

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

Post Grant Review No.: 2023-00026

**PETITION FOR POST GRANT REVIEW OF U.S. PATENT NO. 11,395,838
UNDER 35 U.S.C. §§ 321-329 and 37 C.F.R. §§ 42.1-.80, 42.200-.207**

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Petitioner's Exhibit List

<i>ML Exhibit #</i>	<i>Description</i>
1001	U.S. Patent No. 11,395,838 (“the ’838 Patent”)
1002	U.S. Patent No. 11,395,838 File History
1003	Declaration of Mat Robinson, Ph.D.
1004	<i>Curriculum vitae</i> of Mat Robinson, Ph.D.
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)
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 <i>Faecalibacterium prausnitzii</i> 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)

<i>ML Exhibit #</i>	<i>Description</i>
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 Bacteriology (2 nd 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
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

I. INTRODUCTION

Pursuant to 35 U.S.C. § 321 *et seq.* and 37 C.F.R. § 42.1 *et seq.*, Microbiotica Limited (“Petitioner” or “Microbiotica”) hereby petitions for a post grant review of U.S. Patent No. 11,395,838 (“the ’838 Patent”). Petitioner respectfully submits that Claims 1-19 (the “Challenged Claims”) of the ’838 Patent are unpatentable: (i) under 35 U.S.C. § 112(a) as they are not supported by, nor enabled by, the specification of the ’838 Patent, (ii) under 35 U.S.C. § 112(b) as they fail to particularly point out and distinctly claim the subject matter which the inventors regard as their invention, and (iii) under 35 U.S.C. § 103 in view of the prior art references discussed herein. This Petition demonstrates by a preponderance of the evidence that there is a reasonable likelihood that Petitioner will prevail with respect to at least one of these claims. Accordingly, it is respectfully requested that the Board institute a post grant review of the ’838 Patent pursuant to 37 C.F.R. § 42.208.

II. OVERVIEW

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 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/ μ l human fecal suspension) orally gavaged into a mouse. 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. EX-1003 ¶57.

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 artisan. 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). EX-1003 ¶58.

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. EX-1003 ¶59.

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. EX-1003 ¶60.

Thus, having failed to describe any particularized solution to the problem of providing anticancer treatment, beyond that which was well-known in the art, the Challenged Claims are unpatentable.

III. GROUNDS FOR STANDING (37 C.F.R. § 42.204(A))

Petitioner certifies that the '838 Patent is available for post grant review and that Petitioner is not barred or estopped from requesting a post grant review of the Challenged Claims on the grounds identified herein. 37 C.F.R. § 42.204(a). This Petition is filed pursuant to 37 C.F.R. § 42.206(a).

IV. RELIEF REQUESTED (37 C.F.R. § 42.22(A))

Petitioner respectfully requests institution of a post grant review pursuant to 37 C.F.R. § 42.208 and cancellation of all Challenged Claims on the following grounds:

V. REASONS FOR THE REQUESTED RELIEF

As explained in §§ II and VIII-IX of this Petition and in the attached Declaration of Petitioner's Expert, Mat Robinson, Ph.D., ("Robinson Dec" EX-1003), the concept of administering a "composition" that "comprises" an "isolated or purified" population of bacteria belonging to an entire family that is claimed in

the '838 Patent is not supported, nor enabled, by the specification of the '838 Patent, fails to inform a POSA of the scope of the invention, and/or is obvious over the Honda (EX-1011) in view of Gajewski (EX-1012) and Miquel (EX-1014) references.

As detailed in §§ II and VIII-IX, this Petition and Dr. Robinson explain: (i) why the full scope of the claims is not supported, nor enabled, by the specification of the '838 Patent, (ii) how and why the claims, read in light of the specification and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention; and (iii) where each element is found in the prior art and why each claim would have been obvious to a POSA at the time of the invention.

A. Summary of the '838 Patent

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; EX-1003 ¶61.

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; EX-1003 ¶62.

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). EX-1003 ¶63.

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; EX-1003 ¶64.

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 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.”). EX-1003 ¶65.

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 microbiome (with low diversity and high relative abundance of Bacteroidales...)” was already suggested in the art. *Id.* 158:1-19; EX-1003 ¶66.

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; EX-1003 ¶67.

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 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; EX-1003 ¶68.

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.*; EX-1003 ¶69.

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 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.*; EX-1003 ¶70.

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.*; EX-1003 ¶71.

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; EX-1003 ¶72.

B. Prosecution History

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).

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

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; EX-1003 ¶73.

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 *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; EX-1003 ¶74.

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.*; EX-1003 ¶75.

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.*; EX-1003 ¶76.

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.*; EX-1003, ¶77.

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; EX-1003 ¶78.

C. Claim Construction

The claims should be given “their ordinary and customary meaning” as understood by a person of ordinary skill at the time of the claimed invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312, 1327 (Fed. Cir. 2005). Petitioner proposes that each claim term in the Challenged Claims not identified below be given its plain and ordinary meaning in this proceeding and consistent with this standard, a proposed interpretation for certain claim terms is provided below. For the terms “isolated or purified” the specification sets forth a definition that deviates from the plain and ordinary meaning. It is noted that the interpretations below are applicable to the post grant review sought herein only and should not be construed as constituting, in whole or in part, Petitioner’s own interpretation of any claims for any other purposes, including any litigation. Accordingly, Petitioner expressly reserves the right to present an interpretation of a claim term in other proceedings, which is different, in whole or in part, of that presented in this Petition. EX-1003 ¶79.

1. “subject in need thereof”

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 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.” EX-1003 ¶80.

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; EX-1003 ¶81.

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); EX-1003 ¶81.

2. Wherein Clauses Reciting Intended Results Are Not Limiting

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	<u>wherein</u> administration of the composition <u>results in</u> an increase of CD8 ⁺ T lymphocytes in the tumor.
9	<u>wherein</u> the [administration of the composition <u>results in</u> an increase of]... cytotoxic T lymphocytes.
10	<u>wherein</u> administration of the composition <u>results in</u> 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	<u>wherein</u> administration of the composition <u>results in</u> 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	<u>wherein</u> administration of the composition to the subject <u>results in</u> an increase in CD3, CD8, PD1, FoxP3, Granzyme B and/or PD-L1 expression in a tumor immune infiltrate.
13	<u>wherein</u> administration of the composition to the subject <u>results in</u> a decrease in ROR γ T expression in a tumor immune infiltrate.
14	<u>wherein</u> administration of the composition to the subject <u>results in</u> an increase in CD45 ⁺ , CD3 ⁺ /CD20 ⁺ /CD56 ⁺ , CD68 ⁺ and/or HLA-DR ⁺ cells in the tumor.
15	<u>wherein</u> administration of the composition to the subject <u>results in</u> an increase in the level of innate effector cells in the subject.

16	<u>wherein</u> the [administration of the composition to the subject <u>results in</u> an increase in the level of]... D45 ⁺ CD11b ⁺ Ly6G ⁺ [innate effector] cells.
17	<u>wherein</u> administration of the composition to the subject <u>results in</u> a decrease of the level of suppressive myeloid cells in the subject.
18	<u>wherein</u> [administration of the composition to the subject <u>results in</u> a decrease of the level of]... CD45 ⁺ CD11b ⁺ CD11c ⁺ [suppressive myeloid] cells.

EX-1003 ¶83.

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. *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375-76 (Fed. Cir. 2001). This is particularly true of “wherein” clauses, which often signal recitations of intended results that do not limit claim scope. *Minton v. Nat’l Ass’n of Securities Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003) (“A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.”); *Prometheus Labs. Inc. v. Roxane Labs., Inc.*, No. 11-230, 2013 U.S. Dist. LEXIS 135284, at *14-15 (D.N.J. Sept. 23, 2013) (“wherein” clause reciting benefits achieved by claimed method of treatment did not require “steps or additional processes” and did not limit claim scope). 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.” *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329-30 (Fed. Cir. 2005) (emphasis added); *Prometheus*, 2013 U.S. Dist. LEXIS 135284, at *14; EX-1003 ¶84.

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, 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. EX-1003 ¶86.

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. EX-1003 ¶87.

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 effector cells (expressing CD45+CD11b+Ly6G+) and lower frequency of suppressive myeloid cells (expressing CD11b+en11c+)”). As such, a POSA understood that these are the “outcome measures” and “results” of administering a bacterial composition; they are not steps. EX-1003 ¶88.

Finally, the doctrine of claim differentiation does not require that the “wherein” clauses of the asserted claims be construed as material claim limitations. “The doctrine only creates presumption that each claim in a patent has a different scope; it is not a ‘hard and fast’ rule of construction.” *Bristol-Myers*, 246 F.3d at 1376; *Prometheus*, 2013 U.S. Dist. LEXIS 135284, at *14-15, *18 (holding “wherein” clause that was the sole additional phrase in a dependent claim was a non-limiting description of “desired results”); EX-1003 ¶85.

In this case, 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.*; EX-1003 ¶89.

3. “isolated or purified”

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. EX-1003 ¶90.

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 population to refer to one that has been made “pure by removing any harmful, dirty, or inferior substances from it.” EX-1023; EX-1003 ¶91.

D. Priority Date of the Challenged Claims

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. 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. Petitioner expressly reserves the right to challenge the priority date of the Challenged Claims in other proceedings. EX-1003 ¶92.

E. Person of Ordinary Skill in the Art

A 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, a POSA in the September 27, 2016 timeframe 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. EX-1003, ¶¶24-25.

F. State of the Art

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 are not relied on by Petitioner as grounds for invalidity. Instead these prior art references, 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 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, relied upon by Dr. Robinson, properly included to provide factual support for his opinions, and can be properly considered by the Board 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. EX-1003, ¶93.

1. The Human Gut Microbiome

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 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; EX-1003, ¶94.

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; EX-1003, ¶95.

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 *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.”); EX-1003, ¶96.

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 p.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; EX-1003, ¶97.

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; EX-1003, ¶98.

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 Ruminococcaceae family, the *Ruminococcus* genus, and the genus and species *Faecalibacterium prausnitzii* for therapeutic treatments. EX-1003, ¶99.

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

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.*; EX-1003, ¶100.

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 both therapeutic and adverse effects of anti-cancer interventions either through pharmacodynamic or immunological mechanisms. EX-1007 p.1261; EX-1003, ¶101.

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; EX-1003, ¶102.

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; EX-1003, ¶103.

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.”); EX-1003, ¶104.

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 EX-1003, ¶105.

Indeed, as shown in the illustration to the right, POSAs had concluded that “better management of cancer patients” should be directed at

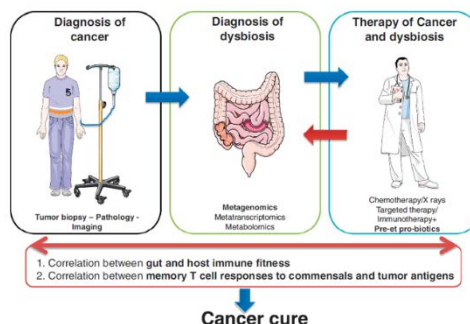
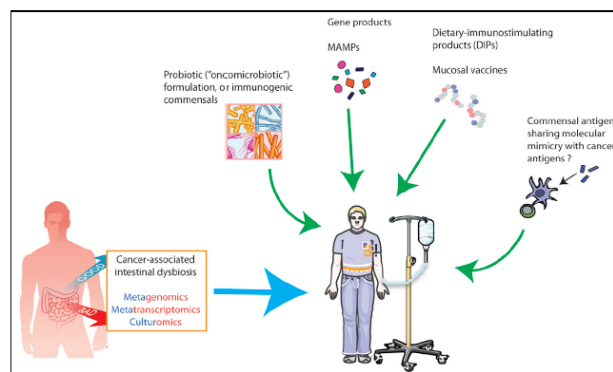


Figure 3 Future prospects and clinical implementations of this work. To date, patients who are being diagnosed with cancer undergo a pathological biopsy and imaging tomography/magnetic resonance to analyze spreading of the malignant process. In the near future, we will need to investigate their intestinal 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 EX-1003, ¶106.

Moreover, this view was shared by others in the field. For instance, Pitt’s Figure 3 (reproduced at right) 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....*

EX-1007 p.1264 (emphasis added); EX-1003, ¶106.

VI. IDENTIFICATION OF CHALLENGES

A. Challenged Claims

All 19 claims of the '838 Patent are challenged in this Petition. EX-1003, ¶107.

B. Statutory Grounds for Challenges

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

EX-1003, ¶107.

International Publication No. WO2015/156419 titled “Composition and Methods for Induction of TH17 Cells” published October 15, 2015 from PCT/USJP2015/061771 filed on April 10, 2015 (Honda)(EX-1011). Honda is prior art under 35 U.S.C. § 102(a)(2), and was not cited, applied by, or disclosed to, the Examiner during prosecution of the ’838 Patent. EX-1003, ¶109.

International Publication No. WO2016196605A1 titled “Treatment of Cancer by Manipulation of Commensal Microflora”, published on December 8, 2016 from PCT/US2016/035228, filed June 1, 2016 (Gajewski)(EX-1012). Gajewski is prior art under 35 U.S.C. § 102(a)(1). Gajewski was cited on the face of the ’838 Patent, but it was not applied nor discussed by the Examiner during prosecution. EX-1003, ¶109.

Printed article “*Faecalibacterium prausnitzii* and human intestinal health” was published in Current Opinion in Microbiology, Vol. 16 pp.255–261 in June 2013 (Miquel)(EX-1014). Miquel is a printed publication at least as early as June 2013, and is prior art under 35 U.S.C. § 102(a)(1). Miquel was cited by the Examiner during prosecution of the ’838 Patent, but was not applied in combination with Honda and Gajewski. EX-1003, ¶109.

VII. 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

35 U.S.C. § 112(a) requires that the '838 Patent specification contain a written description of the invention that is sufficiently detailed that a POSA can reasonably conclude that the inventors had possession of the full scope of the Challenged Claims at the time of filing the application leading to the '838 Patent (*i.e.*, September 27, 2016). 35 U.S.C § 112(a); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). The written description requirement thus “limits patent protection to those who actually perform the difficult work of ‘invention’—that is, conceive of the complete and final invention with *all its claimed limitations*—and disclose the fruits of that effort to the public.” *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1353 (Fed. Cir. 2010) (emphasis added). “[A] mere wish or plan for obtaining the claimed chemical invention” is not enough. *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008).

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. EX-1003, ¶110.

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. EX-1003, ¶111.

As set forth below, this 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. EX-1003, ¶112. Simply put, PO did not possess the full scope of the Challenged Claims as of the earliest priority date of the '838 Patent.

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

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. EX-1003, ¶113.

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 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; EX-1003, ¶114.

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; EX-
1003 ¶115.

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
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; EX-1003 ¶116.

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. EX-1003 ¶117.

2. PO Did Not Possess Any “Composition” For “Administration” To a Human

a. PO Did Not Formulate Any “Compositions” For Administration

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). EX-1003 ¶118.

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. EX-1003 ¶119.

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. EX-1003 ¶120.

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. EX-1003 ¶121.

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 to make and use a composition safe and effective for administration, by every means possible. EX-1003 ¶122.

b. Formulation Strategies Change Depending on the Route of Administration

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. EX-1003 ¶123.

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 “administered” any unprocessed fecal composition (and, no doubt, for good reason!). EX-1003 ¶124.

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*. EX-1003 ¶125.

c. PO Does Not Teach What Bacterial Concentrations Were Used

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/µl 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. EX-1003 ¶126.

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 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. EX-1003 at ¶127.

Instead, the specification then provides a broad range “from about 1 $\mu\text{g/kg/body weight}$ to about 1000 mg/kg/body weight ” – a difference of 1×10^6 – 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 1×10^3 to... 1×10^{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. *Carnegie Mellon Univ.*, 541 F.3d at 1122 (“[A] mere wish or plan for obtaining the claimed chemical invention” is not enough.); EX-1003 ¶128.

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 in possession of a method of administering the *every* conceivable concentration of such bacteria. EX-1003 ¶129.

**d. Bacteria from the “Family of Ruminococcaceae”
Lacks Written Description Support**

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; EX-1003 ¶130.

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 of Ruminococcaceae would *not* result in the claimed “reduction” or “delay” in skin cancer tumor growth. EX-1003, ¶131.

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.*; EX-1003, ¶132.

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 Ruminococcaceae that would *not* result in the claimed “reduction” or “delay” and are found *only* in non-responder feces. EX-1003, ¶133.

e. The “Comprising” Transition Creates Additional Written Description Problems

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. EX-1003 ¶134.

For example, the specification identifies numerous bacterial species, including bacteria of the class Bacteroidia or family Prevotellaceae, 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. EX-1003 ¶135.

As a result, the specification lacks written description support demonstrating that PO was in possession of a composition comprising bacteria from both (i) the family of Ruminococcaceae, and (ii) the class Bacteroidia or family Prevotellaceae (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. EX-1003 ¶136.

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

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 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; EX-1003 ¶137.

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”. EX-1003 ¶138.

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 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. EX-1003 ¶139.

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

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.

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. EX-1003 ¶140.

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. EX-1003 ¶141.

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 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 nowhere 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. EX-1003 at ¶142.

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

35 U.S.C § 112(a) requires that the '838 Patent specification teach a POSA how to make and use the full scope of the Challenged Claims without undue experimentation. 35 U.S.C § 112(a); *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993).

As set forth in §VII.A, 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). EX-1003, ¶143.

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

It is axiomatic that the claims define the invention that an applicant believes is patentable. *In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993). In keeping with the importance of this role, 35 U.S.C. § 112 (b) requires that the claims particularly point out and distinctly claim the subject matter that the patent applicant regards as his or her invention. 35 U.S.C. § 112 (b). “A patent must be precise enough to afford clear notice of what is claimed, thereby ‘appris[ing] the public of what is still open to them.’” *Nautilus Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 909–10 (2014) (citations omitted). As such, the Supreme Court has held 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.” *Id.* at 910.

In this case, application of the *Nautilus* standard to the Challenged Claims renders at least several claim limitations indefinite. *Id.* 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; EX-1003 ¶144.

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. EX-1003 ¶145. This is the definition of indefiniteness, and, in addition, gives rise to lack of enablement across the breadth of the claims.

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. *Nautilus*, 572 U.S. at 910; EX-1003 ¶146. Thus, the Challenged Claims are invalid for indefiniteness under 35 U.S.C. § 112 (b).

- 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**

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. *Nautilus*, 572 U.S. at 910. 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.” EX-1023. But the remaining evidence contained within the patent record negates those inferences. EX-1003 ¶147.

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 “is well understood to mean ‘including but not limited to.’” *Lee v. Mike’s Novelties, Inc.*, 543 Fed. App’x 1010, 1014 (Fed. Cir. 2013) (internal citations omitted); 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. EX-1003 ¶148.

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. Importantly, none of the “experiments” administered an “isolated or purified” population of Ruminococcaceae bacteria. EX-1003 ¶149.

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/µl 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. EX-1003 ¶150.

In the alternative, however, to the extent that the “plain and ordinary” meanings were adopted, then application of such a construction would lead to additional grounds for invalidity, including lack of enablement and written description. 35 U.S.C. §112 (a). 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 U.S.C. § 112 (a). *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1217 (Fed. Cir. 1991) (patent held invalid for lack of enablement for failure to disclose procedure for purifying rEPO or uEPO); EX-1003 ¶151.

b. PO’s “Isolated” Definition Causes More Uncertainty

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 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; EX-1003 ¶152.

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; EX-1003 ¶153.

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.” EX-1003 ¶154.

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. EX-1003 ¶155.

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. Such a definition fails to provide “guideposts” that would allow “a skilled artisan” to draw “meaningfully precise” “objective boundaries” as to scope of this claim limitation with “reasonable certainty.” *Niazi Licensing Corp. v. St. Jude Med. S.C., Inc.*, 30 F.4th 1339, 1349 (Fed. Cir. 2022); EX-1003 ¶156.

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

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); EX-1003 ¶157.

PO's overlapping definitions of "isolated" and "purified" are, therefore, circular, wherein each definition references the other for scope. As a result, the two limitations collapse onto themselves, creating in their wake additional ambiguity as to their intended meaning. EX-1003 ¶158.

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. EX-1003 ¶159.

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 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). *Nautilus*, 572 U.S. at 910 (because there must be “reasonable certainty” of a patent claim’s scope, there must be “reasonable certainty” as to the boundaries of that numerical range); EX-1003 ¶160.

2. The Bacteria in the “Family *Ruminococcaceae*” is a Moving Target

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.*; EX-1003 ¶161.

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

Manual – proposed a 12th genus, *Ethanoligenens*, for the family *Ruminococcaceae*. EX-1015 p.1016, *et seq.* This twelfth genus was not described in Bergey. EX-1003 ¶162.

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. EX-1003 ¶163.

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. *Nautilus*, 572 U.S. at 909–10 (“A patent must be precise enough

to afford clear notice of what is claimed, thereby ‘appris[ing] the public of what is still open to them.’”); EX-1003 ¶164.

**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

Honda is directed to compositions of human-derived bacteria that induce proliferation of Th17 cells. EX-1011 ¶1. In particular, Honda is directed to 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; EX-1003 ¶165.

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”); EX-1003 ¶166.

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 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”); EX-1003 ¶167.

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; EX-1003 ¶168.

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; EX-1003 ¶169.

2. The Gajewski Reference

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

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

administering a bacteria preparation containing *Ruminococcus* – a member of the purported family Ruminococcaceae. EX-1012 p.2, ll.9-19; EX-1003 ¶170.

“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 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); EX-1003 ¶171.

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; EX-1003 ¶172.

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-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; EX-1003 ¶173.

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; EX-1003 ¶174.

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 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 5×10^8 CFU of bacteria” administered in two or more doses. EX-1012 p.6, ll.6-13; EX-1003 ¶175.

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-L1, 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 injection, or administration into lymph nodes, or administration intraperitoneally. EX-1012, p.7, ll.3-6; p.8, ll.15-18; EX-1003 ¶176.

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; EX-1003 ¶177.

3. The Miquel Reference

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; EX-1003 ¶178.

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 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 microbiota “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; EX-1003 ¶179.

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. EX-1003 ¶180.

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

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 *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. EX-1003 ¶181.

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 *Ruminococcus* (within the family Ruminococcaceae that includes *Faecalibacterium*) for addressing cancer in a subject. EX-1003 ¶182.

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; EX-1003 ¶183. Thus, both Honda and Gajewski involved induction of a similar immunoregulatory pathway.

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 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. EX-1003 ¶184.

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. EX-1003 ¶185.

Finally, a POSA would be motivated to modify the teachings of Honda in view of the teachings of Gajewski and Miquel. 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. 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; EX-1003 ¶186.

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. EX-1003 ¶187.

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”

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. EX-1003 ¶188.

To the extent that PO argues that Honda does not expressly disclose “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 “discourag[ing] cancer/tumor growth [or] spread” in Gajewski to encompass “reducing or delaying growth” of skin cancer tumor cells. EX-1003 ¶189.

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; EX-1003 ¶190.

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. EX-1003 ¶191.

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

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, 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; EX-1003 ¶192.

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; EX-1003 ¶193.

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 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; EX-1003 ¶194.

Thus, Honda discloses administering to the subject a composition comprising an isolated or purified population of bacteria belonging to the family Ruminococcaceae. EX-1003 ¶195.

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 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....”). EX-1003 ¶196.

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.*). EX-1003 ¶197.

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. EX-1003 ¶198.

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

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, 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. EX-1003 ¶199.

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 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; EX-1003 ¶200.

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. EX-1003 ¶201.

c. Claim 3

“The method of claim 1, wherein the method further comprises administering an additional anticancer treatment”

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; EX-1003 ¶202.

To the extent that PO asserts that Honda does not disclose this limitation, Gajewski teaches that altering the subject’s microbiome to increase the 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”). EX-1003 ¶203.

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.; EX-1003 ¶204.

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. EX-1003 ¶205.

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”

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. EX-1003 ¶206.

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; EX-1003 ¶207.

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. EX-1003 ¶208.

f. Claim 6

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

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. EX-1003 ¶209.

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”); EX-1003 ¶210.

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. EX-1003 ¶211.

g. Claim 7

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

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. EX-1003 ¶212.

h. Claim 19

“The method of claim 1, wherein the method further comprises administering an immune checkpoint inhibitor”

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. EX-1003 ¶213.

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-L1 or anti-PD-1 antibodies.”). EX-1003 ¶214.

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. EX-1003 ¶215.

i. Claims 8-18

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. EX-1003 ¶216.

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. EX-1003 ¶217.

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 prausnitzii*.”

Honda discloses this limitation in view of Gajewski and Miquel. As also shown above with respect to claim 1, Honda and Gajewski disclose methods 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. EX-1003 ¶218.

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; EX-1003 ¶219.

Miquel teaches that *F. prausnitzii* has been analyzed in numerous diseases including tumors and cancer, and that *F. prausnitzii* abundance in the microbiota “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 pp.258 and 259; EX-1003 ¶220.

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. EX-1003 ¶221.

VIII. The Board Should Not Deny Institution Under 35 U.S.C. § 325(d)

The Board should not exercise its discretion to deny institution under § 325(d) because the grounds asserted in this Petition are neither the same nor substantially the same as nor cumulative to art or arguments presented during prosecution. In determining whether to exercise its discretion under § 325(d), the Board uses a two-part framework. *Advanced Bionics, LLC v. MED-EL*

Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 8 (P.T.A.B. Feb. 13, 2020) (precedential).⁴

Under the first part of the *Advanced Bionics* framework, Gajewski and Miquel were previously before the Office, but none of the combinations asserted in this Petition were previously before the Office. Gajewski was supplied by the Applicant along with over 75 other references, but the Examiner never applied or discussed Gajewski.

Miquel was cited by the Examiner as disclosing a method of “preventing cancer”. In response, PO dropped claim 166 (“the subject is identified as at risk of developing a cancer”) and amended the claim 44 (issued claim 1) from a method of “treating or preventing cancer in a subject” to recite a method of “treating or

⁴ In evaluating the *Advanced Bionics* two-part framework, the Board is guided by the *Becton, Dickinson* factors. *Id.* at 9-10, n. 10 (citing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (P.T.A.B. Dec. 15, 2017)). *Becton, Dickinson* factors (a), (b), and (d) relate to whether the art or arguments presented in the petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics*, 10. Factors (c), (e), and (f) “relate to whether the petitioner has demonstrated a material error by the Office” in its prior consideration of that art or arguments. *Id.*

reducing or delaying tumor growth in a subject in need thereof.” EX-1002 pp.100-109. In Ground 5 of the Petition, Miquel is applied against Claim 4 to show 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. This argument was not previously before the Office, and thus, the Examiner never considered or applied the combination of Honda, Gajewski and Miquel in the same or substantially the same manner as Grounds 4 and 5.

Because the conditions of the first part of the *Advanced Bionics* framework are not met, the Board should decline to exercise its discretion to deny institution under § 325(d) and need not address the second part.

Even if the Board were to consider the second part of the *Advanced Bionics* framework, the Office nonetheless erred in a manner material to the patentability of Challenged Claims. For example, the Examiner never considered any combination of Honda, Gajewski and Miquel. In failing to identify and consider these references and the arguments as presented in the Petition, the Examiner materially erred.

While the Examiner did raise some Section 112 rejections during prosecution, the Examiner did not address the detailed Section 112 issues raised in this Petition directed to written description, enablement and indefiniteness. In

failing to identify and consider these Section 112 issues, the Examiner materially erred.

Accordingly, for at least the above reasons, the Board should not exercise its discretion to deny institution under § 325(d).

IX. MANDATORY NOTICES UNDER 37 C.F.R. §42.8

A. Real Party-in-Interest (37 C.F.R. § 42.8(b)(1))

The real party-in-interest in this Petition is Microbiotica Limited, a private limited company under UK law, having a Registered Office Address of:
Chesterford Research Park, Little Chesterford, Cambridge, England, CB10 1XL.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

1. Judicial Matters

As of the filing date of this Petition and to the best knowledge of Petitioner, the '838 Patent is not involved in any judicial matters.

2. Administrative Matters

As of the filing date of this Petition and to the best knowledge of Petitioner, the '838 Patent is not involved in any administrative matters.

3. Related Patents

As of the filing date of this Petition and to the best knowledge of Petitioner, the '838 Patent is related to U.S. Pat. App. No. 17/814,314, filed July 22, 2022, and Int. Pat. App. No. PCT/US17/53717, filed September 27, 2017. EX-1013.

C. Lead/Back-up Counsel (37 C.F.R. § 42.8(b)(3))

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D. Notice of Service Information (37 C.F.R. § 42.8(b)(4))

Please direct all correspondence to lead and back-up counsel at the above addresses. Petitioner consents to electronic service at the email addresses above.

X. CONCLUSION

For the reasons set forth above, Petitioner has established a reasonable likelihood of prevailing with respect to all claims of the '838 Patent and requests the Board institute post grant review and then cancel all claims as unpatentable.

Respectfully submitted,

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Patrick D. McPherson

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Dated: April 26, 2023

CERTIFICATION OF SERVICE ON PATENT OWNER

Pursuant to 37 C.F.R. §§ 42.6(e), 42.8(b)(4) and 42.105, the undersigned certifies that on the 26th day of April 2023, a complete and entire copy of this Petition for Post Grant Review of U.S. Patent No. 11,395,838 and all supporting exhibits were served via Federal Express, postage prepaid, to the Patent Owner by serving the correspondence address of record for the '838 Patent:

THE BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM
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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24 *et seq.*, the undersigned certifies that this document complies with the type-volume limitations. This document contains 18700 words as calculated by the “Word Count” feature of Microsoft Word 2010, the word processing program used to create it.

Dated: April 26, 2023

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