "isolated or purified" population of bacteria. That is, a composition cannot "comprise" an "isolated or purified" population of Ruminococcaceae bacteria, if it also contains a flora of other bacteria falling outside that claimed taxonomic family. Such a result is contextually incoherent as the population of "Ruminococcaceae" bacteria would no longer be "isolated or purified", but rather part of a mixture of bacteria.

149. The "plain and ordinary" meanings also conflict with the specification of the '838 Patent. Nowhere does the specification describe a composition comprising an "isolated or purified" a population bacteria belonging to the family Ruminococcaceae, nor was PO ever in possession of an "isolated or purified" population of such bacteria, under the plain and ordinary meaning of those terms.



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Importantly, none of the "experiments" administered an "isolated or purified" population of Ruminococcaceae bacteria.

150. Indeed the sole example that provides any information concerning the composition that was administered to mice – Example 5 – discloses only that a "200 µl cleared supernatant from 0.1 g/µ1 human fecal suspension was obtained using a 100 µm strainer and gavaged into mice for 3 doses over 1 week". EX-1001 184:65-185:2. A POSA understood that this disclosure – an aliquot of human feces – would contain millions of bacteria belonging to a host of different taxonomic families and classes. Indeed, a POSA understood that the strained "supernatant" could have decreased the proportional composition of *Ruminococcus* bacteria in the tested sample (*i.e.,* bacteria from the claimed family), but did not eliminate any species of bacteria from the aliquot sample, or otherwise enrich the sample with bacteria from the family Ruminococcaceae. EX-1020, pp.3276-3278 (demonstrating that bacterial members of the *Ruminococcus* genus were higher in the particulate fraction of human fecal samples, than in the liquid fraction). Thus, the singularly described sample administered in the specification is inconsistent with the "plain and ordinary" meaning of an "isolated or purified" population of bacteria belonging to the family Ruminococcaceae.

151. In the alternative, however, to the extent that the "plain and ordinary" meanings were adopted, then application of such a construction would lead to



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additional grounds for invalidity, including lack of enablement and written description. As just discussed, nowhere does the specification support a finding that PO was in possession of an "isolated or purified" population of bacteria belonging to the family Ruminococcaceae, under the "plain and ordinary" meaning of those terms. Nor does the specification describe any methods or procedures enabling a POSA to isolate or purify Ruminococcaceae bacteria from the potentially millions of other bacterial species found in the feces of "responder" or "non-responder" patients. To the contrary, a POSA would have understood that the process of isolating and purifying such a bacterial population would require extensive trial and error, far outside the bounds of routine experimentation. Thus, to the extent that the "plain and ordinary" meaning of "isolated" and "purified" were adopted, the claims of the '838 Patent would be invalid for lack of enablement and lack of written description under 35 USC § 112 (a).

**b. PO's "Isolated" Definition Causes More Uncertainty**

152. Contrary to the "plain and ordinary" meaning, the specification suggests a different construction of "isolated" and "purified." However, rather than clarify the meaning of these claim limitations, the specification adds to the confusion. Beginning with the limitation "isolated", the specification purports to provide a two-part "definition" as follows:

> The term "isolated" encompasses a bacterium or other entity or substance that has been (1) separated from at least some of the



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components with which it was associated when initially produced (whether in nature or in an experimental setting), and/or (2) produced, prepared, purified, and/or manufactured by the hand of man.

EX-1001, 28:40-28:54.

153. The two subparts of PO's "isolated" definition convey incongruous and contradictory meanings. For example, under subpart (1) of the definition, separation *of any kind* is sufficient to "isolate" a bacterium from another component. Ex-1001 28:40-44 ("isolated encompasses… separat[ing] from *at least some* of the components with which it was associated…") (emphasis added). There is no "minimum" amount of separation required, so long as "*at least some*" separation occurs. *Id.* As a simple example demonstrates, under this construction a bacterium could be "isolated" from a bacterial culture without decreasing the overall population density of that bacterial culture in any way. For example, if 200 ml of liquid bacterial culture with a population density of 10 organisms per ml were separated into two containers, each containing 100 ml of the same liquid bacterial culture, the bacteria in each container would be considered "isolated" from each other, while the population density of each bacterial culture (10 organisms per ml) would remain unchanged. Thus, under subpart (1) of PO's definition, the mere act separating the liquid bacterial culture into two containers constitutes "isolation". Ex-1001 28:40-44.



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154. Putting aside the unbridled breadth of subpart (1), PO's definition in subpart (2) sets forth a completely divergent meaning that is unknown in the field of microbiology and incomprehensible to a POSA. Specifically, subpart (2) provides that an "isolated" bacterium is one that is "produced, prepared, purified, and/or manufactured *by the hand of man*." EX-1001, 28:40-28:54 (emphasis added). The phrase "by the hand of man" is not a term of art and has no accepted meaning in the field of microbiology. Nor is that phrase otherwise defined or exemplified in the specification. As a result, a POSA would have no understanding, rooted either in science or the patent record, as to what it means to "produce[], prepare[], purif[y], and/or manufacture[]" a bacterium "by the hand of man."

155. Further compounding this ambiguity is the fact that the only defining element in subpart (1) of the definition – *i.e.,* that there be *at least some* separation of components – is missing entirely in subpart (2). EX-1001, 28:40-28:54. That is, subpart (2) does not require of any form of "separation" to result in an "isolated" bacterium. *Id.* Rather, subpart (2) provides that any bacterium that is "produced, prepared… and/or manufactured by the hand of man" has been "isolated", regardless of whether any steps were taken to separate that bacterium from other components. *Id.* Thus, subparts (1) and (2) of PO's definition are not only incongruous, they are contradictory.



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156. A POSA would be left to speculate as to how any of the potential meanings of subpart (2) relate in any way to the singular concept of "separation" identified in subpart (1) of PO's definition.

### c. PO's Overlapping "Purified" Definition Adds Additional Ambiguity

157. PO's definition of "purified" creates still further confusion concerning the meaning of both the "isolated" and "purified" claim limitations. As set forth in relevant part below, PO's definition of "purified" is overlapping and circular, stating that "a bacterium or a bacterial population may be considered ***purified*** if it is ***isolated*** at or after production…". EX-100128:55-29:11. For example, the specification states:

> The terms "purify," "purifying" and "purified" refer to a bacterium or other material that has been separated from at least some of the components with which it was associated either when initially produced or generated (e.g., whether in nature or in an experimental setting), or during any time after its initial production. ***A bacterium or a bacterial population may be considered purified if it is isolated at or after production***, such as from a material or environment containing the bacterium or bacterial population…

EX-1001, 28:55-29:11 (DEFINITIONS).

158. PO's overlapping definitions of "isolated" and "purified" are, therefore, circular, wherein each definition references the other for scope. As a



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result, the two limitations collapse onto themselves, creating in their wake additional ambiguity as to their intended meaning.

159. For example, the specification provides no guidance to a POSA as to whether a bacterial population could be "isolated" but not "purified", or "purified" but not "isolated", or whether every "isolated" population of bacteria is also considered "purified." Yet Claim 1 uses the disjunctive "or" to describe the claimed population (*i.e.*, "a composition comprising an isolated ***or*** purified population…."), thereby suggesting to a POSA that the two words are intended to have different meanings. EX-1001 at 189:1-6 (emphasis added). The end result is that PO's circular definitions of "purified" leads to the same internal inconsistencies that render its definition of "isolated' indefinite, leaving a POSA without any understanding as to the metes and bounds of these two claim limitations.

160. In addition, the '838 Patent provides no guidance as to what the percentages recited in the definitions of "isolated" and "purified" (EX-1001 28:40-29:11) are relative to or based on. For example, the specification states that the "[i]solated bacteria may be separated from at least about 10% … of the other components" but the reader is not told if that percentage is weight by weight, volume by volume, or some other measure. Similarly, the specification states that "a purified bacterium or bacterial population may contain other material up to



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about 10% … or above about 90%", but again the reader again is not told how one arrives at such percentages. Worse yet, the specification purports to cover such a vast and extensive range of "at least about 10%" or "up to 10%" to "more than about 99%" or "above about 90%", that results in the words "isolate" or "purify" cease to have any meaning at all. Thus, for myriad reasons, the metes and bounds of "isolated or purified" cannot be ascertained from the '838 Patent, and Claim 1 is invalid as indefinite under 35 U.S.C. §112(b).

### 2. The Bacteria in the "Family *Ruminococcaceae*" is a Moving Target

161. Claim 1 of the '838 Patent is indefinite for the additional reason that the claimed "bacteria belonging to the family *Ruminococcaceae*" is a moving target subject to much debate among POSAs. The family of *Ruminococcaceae* bacteria was first made official by microbiologist Rainey in 2009. *See* EX-1015 pp.10 and 1016, *et seq*.

162. The announcement, which was first made in Volume 3 of Bergey's Manual of Systemic Bacteriology (2nd Ed. 2009), initially proposed that the *Ruminococcaceae* family contain 11 genera: *Ruminococcus* (type genus), *Acetanaerobacterium*, *Acetivibrio*, *Anaerofilum*, *Anaerotruncus*, *Faecalibacterium*, *Fastidiosipila*, *Oscillospira*, *Papillibacter*, *Sporobacter*, and *Subdoligranulum*; and at least 28 species of different bacteria. EX-1015 pp.10. However, an article published in 2006 – "after finalization of the content of" Volume 3 of Bergey's



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Manual – proposed a 12th genus, *Ethanoligenens,* for the family *Ruminococcaceae.* EX-1015 p.1016, *et seq*. This twelfth genus was not described in Bergey.

163. Ten years later, however, scientists questioned the validity of the new *Ruminococcaceae* family altogether. For example, in 2019 a microbiologist named Tindall asserted that "the family name *Ruminococcaceae* [of] Rainey … is an illegitimate name … and is … replaced by the earlier, validly published name *Oscillospiraceae*". EX-1016 p.3931. Tindall asserts that there are 27 genera in the *Oscillospiraceae* family, including the 12 genera Rainey characterized under his new *Ruminococcaceae* taxonomic family. *Id.*Since then, no definitive reference has clarified the validity and/or scope of the *Ruminococcaceae* taxonomic family.

164. A POSA would be aware of this inconsistency in taxonomy and, thus, unable to determine the metes and bounds of claim limitation "bacteria belonging to the family *Ruminococcaceae*". The question of infringement turns on which taxonomic definition is applied, which is both ill-defined and subject to change over time. As a result, the metes and bounds of Claim 1 are unclear rendering the claim indefinite.

### D. Grounds 4 and 5: Claims 1-19 are Unpatentable for Obviousness: Detailed Application of Prior Art to the Challenged Claims

#### 1. The Honda Reference

165. Honda is directed to compositions of human-derived bacteria that induce proliferation of Th17 cells. EX-1011 ¶1. In particular, Honda is directed to



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a method for treating, reducing the severity of, or preventing at least one disease or condition, such as infectious diseases or cancer, by orally administering to an individual in need thereof of, a composition comprising bacteria within the family Ruminococcaceae, alone or in combination with an antigen. EX-1011 ¶1; Claim 12.

166. Consistent with what was known in the art, Honda discloses that "[h]undreds of species of commensal microorganisms are harbored in the gastrointestinal tracts of mammals, where they interact with the host immune system." EX-1011 ¶2. The presence of these intestinal bacteria "enhances protective functions of the mucous membranes, enabling the host to mount robust immune responses against pathogenic microbes invading the body." *Id*. Honda teaches that compositions, comprising one or more intestinal commensal bacteria cultured from human feces, can be administered to humans, including bacteria within the purported family Ruminococcaceae. EX-1011 ¶¶6, 10, 12 (identifying "*Ruminococcus* sp. M-1, *Ruminococcus* gnavus… *Ruminococcus* sp. 16442… *Anaerotruncus colihominis*… or a culture supernatant of such bacteria").

167. In one embodiment, Honda teaches a method for obtaining Th17-inducing bacterial compositions comprising, *inter alia*, "obtaining (at least one) sample, such as fecal sample… culturing the sample… and isolating pure bacterial strains from the resulting colonies." EX-1011 ¶23. Honda teaches that the



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bacterial product can be purified and concentrated; for instance from fermentation broth. EX-1011 ¶63. Beneficial commensal bacteria can also be isolated using "serial dilutions of [f]ecal content samples cultured by plating under a strictly anaerobic conditions." EX-1011 ¶23. In another embodiment, Honda discloses the use of antibiotics to screen and isolate useful bacteria from fecal samples, such as *Ruminococcus*, including "(a) obtaining… a fecal sample; (b) treating the sample of (a) with ampicillin; (c) culturing the ampicillin-treated sample of (b) and isolating pure bacterial strains." EX-1011 ¶23; ¶42 ("'human-derived bacteria' means bacterial species… isolated from a fecal sample… obtained from a human individual or whose ancestors were isolated").

168. In other embodiments, Honda teaches how to formulate and administer the compositions. Honda teaches that the commensal bacterial compositions can be administered by a variety of routes, including orally, and can be formulated into several different oral forms (*e.g.*, powders, lyophilizates, liquids formulation, etc.). EX-1011 ¶¶21, 55. Honda teaches a variety of excipients, carriers, and other additives useful for formulating a pharmaceutically acceptable preparation for oral ingestion. EX-1011 ¶¶57-60. Honda discloses that the bacterial concentration "is generally 0.01 mg/kg body weight to 100 mg/kg body weight, and in specific embodiments, 1 mg/kg body weight to 10 mg/kg body weight." EX-1011 ¶64.



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169. In still another embodiment, Honda teaches a method to determine whether the desired Th17 cell proliferation effect has been induced (*i.e.,* through a measurement index comparing the number, ratio, function, or expression of Th17 cells), including specific means by which to measure that effect (*e.g.,* northern blotting, RT-PCR, radioimmunoassays, etc.). EX-1011 ¶71. Finally, Honda teaches that the commensal bacterial composition can be used as an adjuvant to a vaccine or cancer treatment. EX-1011 ¶¶17, 52.

**2. The Gajewski Reference**

170. Gajewski is directed at methods of treatment and/or prevention of cancer by manipulation of commensal microflora.[3]EX-1012 p.1, ll.10-13. In particular, Gajewski claims a method of treating or preventing cancer in a subject comprising administering a bacteria preparation containing *Ruminococcus* – a member of the purported family Ruminococcaceae. EX-1012 p.2, ll.9-19.

171. "Fueled by recent clinical success in immunotherapy cancer treatments," Gajewski conducted a series of experiments to examine the effects of microbial composition on spontaneous antitumor immunity. EX-1012 p.43, ll. 30-53:15. Like PO, Gajewski compared skin cancer melanoma growth in two cohorts

[3] Gajewski (EX-1012) is the printed publication of PCT/US2016/035228, filed June 1, 2016 (EX-1013).



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of mice derived from Jackson Laboratory (JAX) and Taconic Farms (TAC) which were known to have distinct commensal microbiota. EX-1012 p.47, ll.7-16 and Figure 1A-H. Using a murine melanoma mode, Gajewski found that JAX and TAC mice exhibited significant differences in melanoma growth rate, with tumors growing more aggressively in TAC mice. EX-1012 p.47, ll.7-16 and (Figure 1A-H).

172. To directly test the role of commensal bacteria in regulating anti-tumor immunity, Gajewski transferred fecal suspensions from the JAX mice (*i.e.,* "responder" feces) by oral gavage into the TAC mice (*i.e*., "non-responders") prior to tumor implantation. EX-1012 p.47, ll.7-16 and Figure 1A-H. Gajewski found that this fecal transfer was sufficient to delay tumor growth and enhance induction and infiltration of tumor-specific CD8* T cells, therefore demonstrating a microbe- or microbial product-derived effect. EX-1012 p.47, ll.7-16 and Figure 2A-C and 5B.

173. Next, Gajewski compared the fecal bacterial content in the cohorts of mice to identify the specific bacteria associated with the anti-tumor immune responses. EX-1012 p.48, ll.17-p.49, ll.24 and Figure 8A-C. Comparative analysis of specific bacterial taxa showed that 97 taxa were significantly more abundant in JAX mice relative to TAC mice, and 15 taxa were significantly increased in JAX-



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fed TAC mice relative to TAC-fed TAC mice, including bacteria belonging to the genera *Ruminococcus*. EX-1012 p.49, ll.3-24 and Figure 8A-C.

174. Gajewski demonstrates that modulation of levels and/or identity of the microflora in a subject could facilitate treatment of cancer/tumor within the subject (*e.g.,* immunotherapy, chemotherapy, etc.), enhance the endogenous immune response, decrease immune evasion or other inhibitory mechanisms to treatment of endogenous immune response, and improve cancer outcomes for the subject. EX-1012 p.23, ll.3-19. The presence of these beneficial microbes "creates an environment or microenvironment (*e.g.*, metabolome) that is conducive to the treatment of cancer and/or inhibits cancer/tumor growth" including, in particular, with co-administration of adjuvant anti-cancer therapies. EX-1012 p.22, ll.18-28.Thus, Gajewski concludes that "the presence or increased level of one or more… types of bacteria in a subject," including bacteria belonging to the genus *Ruminococcus*, "discourages cancer/tumor growth, spread, and/or evasion of treatment/immune response." EX-1012 p.21, ll. 31-p.23, ll.31.

175. Gajewski also teaches how to formulate and administer the commensal bacterial compositions. EX-1012 p.6, ll.6-13. For example, Gajewski discloses isolating or purifying bacteria from fecal material, such as by dilution or filtering. EX-1012 p.27, ll.17-26. Gajewski teaches that the composition can be formulated in a wide variety of dosage forms with one or more pharmaceutically



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acceptable carriers, solubilizers, diluents, and binders. EX-1012 p.25, ll.10-p.26, ll. 20. Gajewski teaches that the formulation can be administered by oral, rectal, or topical administration, or by inhalation or injection. EX-1012 p.6, ll.6-13. Gajewski teaches a range of effective bacterial concentrations that can be administered, including in one embodiment "at least about 5x10 CFU of bacteria" administered in two or more doses. EX-1012 p.6, ll.6-13.

176. Gajewski also teaches that the commensal bacterial composition can be co-administered with additional anticancer treatments including, *inter alia*, immune checkpoint inhibitors, interfering nucleic acid molecules, and additional cancer therapies to create an enhanced effect. EX-1012 p.6, ll.18-p.7, ll.6. For example, in one embodiment, the method includes co-administration with an immune checkpoint inhibitor such as CTLA4, PD-1, PD-LI, PD-L2, A2AR, B7-H3, B7-H4, BTLA, KIR, LAG3, TIM-3 or VISTA. *Id.* In another embodiment, the method includes co-administration with an interfering nucleic acid molecule such as an siRNA molecule, an shRNA molecule, or an antisense RNA molecule. *Id.* In yet a further embodiment, the method includes co-administration with an additional cancer therapy, including surgical, radiation and/or chemotherapeutic cancer intervention. EX-1012 3, ll.5-16. These co-administered cancer therapies can be by injection, intravenous, intramuscular, intratumoral or subcutaneous



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injection, or administration into lymph nodes, or administration intraperitoneally. EX-1012, p.7, ll.3-6; p.8, ll.15-18.

177. Moreover, the commensal bacterial compositions of Gajewski were useful for treating a wide-range of skin cancers, including, *inter alia*, malignant melanoma, basal cell carcinoma, and Kaposi's carcinoma. EX-1012 p.5, ll.13 - p.6, ll.1-5; p.41, ll.15-20. Gajewski notes that "[h]arnessing the host immune system constitutes a promising approach for the treatment of cancer because of its potential to specifically target tumor cells while limiting harm to normal tissue…." EX-1012 p.1, ll.15 - p.2, ll. 2.

**3. The Miquel Reference**

178. The Miquel reference, discusses the role of *F. prausnitzii* in balancing immunity in the intestine and the mechanisms involved.EX-1014 p.255-261. Miquel reports that *F. prausnitzii*, a member of the family Ruminococcaceae, is the most abundant bacterium in feces of healthy adults. EX-1014 p.255-256. Miquel describes the increasing number of studies, beginning in the mid-2000's, that have demonstrated "the importance of this highly metabolically active commensal bacterium as a component of the healthy human microbiota." EX-1014 p.255.

179. For example, Miquel teaches that one of the known metabolic functions of *F. prausnitzii* is its abundant butyrate production. EX-1014 p.256. "Butyrate plays a major role in gut physiology and it has… numerous beneficial



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effects for health through protection against pathogen invasion, modulation of immune system and reduction of cancer progression." EX-1014 p.256. As a result, Miquel teaches that *F. prausnitzii* has been analyzed in numerous diseases including tumors and cancer, and that *F. prausnitzii* abundance in the microbiotica "is a good intestinal health indicator." EX-1014 p.256. Miquel concludes that it "could be useful to develop therapeutic strategies and personalized medicine" and that "modulation of *F. prausnitzii* abundance, for example using prebiotics and/or probiotics and/or formulations that permit survival through the upper part of the intestinal tract might have prophylactic or therapeutic applications in human health." EX-1014 p.258-259.

180. While Miquel was cited during prosecution of the '838 Patent, it was not used in combination with Honda, or in combination with Honda and Gajewski as set forth in this Petition.

#### 4. The Motivation to Combine the Teachings of Honda in view of Gajewski, and to Combine Honda in view of Gajewski and Miquel

181. A POSA would recognize that all of Honda, Gajewski and the '838 Patent pertain to bacteria, especially bacteria of the purported family Ruminococcaceae (that include *Ruminococcus* and *F. prausnitzii*) for addressing cancer in a subject; and both Honda and Gajewski pertain to bacteria of



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*Ruminococcus* for addressing cancer in a subject. A POSA would be motivated to modify the teachings of Honda with the teachings of Gajewski for several reasons.

182. First, a POSA would be motivated to apply Honda's more generalized teachings relating to "cancer" treatment to the specific cancers recited in Gajewski, including skin cancers. While Honda teaches the use of *Ruminococcus* for treatment of diseases and cancer, it does not specifically identify a subset of cancers for which it is useful. A POSA would recognize that Gajewski identifies many specific forms of cancer, including skin cancer tumors, for which compositions comprising *Ruminococcus* bacteria would be useful. Moreover, a POSA would have expected the methods taught in Honda to be successful on the specific cancers identified in Gajewski because, as the '838 Patent acknowledges, numerous prior art studies had already suggested that "[c]ompositional differences in the microbiome may also influence cancer development and response to therapy" including "a high abundance of *Faecalibacterium*."EX-1001 1:44-49; 152:63-153:20; 154:23-28 (discussing published data showing "patients with a higher abundance of *Faecalibacterium* had a prolonged [progression-free survival] compared to those with a higher abundance of *Bacteroides* in the gut microbiome."). Thus, it was state of the art to modify bacterial microbiomes for purposes of treating cancer, and both Honda and Gajewski pertain to bacteria of



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*Ruminococcus* (within the family Ruminococcaceae that includes *Faecalibacterium*) for addressing cancer in a subject.

183. A POSA would also have had a reasonable expectation of success because both Honda and Gajewski demonstrated a delay in tumor growth through a similar mechanism of action instigated by administration of beneficial commensal bacteria. For example, Honda demonstrated that beneficial commensal bacteria increased infiltration of Th17 cells which, in turn, were known in the art to enhance induction and infiltration of tumor-specific CD8* T cells. EX-1011 ¶¶6, 10, 12, 71. Meanwhile, Gajewski demonstrated a similar microbe- or microbial product-derived effect, wherein beneficial commensal bacteria were found to enhance induction and infiltration of tumor-specific CD8* T cells to delay tumor growth. EX-1012 p.47, ll.7-16 and Figure 2A-C and 5B. Thus, both Honda and Gajewski involved induction of a similar immunoregulatory pathway.

184. Second, a POSA would be motivated to employ the specific processing procedures of Honda to the fecal bacterial samples disclosed in Gajewski. While Gajewski teaches a bacteria preparation containing *Ruminococcus* that can be derived from fecal material or fecal material that has been processed, a POSA would have recognized that Gajewski does not disclose specific procedures for isolating or purifying these bacterial populations. Honda, however, teaches specific procedures for purifying and concentrating commensal



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bacteria including, for instance, from fermentation broth. As such, a POSA would have been motivated to employ the specific purification and concentration techniques taught in Honda, to the *Ruminococcus* bacteria preparations taught in Gajewski, in order to create isolated or purified compositions useful for treatments of skin cancer tumors. Moreover, a POSA would have expected the purification and concentration techniques taught in Honda to be successful because Honda successfully used those techniques to isolate *Ruminococcus* bacteria.

185. Third, a POSA would be motivated to employ the composition comprising Ruminococcaceae bacteria with other adjuvant cancer therapies, such as immune checkpoint inhibitors, as taught in Gajewski. Gajewski teaches that increasing the levels of certain bacteria, including bacteria from the genus *Ruminococcus*, can enhance the effect of co-administered anti-cancer therapies (*e.g.*, immunotherapy, chemotherapy, etc.) as well as enhance the endogenous immune response (Th17 cell proliferation) studied in Honda, in order to improve cancer outcomes for the subject. EX-1012 p.23, ll.3-19.Informed by Honda's generic reference to "adjuvant therapies", a POSA would recognize that Gajewski teaches a number of specific adjuvant therapies that, when co-administered with certain commensal bacteria, can create an even greater anti-cancer effect.

186. Finally, a POSA would be motivated to modify the teachings of Honda in view of the teachings of Gajewski and Miquel. Miquel teaches that



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"*Faecalibacterium prausnitzii* is the most abundant bacterium" in feces of healthy adults, and is one of the most prolific members of the Ruminococcaceae family. EX-1014 pp.255-256.Miquel further teaches that *F. prausnitzii* has been analyzed in numerous diseases including tumors and cancer, and concludes that "modulation of *F. prausnitzii* abundance, for example using prebiotics and/or probiotics and/or formulations that permit survival through the upper part of the intestinal tract might have prophylactic or therapeutic applications in human health." EX-1014 pp.256 and 259.

187. Given the prominence of *Faecalibacterium prausnitzii* in human feces, a POSA would have recognized that the fecal compositions administered in Honda and Gajewski would have contained beneficial Ruminococcaceae bacteria of the species *Faecalibacterium prausnitzii.* A POSA would have further recognized the major role these butyrate producing bacteria play in the physiology of the human gut, including the "numerous beneficial effects for health through protection against pathogen invasion, modulation of immune system and reduction of cancer progression" as taught by Miquel. EX-1014 p.256. As a result, a POSA would have been motivated to administer a composition comprising bacteria from the species *F. prausnitzii* as taught by Miguel to delay or reduce growth of skin cancer tumors as taught by the combination of Honda and Gajewski.



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### 5. Detailed Application of Honda in view of Gajewski

#### a. Claim 1

##### i. "A method of reducing or delaying growth of a skin cancer tumor in a subject in need thereof, comprising"

188. To the extent the preamble is a limitation Honda discloses "a method for treating, aiding in treating, reducing the severity of, or preventing… cancer in an individual… comprising by administering a composition" comprising "one or more bacteria selected from the group consisting of… *Ruminococcus* sp. M-1, *Ruminococcus* gnavus" to a subject in need thereof of. EX-1011 ¶1; Claims 2 and 12. Honda does not exclude skin cancer from the type of cancers that could be treated and thus a POSA understood Honda's teachings of "treating, aiding in treating, reducing the severity of, or preventing" cancer to include "reducing or delaying" the growth of a skin cancer tumor.

189. To the extent that PO argues that Honda does not expressly discloses "skin" cancer, Gajewski teaches "A method of treating or preventing cancer in a subject" by "administering a beneficial microbes to the subject" selected "from the genera *Ruminococcus*." EX-1012 Claims 1-4. Moreover, Gajewski demonstrated that "the presence or increased level of one or more… types of bacteria in a subject," including bacteria belonging to the genus *Ruminococcus*, "discourages cancer/tumor growth, spread, and/or evasion of treatment/immune response." P.21, ll. 31-p.23, ll.31. A POSA understood that the methods of "discourage[ing]



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cancer/tumor growth [or] spread" in Gajewski to encompass "reducing or delaying growth" of skin cancer tumor cells.

190. Moreover, Gajewski teaches that the commensal bacterial compositions disclosed therein, including from the genus *Ruminococcus*, were useful for treating skin cancers, including, *inter alia*, malignant melanoma, basal cell carcinoma, and Kaposi's carcinoma. EX-1012 p.5, ll.13 - p.6, ll.1-5; p.40 ll.27 – p.41 ll.15-20 ("term 'melanoma' is taken to mean a tumor … of the skin"), p.41 ll. 21-25 ("tumors that can be treated and/or prevented using methods described herein include… skin cancer"); and cl. 30. Gajewski notes that "[h]arnessing the host immune system constitutes a promising approach for the treatment of cancer because of its potential to specifically target tumor cells while limiting harm to normal tissue…." EX-1012 p.1, ll.15 - p.2, ll. 2.

191. For these reasons, and those in the Motivation to Combine section, a POSA would have been motivated to modify the methods disclosed in Honda to reduce or delay growth of the skin cancer tumors taught by Gajewski, and would be certain of its success.

**ii. "administering to the subject a composition comprising an isolated or purified population of bacteria belonging to the family Ruminococcaceae"**

192. Honda discloses this limitation, alone, or in view of Gajewski. For example, claims 2 and 12 of Honda claim "a method for treating, aiding in treating,



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reducing the severity of, or preventing… cancer in an individual… by administering a composition" comprising "one or more bacteria selected from the group consisting of… *Ruminococcus* sp. M-1, *Ruminococcus* gnavus … *Ruminococcus* sp. 16442… *Anaerotruncus colihominis*… or … a culture supernatant of [the] one or more bacteria" to a subject in need thereof of. EX-1011 ¶1; Claims 2, 12.

193. Honda teaches specific methods for "isolating or purifying" the desired intestinal commensal bacteria. EX-1011 ¶¶23, 63. For example, Honda teaches that the bacteria in the composition "can be manufactured using fermentation techniques" and "***purified*** and concentrated from the fermentation broth by techniques such as centrifugation and filtration." EX-1001, ¶63 (emphasis added). Beneficial commensal bacteria can also be isolated using "serial dilutions of [f]ecal content samples cultured by plating under a strictly anaerobic conditions." EX-1011 ¶23. In another embodiment, Honda discloses the use of antibiotics to screen and isolate useful bacteria from a fecal sample, such as *Ruminococcus*. EX-1011 ¶23; ¶42.

194. Table 1 of Honda identifies three *Ruminococcus* bacterial strains "isolated from the [f]ecal contents of mice colonized with human patient stool and treated with ampicillin" and found to "strongly induce the… proliferation and accumulation of Th17 cells" that are responsible for fighting infections and



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cancer.EX-1011 Table 1, ¶¶5, 33. Honda further discloses administering these commensal bacterial strains to humans to as pharmaceuticals and as food ingredients. EX-1011 ¶¶21, 55 (disclosing oral administration of powders, lyophilates, liquid formulations, encapsulates, or in a food matrix such as yogurt or a drink). Moreover, Honda teaches a variety of excipients, carriers, and other additives useful for formulating pharmaceutically acceptable preparations and effective concentrations of bacteria. EX-1011 ¶¶57-60, 64.

195. Thus, Honda discloses administering to the subject a composition comprising an isolated or purified population of bacteria belonging to the family Ruminococcaceae.

196. To the extent that PO asserts that Honda does not disclose this claim limitation, Gajewski cures any alleged deficiencies. Gajewski teaches "a method of treating or preventing cancer in a subject" by "administering beneficial microbes to the subject" selected "from the genera *Ruminococcus*." EX-1012 Claims 1-6. Gajewski teaches increasing the presence of certain commensal microbes, including from the genus *Ruminococcus*, can enhance the subject's clinical response to immunotherapies and facilitate one or more co-treatments to improve cancer outcomes for the subject. EX-1012, P.23, ll.3-31. Gajewski teaches these beneficial commensal bacteria can be isolated and purified from donor "fecal material" by "diluting," "filtering," and "testing (*e.g.,* for pathogens or detrimental



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microbes)." EX-1012 p.27, ll. 19-29 ("Donor microflora (*e.g.,* fecal material)" may be purified "to remove one or more components" such as "parasitic of detrimental microbes" or "(c)ontaminants within the donor sample….").

197. As discussed above, Gajewski teaches that the commensal bacterial compositions can be formulated into a variety of different compositions (EX-1012 p.25, ll.10-p.26, ll. 20), that can be administered to a subject through numerous means (EX-1012 p.6, ll.6-13), and can contain a wide range of effective bacterial concentrations (*id.*).

198. For these reasons, and those in the Motivation to Combine section, a POSA would have been motivated to modify Honda to use the methods of administering a composition comprising an isolated or purified population of bacterial belonging to the family Ruminococcaceae as taught by Gajewski, and would be certain of its success.

**b. Claim 2**

***"The method of claim 1, wherein the skin cancer is selected from basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget's disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma"***

199. Honda discloses this limitation, alone, or in view of Gajewski. For example, claims 2 and 12 of Honda claim "a method for treating, aiding in treating,



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reducing the severity of, or preventing… cancer in an individual…." EX-1011 ¶1; Claims 2, 12. A POSA would recognize that Honda's disclosure of a method of delaying or reducing growth of cancer to include skin cancers tumors, including the skin cancers specifically identified in Claim 2 of the '838 Patent. A POSA would also recognize that at least some of the cancers identified in claim 2 (*e.g.,* Paget's disease, Leiomyosarcoma, and Angiosarcoma), can occur in other regions of the body apart from skin.

200. To the extent that PO asserts that Honda does not specifically disclose this limitation, Gajewski elaborates on the various types of cancer that can be treated through administration of compositions comprising bacteria "from the genera *Ruminococcus*." EX-1012, Claims 1-6. Specifically, Gajewski identifies numerous types of skin melanoma whose growth can be delayed or reduced using the disclosed methods. EX-1012, p.37, ll.21- p.42, ll.20 (identifying, *inter alia*, "Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, acral- lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, nodular melanoma subungal melanoma, and superficial spreading melanoma"); EX-1012, p.41, ll.15-20 ("term 'melanoma' is taken to mean a tumor … ***of the skin***") (emphasis added); p.41, ll. 21-25 ("tumors that can be treated and/or prevented using methods described herein include … ***skin cancer***") (emphasis added); and cl. 30. In



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addition, Gajewski teaches delaying or reducing growth of various other skin cancers specifically recited in claim 2 of the '838 Patent, including "basal cell carcinoma… spindle cell carcinoma… squamous carcinoma, squamous cell carcinoma… [and] Kaposi's sarcoma." EX-1012, p.40, ll.27 – p.41, ll.6.

201. A POSA would be motivated to modify the teachings of Honda to delay or reduce growth of the specific skin cancer tumors disclosed in Gajewski for the reasons discussed in the Motivation to Combine section.

**c. Claim 3**

***"The method of claim 1, wherein the method further comprises administering an additional anticancer treatment"***

202. Honda discloses this limitation, alone, or in view of Gajewski. For example, Honda teaches that the commensal "bacterial composition can be used as an adjuvant to a vaccine for the prophylaxis or treatment of an infectious disease or cancer." EX-1011 ¶17. Honda teaches that "the bacterial composition may also be administered as an adjuvant in combination with antigenic material." EX-1011 ¶52. A POSA understood that both vaccine and antigenic materials are types of "additional anticancer treatments." Moreover, Honda further teaches that the "antigenic material can be co-administered, administered before, or after the bacterial composition." EX-1011 ¶52.

203. To the extent that PO asserts that Honda does not discloses this limitation, Gajewski teaches that altering the subject's microbiome to increase the



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presence of certain commensal microbes, enhances the subject's clinical response to immunotherapies and, thus, increases effectiveness of adjuvant therapies.EX-1012, p.21, ll.13- p.24, ll.15. Gajewski elaborates on the specific anticancer treatments that can be co-administered with compositions comprising *Ruminococcus* bacteria. EX-1012, Claims 14-18 and 20 ("The method of claim 1 "further comprising surgical, radiation and/or chemotherapeutic cancer intervention").

204. For example, Gajewski teaches that the commensal bacterial compositions can be co-administered with additional anticancer treatments such as immune checkpoint inhibitors, interfering nucleic acid molecules, monoclonal antibodies, angiogenesis inhibitors, antibiotics, and additional cancer therapies (including surgical, radiation and/or chemotherapeutic cancer intervention). EX-1012, 3, ll.5-16; p.6, ll.18-p.7, ll.6. These co-administered cancer therapies "may be administered via injection (*e.g.,* intravenously, intratumorally, subcutaneously, or into lymph nodes), but may also be administered orally, topically, or via aerosol." *Id.*.

205. A POSA would be motivated to modify the teachings of Honda to employ the specific adjuvant anticancer therapies disclosed in Gajewski for the reasons discussed in the Motivation to Combine section.



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**d. Claim 5**

***"The method of claim 3, wherein the anticancer treatment is surgical therapy, chemotherapy, radiation therapy, hormonal therapy, immunotherapy, small molecule therapy, receptor kinase inhibitor therapy, anti-angiogenic therapy, cytokine therapy, cryotherapy or a biological therapy"***

206. Honda alone, or Honda in view of Gajewski, discloses this limitation for the same reasons as discussed with respect to the "anticancer treatment" step of Claim 3.

207. In addition, Gajewski describes additional "anticancer therapies" that can be co-administered with the methods described therein, including "hormones," "monoclonal antibodies," "gene therapy techniques," "antisense therapy techniques," and "angiogenesis inhibitors." EX-1012, p.34, l.3 - p.35, l.3; Claims 14-18; 20.

208. A POSA would be motivated to modify the teachings of Honda to use the specific adjuvant anticancer therapies disclosed in Gajewski for the reasons discussed in the Motivation to Combine section.

**e. Claim 6**

***"The method of claim 5, wherein the biological therapy is a monoclonal antibody, siRNA, miRNA, antisense oligonucleotide, ribozyme or gene therapy"***

209. Honda alone, or in view of Gajewski, discloses this limitation for the same reasons as discussed with respect to the "anticancer treatment" steps of Claims 4 and 5.



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210. In addition, Gajewski describes additional "anticancer therapies" including "biological therapies" that can be co-administered with the methods described therein, including interfering nucleic acid molecules such as "an siRNA molecule, an shRNA molecule, or an antisense RNA molecule." EX-1012 p.6, ll.18-26; EX-1012 p.34, l.3 – p.35, l.3 (listing exemplary anticancer agents for co-administration, including "monoclonal antibodies," "gene therapy techniques," and "antisense therapy techniques").

211. A POSA would be motivated to modify the teachings of Honda to use the specific adjuvant biological therapies disclosed in Gajewski for the reasons discussed in the Motivation to Combine section.

**f. Claim 7**

***"The method of claim 3, wherein the anticancer treatment is administered intratumorally, intraarterially, intravenously, intravascularly, intrapleuraly, intraperitoneally, intratracheally, intrathecally, intramuscularly, endoscopically, intralesionally, percutaneously, subcutaneously, regionally, stereotactically, orally or by direct injection or perfusion"***

212. Honda alone, or Honda in view of Gajewski, discloses this limitation for the same reasons as discussed with respect to the anticancer "administration" step of Claim 3.

**g. Claim 19**

***"The method of claim 1, wherein the method further comprises administering an immune checkpoint inhibitor"***



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213. Honda alone, or Honda in view of Gajewski, discloses this limitation for the same reasons as discussed with respect to the "anticancer treatment" step of Claim 3.

214. In addition, Gajewski provides that the recited "methods [can] further comprise administering to the subject an immune checkpoint inhibitor." EX-1012, p.6, ll.18-30. Gajewski teaches a number of different useful immune checkpoint inhibitors, including use of "a protein or polypeptide," "antibody or antigen-binding fragment thereof," or that "the immune checkpoint protein is selected from the group consisting of CTLA4, PD-1, PD-L1, PD-L2, A2AR, B7-H3, B7-H4, BTLA, KIR, LAG3, TIM-3 or VISTA." *Id.* ("the immune checkpoint inhibitor is an interfering nucleic acid molecule" such as "an siRNA molecule, an shRNA molecule or an antisense RNA molecule"); EX-1012, p.6, ll.26-30 ("the immune checkpoint inhibitor [can be] selected from the group consisting of nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, STI-A1110, TSR-042, RG-7446, BMS- 936559, BMS-936558, MK-3475, CT 01 1, MPDL3280A, MEDI-4736, MSB-0020718C, AUR-012 and STI-A1010"); and EX-1012, claim 16 ("wherein the immunotherapy comprises … anti-CTLA-4 antibodies and/or anti-PD-Ll or anti-PD-1 antibodies.").



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215. A POSA would be motivated to modify the teachings of Honda to use the specific adjuvant immune checkpoint inhibitor disclosed in Gajewski for the reasons discussed in the Motivation to Combine section.

**h. Claims 8-18**

216. Honda alone, or Honda in view of Gajewski, discloses this limitation for the same reasons as discussed with respect to the "administration" step of Claim 1.

217. Claims 8-18 depend directly or indirectly on claim 1, and as discussed above in Section V.C.2, provide no affirmative limitation on the claimed "administering" step, on the "composition," on the "population of bacteria," or any other recitation of claim 1. Rather, the wherein clauses set forth in claims 8-18 speak to desiderata – desired outcomes (*e.g.,* "wherein administration... results in…"), without any recitation of additional steps to achieve the desiderata. Accordingly, claims 8-18 do not further limit claim 1, and claims 8-18 are obvious for the same reasons discussed with respect to claim 1.

### 6. Claim 4 is Obvious Over the Honda (WO '419) in view of Gajewski (WO '605) and Miquel

**a. Claim 4**

***"The method of claim 1, wherein the population of bacteria comprises the bacteria Faecalibacterium prausnitzi."***

218. Honda discloses this limitation in view of Gajewski and Miquel. As also shown above with respect to claim 1, Honda and Gajewski disclose methods



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of reducing or delaying growth of cancer, including skin cancer tumors, through administration of commensal bacterial compositions derived from human and mice feces comprising bacteria from the genus *Ruminococcus*. *See* § VIII(D)(5)(a); *see also* EX-1013, ¶1 (disclosing "as an active component, human-derived bacteria… isolated and cultured from… a fecal sample"); EX-1012 p.47, ll.7-16 and Figure 1A-H (disclosing the transfer of fecal suspensions from the JAX mice (*i.e.,* "responder" feces) by oral gavage into the TAC mice). Honda and Gajewski do not, however, specifically disclose the administration of compositions comprising *Faecalibacterium prausnitzii* bacteria, which belong to the Ruminococcaceae family.

219. However, Miquel teaches that "*Faecalibacterium prausnitzii* is the most abundant bacterium" in feces of healthy adults, and is one of the most prolific members of the Ruminococcaceae family. EX-1014 pp.255-256 ("*F. prausnitzii* species are a major representative of… Ruminococcaceae family."). Miquel describes the known "importance of this highly metabolically active commensal bacterium as a component of the healthy human microbiota," including their abundant butyrate production. EX-1014 pp.255-256.

220. Miquel teaches that *F. prausnitzii* has been analyzed in numerous diseases including tumors and cancer, and that *F. prausnitzii* abundance in the microbiotica "is a good intestinal health indicator." EX-1014 p.256. Miquel



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concludes that it "could be useful to develop therapeutic strategies and personalized medicine" and that "modulation of *F. prausnitzii* abundance, for example using prebiotics and/or probiotics and/or formulations that permit survival through the upper part of the intestinal tract might have prophylactic or therapeutic applications in human health." EX-1014 pp. 258 and 259.

221. Thus, a POSA would have been motivated to combine the teachings of Honda and Gajewski to include the specific *F. prausnitzii* bacterial species taught in Miquel, for the reasons discussed in the Motivation to Combine section.

## X. CONCLUSION AND DECLARATION

222. My findings and opinions set forth in this Declaration are based on my work and examination to date. I may continue my examinations in view of additional documents or other factual evidence over the course of this proceeding that may necessitate supplementing and/or refining my opinions. I reserve the right to add to, alter, or delete my opinions and my Declaration upon discovery of additional information. I reserve the right to make such changes as necessary.

223. In signing this Declaration, I understand that the Declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for



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cross-examination within the United States during the time allotted for cross-examination.

224. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, of Title 18 of the United States Code.

[SIGNATURE ON FOLLOWING PAGE]



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Dated: April 26, 2023 By: ___/Matthew J. Robinson/_____
Matthew Robinson



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