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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.

PGR2023-00026
Patent 11,395,838 B2

Before JEFFREY N. FREDMAN, SUSAN L. C. MITCHELL, and JAMIE T. WISZ, *Administrative Patent Judges*.

MITCHELL, *Administrative Patent Judge*.

DECISION
Denying Institution of Post-Grant Review
35 U.S.C. § 324(a)

I. INTRODUCTION

On April 26, 2023, Microbiotica, Limited ("Petitioner") filed a Petition for Post-Grant Review of claims 1–19 of U.S. Patent No. 11,395,838 B2 (Ex. 1001, "the '838 patent"). Paper 2 ("Pet."). On August 22, 2023, Board of Regents, The University of Texas System ("Patent Owner") filed a Preliminary Response. Paper 7. Petitioner filed an authorized Reply to Patent Owner's Preliminary Response, *see* Papers 8, 10, and Patent Owner filed an authorized Sur-Reply to Patent Owner's Preliminary Response, *see* Paper 8 and 11.

Institution of post-grant review is authorized by statute only when "the information presented in the petition . . . demonstrate[s] that it is more likely than not that at least 1 of the claims challenged in the petition is unpatentable."[1] 35 U.S.C. § 324; *see* 37 C.F.R. § 42.4. Upon considering the Petition, Preliminary Response, and the cited evidence, we conclude that Petitioner has not satisfied its burden under 35 U.S.C. § 324 to show that it is more likely than not that at least 1 of the claims challenged in the Petition is unpatentable.

A. Real Parties in Interest

Petitioner identifies itself as real party in interest. Pet. 88. Patent Owner identifies itself as real party in interest, but also states that the "Parker Institute for Cancer Immunotherapy has certain rights in U.S. Patent No. 11,395,838." Paper 3, 1.

[1] Petitioner mistakenly applies the reasonable likelihood standard for an *inter partes* review proceeding. *See* Pet. 1, 89. The correct standard that we apply here for a post-grant review is whether we determine that it is more likely than not that at least one of the challenged claims in the patent is unpatentable.

B. Related Matters

Petitioner and Patent Owner list two patent applications as related matters. Pet. 88; Paper 3, 1. Patent Owner states "[t]he '838 patent is a national-stage entry of International Patent Application No. PCT/US2017/053717, filed September 27, 2017. Pending U.S. Patent Application No. 17/814,314, filed July 22, 2022, claims the benefit of the '838 patent." Paper 3, 1.

C. The '838 Patent (Ex. 1001)

The '838 patent, titled "Methods for Enhancing Immune Checkpoint Blockade Therapy by Modulating the Microbiome," issued July 26, 2022, identifying Board of Regents, The University of Texas System, as the applicant and assignee. *See* Ex. 1001, codes (71), (73). The named inventor of the '838 patent is Jennifer Wargo. *See id*. at code (72).

The '838 patent describes methods and compositions for treating cancer by modulating the microbiome by administration of butyrate and/or butyrate-producing bacteria to enhance the efficacy of immune checkpoint blockade. *See* Ex. 1001, Abstr., 22:51–55. The '838 patent points to the discovery that using immune checkpoint inhibitors for the treatment of melanoma "has shown tremendous promise," but these immune checkpoint inhibitors can be associated with substantial toxicity and only some patients may benefit. *Id*. at 1:24–38. Treating with immune checkpoint inhibitors shows response rates of only 15 to 40 percent in patients with widespread melanoma. *See id*. at 22:44–48.

The '838 patent describes an "immune checkpoint" as "a component of the immune system which provides inhibitory signals to its components in order to regulate immune reactions," *see id*. at 26:33–36, and an "immune

checkpoint inhibitor" as "any compound inhibiting the function of an immune checkpoint protein," including "reduction of function and full blockade." *See id*. at 27:43–46. PD-1 and its ligands PD-L1 and PD-L2 are such immune checkpoint proteins. *See id*. at 26:36–39. PD-1 is a checkpoint protein on the surface of immune cells called T cells, and normally acts as an "off switch" that prevents the T cells from attacking other cells in the body. *See* Ex. 1024, Abstr., 256–257; Ex. 1025, 3.

The '838 patent also points to the discovery of the role of the host gastrointestinal microbiome, including in the tumor and the gut, in responses to cancer therapy, but states "there is a significant translational knowledge gap, and there is an unmet need for therapeutic strategies to enhance responses to immune checkpoint blockade in melanoma, and other cancers." *See* Ex. 1001, 1:44–53.

The '838 patent describes several studies including of a large cohort of patients with metastatic melanoma undergoing systemic treatment, with a subset of those patients receiving PD-1-based immunotherapy. *See* Ex. 1001, 22: 55–58, 151:14–187:10. Samples of the oral and gut microbiome of these patients were characterized via 16S rRNA gene sequencing and metagenomic whole genome shotgun sequencing. *See id*. at 22:58–61, 152:6–17. The inventor observed significant higher diversity and increased abundance of specific bacteria within the order Clostridiales and the family Ruminococcaceae in the gut microbiome of responders versus non-responders to PD-1-based immunotherapy. *See id*. at 22:61–23:1, 154:1–22. The species *Faecalibacterium prausnitzii* was found to be more abundant in responders and "are known to produce short chain fatty acids such as butyrate, which help sustain the integrity of specific cells within the

gut (i.e., enterocytes) and may enhance immunity." *See id*. at 23:3–6, 154:12–22, 181:57–182:4 (butyrate provides substrate to facilitate a favorable gut microbiome). Non-responders, however, had low levels of these bacteria and significantly higher levels of Bacteroidales bacteria that has been shown to down-regulate systemic immune responses. *See id*. at 23:7–11, 154:12–22. Another study described in the '838 patent showed that modulating the gut microbiome "by co-housing Taconic and Jackson mice and oral administration of short chain fatty acids (e.g., butyrate) resulted in delayed tumor outgrowth in mice with a less favorable gut microbiome (Jackson mice)." *See id*. at 23:14–19, 181:27–182:4.

The '838 patent concludes from these studies that:

> These results from human and murine studies have potentially far-reaching implications to enhance responses to immune checkpoint blockade via modulation of the gut microbiome.
>
> Importantly, the present studies show that patients with a "favorable" gut microbiome (with high diversity and high relative abundance of bacteria of the order Clostridiales and/or family Ruminococcaceae) have enhanced systemic and anti-tumor immune responses mediated by enhanced antigen presentation at the level of lymph node and tumor, as well as preserved effector T cell function in the periphery and the tumor microenvironment. In contrast, patients with an "unfavorable" gut microbiome (with low diversity and high relative abundance of bacteria of the order Bacteroidales) have impaired systemic and anti-tumor immune responses mediated by limited intratumoral infiltration of both lymphoid and myeloid elements, weakened antigen presentation capacity, and skewing towards immunoregulatory cellular and humoral elements in the periphery, including Treg and MDSC.

Ex. 1001, 23:19–38, 158:1–20.

Further studies in the mouse melanoma model system showed mice receiving fecal microbiota transplantation from the responder population had decreased tumor growth and increased response to anti-PD-1 therapy, higher percentages of innate effector cells, lower frequency of suppressive myeloid cells in the spleen, and an increased number of CD45+ immune and CD8+ T cells in the gut. *See* Ex. 1001, 23:39–52, 182:11–186:18.

D. Challenged Claims

Petitioner challenges all nineteen claims of the '838 patent, which are method claims. Pet. 1, 29–30. Only claim 1 is independent. Claims 2–4, 8, 10–15, 17, and 19 depend directly from claim 1, and claims 5–7, 9, 16, and 18 depend indirectly from claim 1. Ex. 1001, 189:1–190:35.

Claim 1 is representative and reproduced below:

> 1. A method of reducing or delaying growth of a skin cancer tumor in a subject in need thereof, comprising administering to the subject a composition comprising an isolated or purified population of bacteria belonging to the family Ruminococcaceae.

Ex. 1001, 189:2–6.

E. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–19 of the '838 patent on the following grounds, *see* Pet. 29–30:

Claim(s) Challenged	35 U.S.C. §[2]	Reference(s)/Basis
1–19	112(a)	Lack of written description

[2] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), included revisions to 35 U.S.C. § 103 that became effective on March 16, 2013, before the filing of the applications to which the '838

Claim(s) Challenged	35 U.S.C. §[2]	Reference(s)/Basis
1–19	112(a)	Lack of enablement
1–19	112(b)	Indefiniteness
1–3, 5–19	103	Honda,[3] Gajewski[4]
4	103	Honda, Gajewski, Miquel[5]

Petitioner submits the Declaration of Matthew Robinson, Ph.D. (Ex. 1003) in support of institution of post-grant review. Pet. 1. Patent Owner submits the Declaration of Wendy S. Garrett, M.D., Ph.D. (Ex. 2001). Prelim. Resp. 16.

II. ANALYSIS

A. Eligibility for Post-Grant Review

The post-grant review provisions set forth in Section 6(d) of the AIA apply only to patents subject to the first-inventor-to-file provisions of the AIA. *See* AIA § 6(f)(2)(A) ("The amendments made by subsection (d) . . . shall apply only to patents described in section 3(n)(1)."). Patents subject to the first-inventor-to-file provisions are those that issue from applications "that contain[] or contained at any time . . . a claim to a claimed invention that has an effective filing date as defined in section 100(i) of title 35, United

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patent claims priority. Therefore, we apply the AIA versions of Sections 112 and 103.

[3] Kenya Honda et al., WO 2015/156419 A1, published Oct. 15, 2015 (Ex. 1011, "Honda").

[4] Thomas Gajewski et al., WO 2016/196605 A1, published Dec. 8, 2016 (Ex. 1012, "Gajewski").

[5] Miquel et al., *Faecalibacterium prausnitzii and human intestinal health*, 16 CURRENT OPINION IN MICROBIOLOGY 255–261 (2013) (Ex. 1014, "Miquel").

States Code, that is on or after" March 16, 2013. *Id.* § 3(n)(1). Our rules require that each petitioner for post-grant review certify that the challenged patent has an effective filing date that renders the patent available for post-grant review. 37 C.F.R. § 42.204(a) ("The petitioner must certify that the patent for which review is sought is available for post-grant review."). In addition, "[a] petition for a post-grant review may only be filed not later than the date that is 9 months after the date of the grant of the patent or of the issuance of a reissue patent (as the case may be)." 35 U.S.C. § 321(c); *see also* 37 C.F.R. § 42.202(a) (accord).

Petitioner does not provide a statement that the '838 patent is eligible for post-grant review. *See generally* Pet. On this record, we determine that the '838 patent is eligible for post-grant review. Specifically, the earliest provisional application leading to the '838 patent was filed on September 27, 2016, the date which Petitioner asserts is the priority date of the challenged claims. *See* Ex. 1001, code (60); Pet. 21. The earliest priority date therefore falls after March 16, 2013. Also, this Petition was filed on April 26, 2023, which is nine months after July 26, 2022, the issue date of the '838 patent. Ex. 1001, code (45).

B. Person of Ordinary Skill in the Art

Factual indicators of the level of ordinary skill in the art include "the various prior art approaches employed, the types of problems encountered in the art, the rapidity with which innovations are made, the sophistication of the technology involved, and the educational background of those actively working in the field." *Jacobson Bros., Inc. v. U.S.*, 512 F.2d 1065, 1071 (Ct. Cl. 1975), *quoted with approval in Orthopedic Equip. Co. v. U.S.*, 702 F.2d 1005, 1011 (Fed. Cir. 1983).

According to Petitioner, a person of ordinary skill in the relevant art ("POSA") "would have had education and/or experience in the field of microbiology and/or oncology, and knowledge of the scientific literature concerning the same." Pet. 21 (citing Ex. 1003 ¶¶ 24–25). Petitioner also states that 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." *Id.*

Patent Owner counters that Petitioner has set the level of skill of a person of ordinary skill in the art too low. Prelim. Resp. 9–11; Ex. 2001 ¶ 25. Patent Owner asserts that a POSA would have a more advanced degree than a bachelor of science and would have more specific work experience. *Id.* For instance, Patent Owner asserts:

> A POSA for the '838 Patent typically would have an advanced degree, such as an M.D. or a Ph.D., with experience and training in oncology, have several years of experience with administering oncology treatments to subjects and evaluating results of such treatments, and have experience or knowledge in microbiome science and its modulation, inclusive of studies that involve stool microbiome profiling, as well as experience in, or knowledge of, related research and development of bacterial-based cancer treatments. A POSA may also have worked as part of a multi-disciplinary team and drawn upon not only his or her own skills, but also taken advantage of certain specialized skills of others in the team, to solve a given problem. For example, such a team may include a clinician, an immunologist, microbiologist, bioinformatician, molecular biologist, manufacturing specialist, and/or pharmaceutical formulator.

Prelim. Resp. 9–10 (citing Ex. 2001 ¶¶ 26–27).

Patent Owner concludes that by applying the inappropriately low level of skill of a POSA, "Petitioner overstates the amount of guidance needed in

the specification to describe and enable the claimed methods." Prelim. Resp. 11. Patent Owner confirms, however, that all arguments on all grounds presented in the Preliminary Response "apply regardless of which party's POSA definition is used." Prelim. Resp. 11 n.2.

We disagree with Patent Owner that a POSA is required to have a more advanced degree and such specialized experience in the relevant field. Petitioner's definition includes education and/or experience in the relevant fields and knowledge of the scientific literature in these fields. Petitioner also provides a sliding scale requiring more experience for those with less formal education in the relevant fields. Petitioner's definition of a POSA appears commensurate with the level of skill reflected in the asserted art in this case, as well as the '838 patent itself. Therefore, we apply Petitioner's proposed level of ordinary skill in the art to determine whether it is more likely than not that Petitioner would prevail with respect to at least one of the claims challenged in the Petition. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (stating prior art itself can reflect the appropriate level of ordinary skill in the art).

C. Claim Construction

We construe claims "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b)." 37 C.F.R. § 42.200 (2019). Therefore, we construe the challenged claims under the framework set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–19 (Fed. Cir. 2005) (en banc). Under this framework, claim terms are given their ordinary and customary meaning, as would be understood by a person of ordinary skill in the art, at the time of the invention, in light of the language of the claims, the specification, and the

prosecution history of record. *Id*. Only those terms that are in controversy need be construed, and only to the extent necessary to resolve the controversy. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co*., *Matal*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

Petitioner offers constructions for the following claim terms or phrases: "subject in need thereof" and "isolated or purified." *See* Pet. 15, 20. Petitioner also asserts that the "wherein" clauses in claims 8–18 are non-limiting statements of intended results. Pet. 16–20. We find that we need only address the meanings of claim phrases "subject in need thereof" and "isolated or purified."

1. "subject in need thereof"

Petitioner asserts that a "subject in need thereof" is "a human or non-human, such as primates, mammals, and vertebrates," as expressly set forth in the Specification of the '838 patent. Pet. 15 (citing Ex. 1003 ¶¶ 80–81); Ex. 1001, 27:50–52. Dr. Robinson, Petitioner's declarant, stated that this definition was confirmed by use of the term "subject" throughout the Specification of the '838 patent to refer to both human patients and non-human mice. Ex. 1003 ¶ 82 (citing Ex. 1001, 18:28–34, Figs. 9A, 9B, 25:64–26:23, 139:25–33).

Patent Owner does not specifically address the definition of the claim phrase a "subject in need thereof." *See generally* Prelim. Resp.

Petitioner's definition set forth above addresses what the claim term "subject" encompasses, and does not address the remainder of the claim phrase "in need thereof." Therefore, we too will address the meaning of the claim term "subject."

A patentee may act as a lexicographer, but must do so in the specification with "reasonable clarity, deliberateness, and precision." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Here, the Patent Owner has provided an express definition of "subject."

> "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. As Dr. Robinson points out, Patent Owner consistently uses the term "subject" throughout the Specification of the '838 patent consistent with this definition. *See* Ex. 2003 ¶¶ 81–82 (citing Ex. 1001, 18:28–34, Figs. 9A, 9B, 25:64–26:23, 139:25–33).

We determine on the record before us that the term "subject" refers to "a human or non-human, such as primates, mammals, and vertebrates."

2. "isolated or purified"

Petitioner asserts that the claim phrase "isolated or purified" population of bacteria belonging to the family Ruminococcaceae as it appears in claim 1 of the '838 patent "when read in view of the claims, the specification and the prosecution history, fail reasonably [to] inform a POSA as to the scope of the claimed invention. Neither the 'plain and ordinary' meaning of these terms, nor the meaning [Patent Owner] chose to ascribe these terms in the 'definitions' section of the specification, afford a POSA a clear notice of what is claimed and what is not." Pet. 20 (citing Ex. 1003 ¶ 90).

In the event that we find these terms "isolated" and "purified" not indefinite, Petitioner offers a "plain and ordinary" meaning of each term as follows. Pet. 20. Petitioner defines "isolated" as at least including "a single species of bacterium obtained in a pure culture." *Id.* (citing Ex. 1022).

Petitioner defines a "purified" bacterial population as referring to such a population that has been made "pure by removing any harmful, dirty, or inferior substances from it." *Id.* (citing Ex. 1023; Ex. 1003 ¶ 91).

Patent Owner responds that Petitioner's construction of "isolated" and "purified" disregards the ability of a patentee to be his or her own lexicographer, which can override the ordinary meaning of a term. Prelim. Resp. 8–9.

Because the meaning of the claim terms "isolated" and "purified" is inextricably linked with Petitioner's indefiniteness ground, we will address the meaning of those terms in the context of that ground as set forth below. *See infra* Section II.F.

D. Lack of Written Description

Petitioner asserts that the Specification of the '838 patent cannot support the breadth of the claims, especially the "limitless range" of the claim terms "administering," "subject," "composition," and "skin cancer tumor" as used in all claims at issue. Pet. 31–32. Specifically, Petitioner asserts that:

> 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*. P[atent] O[wner] 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.

Pet. 32 (citing Ex. 1003 ¶ 111).

Petitioner reviews the Examples set forth in the Specification of the '838 patent and states that Patent Owner did not administer any "composition" to a human "subject." Pet. 33–40. Petitioner asserts that the only experiments with humans described in the '838 patent involve characterization of gut and buccal microbiome of metastatic melanoma patients using genomic sequencing to identify patients who responded to immunotherapy and those that did not, respectively denominated "responders" and "non-responders." Pet. 33–34 (citing Ex. 1001, 151:60–152:62, 153:15–49; Ex. 1003 ¶¶ 113–114). Petitioner reports that "bacteria from the family Ruminococcaceae were found in *both* the "responder" and "non-responder" fecal samples. Pet. 34 (citing Ex. 1001, Tables 1, 2; Ex. 1003 ¶ 115).

Petitioner notes that the second set of experiments described in the examples of the '838 patent involve the mouse melanoma model system. Pet. 34.

> 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. 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.

Pet. 34 (citing Ex. 1001, 181:21–184:44). Petitioner notes that the samples of human feces were uncharacterized and non-sterile that were gavaged directly into the stomachs or small intestines of the mice. *Id.* Petitioner concludes that the only "composition" of the claimed bacteria was this "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." Pet. 35 (citing Ex. 1003 ¶ 117).

Petitioner also points to the uncertainties in formulation strategies for living organisms such as bacteria including various physicochemical, biopharmaceutical, and biological barriers to therapeutic effectiveness and clinical applicability. Pet. 35–38 (citing Ex. 1003 ¶¶ 118–125). Petitioner concludes that "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*." Pet. 38 (citing Ex. 1003 ¶ 125). Petitioner also asserts that the Specification of the '838 patent fails to disclose the concentration of bacteria used in the mouse experiments, or 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)." Pet. 39 (citing Ex. 1003 ¶ 126).

Petitioner further asserts that because several species of Ruminococcaceae are found to be more abundant in "non-responders" as shown in Table 2 of the '838 patent, "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." Pet. 41 (citing Ex. 1003 ¶ 131; Ex. 1001, 15:35–55 (referencing alleged statement these "non-responder" bacterial species "are predicted to not have a favorable response to the immune checkpoint inhibitors")). Petitioner also pointed to Table 1 as showing fifteen different Ruminococcaceae bacteria that were found only in

fecal samples of non-responder patients. Pet. 42 (citing Ex. 1001, Table 1, 173:22–27).

Petitioner asserts that the use of the transition phrase "comprising" in claim 1 would allow inclusion in the claimed composition of additional bacteria such as Bacteroidia that are known to have a detrimental effect on the anti-tumor immune response. Pet. 42–43. Finally, Petitioner asserts that:

> 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 have not understood PO to be in possession of a method of treating every type of "skin cancer tumor" in every type of subject.

Pet. 44 (citing Ex. 1001, 13:12–24; Ex. 1003 ¶ 137).

Patent Owner responds that Petitioner is applying the wrong test for whether a claim has adequate written description support. *See* Prelim. Resp. 47–49. Patent Owner points out that the written description requirement does not mandate either examples or an actual reduction to practice as Petitioner asserts here. *Id.* at 48 (citing *Alcon Res. Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1190 (Fed. Cir. 2014)). Patent Owner points out that written description tests "whether the skilled reader of the patent disclosure can recognize that what was claimed corresponds to what was described." *Id.* (citing *Alcon*, 745 F.3d at 1191). This mistake, Patent Owner asserts, demonstrates Petitioner failed to meet the burden necessary to satisfy a written description challenge. *Id.*

Patent Owner also asserts that Petitioner has failed to show that the species exemplified in the specification are not representative of the claimed

genus. Prelim. Resp. 50–53. For instance, Patent Owner asserts that Petitioner has ignored the clinical data in the '838 patent, has failed to demonstrate that the mouse melanoma model used in the '838 patent is not predictive of other subjects and other types of skin cancer, and has misrepresented data in the '838 patent that shows a positive association of Ruminococcaceae with tumor reduction. *Id.* at 50–54.

Patent Owner points to clinical data in the '838 patent for the examples involving human patients that Petitioner does not address. *See* Prelim. Resp. 50–51.

> For example, Petitioner ignored that Example 1 assessed actual *clinical responses* associated with Ruminococcaceae abundance in human melanoma patients. According to Example 1, patients with a high abundance of Ruminococcaceae had "a significantly prolonged PFS [progression-free survival] versus those with low abundance." Further, there was "a higher density of CD8+ T lymphocytes" in the immune cells that infiltrate tumor tissue and in the systemic circulation prior to administrating any anti-tumor therapy of responders versus non-responders . . . . [h]igher density of CD8+ T lymphocytes indicates anti-tumor activity.

Prelim. Resp. 50–51 (citing Ex. 1001, 154:12–20, 156:9–157:9, Figs. 3E, 4A–D, Table 6; Ex. 2001 ¶ 58) (first alteration in original).

Patent Owner also points to evidence that mouse models of melanoma are the most widely used preclinical models for skin cancer such as melanoma, *see* Prelim. Resp. 52 (citing Ex. 2013, Abst., 83; Ex. 2001 ¶ 59), and Petitioner has not shown otherwise. Patent Owner also asserts that Petitioner has not explained why melanoma is not representative of other skin cancers encompassed within the claims. *See* Prelim. Resp. 53–54. Patent Owner states:

> Petitioner has not denied, and cannot deny, that the specification discloses that administering FMT abundant in Ruminococcaceae resulted in a statistically significant (p=0.04) delay in melanoma tumor growth by day 14 in mice ("FMT1"). EX1001, 182:7-50, Example 4, FIG. 25B; EX2001, ¶¶60-61. The specification also discloses that Patent Owner "validate[d]" their FMT1 findings by "using stools from different [] patients" ("FMT3"), as well as showed that FMT "enhances response to αPDL-1 therapy" ("FMT2"). EX1001, 182:62-65; 184:27-30, Example 4, FIGs. 28A–C, 32A–C; EX2001, ¶¶60-62.

Prelim. Resp. 53 (alterations in original).

Patent Owner also asserts that Petitioner misreads the data set forth in the '838 patent that "demonstrates that the gut microbiota from responders was differentially enriched in Ruminococcaceae bacteria." Prelim. Resp. 54 (citing Ex. 1001, Figs. 2C–E; Ex. 2001 ¶ 65). Patent Owner states that the presence of some Ruminococcaceae species in non-responders does not undermine this observation. *Id*. at 55.

Finally, Patent Owner asserts that Petitioner failed to assess a POSA's knowledge as of the filing date of the '838 patent, instead assessing such knowledge at the priority date for the '838 patent a year earlier than the filing date. *See* Prelim. Resp. 56–60. Petitioner did not, Patent Owner asserts, appropriately consider the knowledge a POSA would have had of the many technical details, such as excipients, route of administration, and concentration, related to bacteria-based formulation and administration that Patent Owner is not required to repeat in the '838 patent. *Id*. at 58–59.

1. Analysis

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed.

Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")), *see* 35 U.S.C. § 322(a)(3) (stating same for post grant reviews). This burden of persuasion never shifts to the patent owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

In defining the written description requirement of 35 U.S.C. § 112, the Federal Circuit has stated:

> The "written description" requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed. The written description requirement thus satisfies the policy premises of the law, whereby the inventor's technical/scientific advance is added to the body of knowledge, as consideration for the grant of patent exclusivity.
>
> The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science.

Capon v. Eshhar, 418 F.3d 1349, 1357 (Fed. Cir. 2005) (citations omitted); *see Ariad*, 598 F.3d at 1351 (stating written description describes the invention sufficiently to convey to a person of skill in the art that the

patentee had possession of the claimed invention at the time of the application, i.e., that the patentee invented what is claimed).

The written description requirement does not require a re-description of what was already known. *Capon*, 418 F.3d at 1357. Determining whether the specification of a patent adequately supports the breadth of generic claims to biological subject matter, however, depends on "the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter." *Id*. at 1359.

"Unpredictable" fields of science usually require a focus on the exemplification in the specification to determine if there is adequate written description support. *Capon*, 418 F.3d at 1358. It is not necessary, however, for "every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention." *Id*. at 1359.

In applying this rubric to the challenged claims, we determine that Petitioner has failed to show that it is more likely than not that it will prevail in establishing any challenged claim lacks written description. We begin our analysis with what Patent Owner has described in the Specification of the '838 patent.

The problem addressed by the '838 patent was to improve responses to immunotherapy, such as immune checkpoint inhibitors, because these inhibitors "can be associated with substantial toxicity and only a subset of patients may benefit." Ex. 1001, 1:24–38. The '838 patent notes an increasing appreciation in the art for the role of the host microbiome,

including in the tumor and the gut, in responses to cancer therapy. *Id*. at 1:44–53. In exploring this connection, the '838 patent describes five examples that characterize the oral and gut microbiome of 112 melanoma patients before beginning treatment with PD-1 blockade (Examples 1 and 2) and that modulate the gut microbiome by fecal microbiota transplantation (FMT) in the murine melanoma model to enhance anti-tumor response (Examples 3 through 5). *See* Ex. 1001:151:14–187:10. Petitioner does not address much of the data provided in these examples or how this data does or does not provide written description support for the claims. Dr. Garrett, Patent Owner's declarant, performs this analysis.

For instance, Dr. Garrett explains that Example 1 in the '838 patent not only characterizes gut and buccal (oral) microbiomes of metastatic patients, but "provides data from human melanoma patients undergoing anti-PD-1 therapy that demonstrates clinical response is associated with Ruminococcaceae bacteria." Ex. 2001 ¶ 58 (citing Ex. 1001, Figs. 1–24). Dr. Garrett further testifies that:

> Indeed, Example 1 of the '838 Patent disclosed that human melanoma patients with a high abundance of Ruminococcaceae had "significantly prolonged PFS [progression-free survival] versus those with low abundance," which a POSA would have understood to mean there is an association between increased abundance of Ruminococcaceae and delaying growth of melanoma. EX1001, 154:18–20, 156:9–157:9; FIGs. 4A–D, 18–22. Moreover, Example 1 discloses that after comparing the tumor associated immune infiltrates [immune cells that infiltrate tumor tissue] a "higher density of CD8+ T lymphocytes in baseline samples [taken prior to administering any anti-tumor therapy] of [responders] versus [non-responders]" were observed. EX1001, 156:9–157:9, FIGs. 4A–D, 18–22. CD8+ T lymphocytes are "direct cancer cell killers" within the tumor, and the "density and distribution [of CD8+ T

> cells in tumor infiltrate] was shown to independently predict . . . survival in patients with melanoma." EX2016, 124. Specifically, a major determinant of responsiveness to immunotherapy "is the presence of effector CD8 T-cells in tumors *prior to initiating therapy*," as was described in the '838 Patent. EX2017, 3. Therefore, a POSA would have understood that the high density of CD8+ T lymphocytes shown in tumors of responder patients, which are enriched for Ruminococcaceae, indicates anti-tumor activity. EX2017, 3. Although these clinical data are absent in Dr. Robinson's discussion, the specification would inform a POSA that the inventors of the '838 Patent had possession of a composition for reducing or delaying growth of skin cancer in humans.

Ex. 2001 ¶ 58 (first and fourth through seventh alteration in original; footnotes omitted).

Dr. Garrett also testifies that a POSA would have known mouse models had been extensively used to predict clinical response in humans and experiments in such models are clinically relevant to the treatment of humans. Ex. 2001 ¶ 59. Dr. Garrett points to references that confirm that the mouse melanoma model used in the Examples in the '838 patent "recapitulates the immune system interactions that would have an effect on disease progression in humans." *Id*. (citing Ex. 2013, 81–82, 84; Ex. 2014, 550).

Dr. Garrett also discusses the reliability and the statistical significance of the data in Example 4 of the '838 patent that "describes three fecal microbiome transplantation experiments (FMT1, FMT2, and FMT3) in which germ-free mice [lacking an endogenous microbiome] were transplanted with human stool from a responder (R-FMT) or from a non-responder (NR-FMT) to anti-PD-1 therapy and then injected with melanoma cells." Ex. 2001 ¶ 60 (citing Ex. 1001, 182:11–25). Dr. Garrett discusses the sufficiency of the data in Example 4, *see id*. ¶¶ 61–64, and concludes

that "[t]hese experiments demonstrated FMT from responder patients, abundant in Ruminococcaceae, resulted in a statistically significant (p=0.04) delay in melanoma growth in mice (FMT1), which was 'validate[d]' by 'using stools from different [] patients' in FMT3, and resulted in an 'enhanced response to PD-L1 therapy' in FMT2." Ex. 2001 ¶ 60 (citing Ex. 1001, 182:62–65, 184:27–30, Example 4, Figs. 28A–C, 32A–C) (second and third alteration in original).

Dr. Garrett also responds to Dr. Robinson's complaint that bacteria from the family Ruminococcaceae were found in the fecal samples of patients who responded to immunotherapy and those that did not. *See* Ex. 2001 ¶¶ 65–66. Dr. Garrett points out that the '838 patent showed that "Ruminococcaceae were the most distinguishing taxa of the responder gut microbiota." *Id.* ¶ 65 (citing Ex. 1001, 153:12–40, 154:5–10, 153:37–45, Figs. 2C–F, 3D, Tables 4–5).

> The '838 Patent disclosed using linear discriminant analysis of effect size (LEfSe), which "detect[s] bacterial organisms and functional characteristics differentially abundant between two or more microbial environments," to identify the taxonomic differences in the gut microbiome between responders and non-responders. EX1001, 153:28–34; EX2015, 3. Ruminococcaceae were consistently the most differentially-abundant gut bacteria in responder patients, which was shown with a high degree of statistical significance ($p<0.001$) and effect size in Figure 2E. EX1001, FIG. 2E. Within the family Ruminococcaceae, the genus *Faecalibacterium* and species *Faecalibacterium prausnitzii* were also significantly differentially-abundant in responder patients ($p<0.05$). Thus, a POSA would have understood the '838 Patent to disclose the gut microbiota of responder patients were clearly enriched for Ruminococcaceae on all taxonomic levels. EX1001, 153:12–40, 154:5–10, 153:37–45, FIGs. 2C-F, 3D, Tables 4–5.

> Further, even if Ruminococcaceae bacteria were present in nonresponders as alleged by Dr. Robinson, they were not shown to be significantly *differentially abundant* in non-responders. EX1001, FIGs. 2C-E, 3D.

Ex. 2001 ¶¶ 65–66 (alteration in original).

Finally, Dr. Garrett describes the considerable knowledge that a POSA would have had in formulating and administering bacterial compositions. Ex. 2001 ¶¶ 67–69. Dr. Garrett concludes that "[e]ven a POSA meeting Dr. Robinson's lower defined skill level would have understood how to formulate and administer bacterial compositions, including FMT and bacterial-based compositions, in light of the specification and numerous references." *Id*. at 67.

At a minimum, Dr. Garrett's testimony described above shows that Petitioner does not provide sufficient analysis of the full disclosure of the '838 patent and what a POSA would have known from the state of the art for the written description ground. As the law makes clear, "the written description requirement does not require a re-description of what was already known," *Capon*, 418 F.3d at 1357, and not every permutation of a generic claim need be operable within a generally operable invention, *id*. at 1359. *See Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness . . . is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.") *Brana* held "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995).

Petitioner analyzes the written descriptive support for the scope of the claims in a way that is divorced from the full disclosure of the '838 patent and what a POSA would have known. For instance, Dr. Robinson focuses on the alleged lack of a claimed composition administered to a human subject. *See* Ex. 1003 ¶¶ 113–136. As Patent Owner points out, "[t]here is no requirement that [a] disclosure contain 'either examples or an actual reduction to practice.'" Prelim. Resp. 48 (quoting *Alcon Research Ltd. v. Barr Laboratories, Inc.*, 745 F.3d 1180, 1190 (Fed. Cir. 2014)) (first alteration in original). Also, as Dr. Garrett points out, Dr. Robinson did not address much of the clinical data from Example 1 that Dr. Garrett asserts describes the claimed composition. *See* Ex. 2001 ¶ 58.

Dr. Robinson also focused almost exclusively on the content within the four corners of the Specification of the '838 patent and did not fulsomely address the knowledge that a POSA would have had. *See* Ex. 2001 ¶¶ 113–136; *see also* Ex. 2001 ¶ 119 ("However, the specification fails to disclose a single such composition that was actually created. And the specification is silent as to any experimental conditions necessary to formulate any of these theoretical, and assumed, compositions."); Ex. 2001 ¶ 137 ("Given that the specification identifies dozens of different types of 'skin cancer tumors', and [Patent Owner] 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 [Patent Owner] to be in possession of a method of treating every type of 'skin cancer tumor' in every type of subject."). Dr. Garrett provided this context of a POSA's knowledge

that would be brought to bear when reading the Specification of the '838 patent to understand the technology that is patented. *See* Ex. 2001 ¶¶ 57–69.

2. Conclusion on Written Description Grounds

Petitioner has failed to show that it is more likely than not that it would prevail in showing that any of claims 1–19 lack written description support.

E. Lack of Enablement

Petitioner relies on one sentence in the Petition as support for its lack of enablement ground. Pet. 47. Petitioner states that "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." *Id.* (citing Ex. 1003 ¶ 143). Petitioner is making the same argument for its lack of enablement challenges that it does for its lack of written description challenges. *See* Pet. 47 (referring to section of Petition involving the written description argument).

Patent Owner responds that Petitioner has failed to demonstrate that any experimentation would have been "undue" in view of the *Wands* factors that provide a helpful framework for assessing enablement. Prelim. Resp. 60–60 (citing *In re Wands*, 858 F.3d 731, 737 (Fed. Cir. 1988)). Patent Owner also states that not only is the Petition conclusory on the lack of enablement challenge, but Dr. Robinson's declaration is, in turn, equally conclusory and unsupported and is entitled to little to no weight under our rules. Prelim. Resp. 61 (citing 37 C.F.R. § 42.65(a)).

1. Analysis

The specification must enable a person of ordinary skill in the art to make and use the claimed invention. *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). Also, the disclosure of the specification must be commensurate in scope with the claim under consideration. *See In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991).

Section 112(a) requires that the patent specification enables those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *Koito Mfg. Co., Ltd. v. Turn-Key-Tech, LLC*, 381 F.3d 1142, 1155 (Fed. Cir. 2004). The factors set forth by our reviewing court in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) may be considered when determining whether a disclosure calls for undue experimentation. These factors are: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *Wands*, 858 F.2d at 737.

Petitioner's enablement challenge repeats the written description arguments in one sentence, and provides no more analysis, much less under the *Wands* factors set forth above. *See* Pet. 47. As we found in addressing the written description arguments, Petitioner does not provide sufficient analysis of the full disclosure of the '838 patent and what a POSA would have known from the state of the art, and here no further analysis is provided for the lack of enablement challenge concerning whether any

experimentation necessary to make and use the full scope of the claimed invention is undue.

2. Conclusion on Enablement

Petitioner has failed to show that it is more likely than not that it would prevail in showing that any of claims 1–19 are not enabled.

F. Indefiniteness

Petitioner contends that claims 1–19 are indefinite because the claim terms "isolated," "purified," and "bacteria belonging to the family Ruminococcaceae" set forth in claim 1, "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." Pet. 69. Petitioner acknowledges that the Patent Owner expressly defined the claim terms "isolated" and "purified," but Petitioner asserts that these express definitions conflict with the plain and ordinary meaning of these terms. Pet. 50.

According to Petitioner, a POSA applying the plain and ordinary meaning of "an isolated or purified population of bacteria belonging to the family Ruminococcaceae" as set forth in claim 1, *when viewed in isolation*, "might reasonably construe the 'isolated' limitation to reference a bacterial population that contains 'a single species of a bacterium obtained in a pure culture.' 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.'" Pet. 50 (citing Exs. 1022, 1023).

Petitioner also asserts that in applying the plain and ordinary meaning for isolated and purified "none of the 'experiments' administered an

'isolated and purified' population of Ruminococcaceae bacteria" because Example 5 discloses a supernatant from human fecal suspension that "would contain millions of bacteria belonging to a host of different taxonomic families and classes." Pet. 51 (citing Ex. 1003 ¶ 149; Ex. 1001, 184:65–185:2).

Petitioner also asserts that the two subparts of the express definition provided for "isolated" contradict each other, *see* Pet. 53–55, and the overlap between the express definitions of "isolated" and "purified" are circular and ambiguous, *see* Pet. 56–58. Finally, Petitioner asserts that the bacteria in the family Ruminococcaceae is a "moving target" creating further inappropriate ambiguity. *See* Pet. 58–60.

Patent Owner responds that its express definitions of "isolated" and "purified" control here. Prelim. Resp. 66–67. In reviewing the arguments that Petitioner makes with regard to these express definitions, Patent Owner asserts that Petitioner has failed under the *Nautilus* standard to show that the *claims*, not individual claim terms, are indefinite. Prelim. Resp. 67–69 (citing *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014)). Patent Owner also asserts that Petitioner has not shown that a POSA would not have understood the meaning of "bacteria belonging to the family Ruminococcaceae" as of the filing date of the '838 patent. *Id.* at 69–70.

1. Analysis

"The specification [of a patent] shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention." 35 U.S.C. § 112(b) (2018). A patent "is invalid for indefiniteness 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." *Nautilus*, 572 U.S. at 901; *see* USPTO Memorandum, Approach to Indefiniteness Under 35 U.S.C. § 112 in AIA Post-Grant Proceedings (Jan. 6, 2021). [6]

We find it important to note again here as we did in our claim construction section, *see supra* Section II.C., that claim construction requires reading the claims "in light of the language of the claims, the specification, and the prosecution history of record," and not in isolation. *See Phillips*, 415 F.3d at 1312–19. We also find it appropriate to reiterate here that a patentee may act as a lexicographer if it does so in the specification with "reasonable clarity, deliberateness, and precision." *In re Paulsen*, 30 F.3d at 1480. Petitioner did not follow these principles in constructing its indefiniteness argument.

Petitioner's attempt to craft a plain and ordinary meaning of claim terms viewed in isolation is not an appropriate way to construe claims. *See* Pet. 50. Petitioner also inappropriately rejected Patent Owner's express definitions of "isolated" and "purified" in favor of its plain and ordinary meaning definitions crafted by reading the claims in isolation. *See id*.

Patent Owner acted as its own lexicographer and expressly defined "isolated" and "purified" 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

[6] *Available at* https://www.uspto.gov/sites/default/files/documents/IndefinitenessMemo.pdf?utm_campaign=subscriptioncenter&utm_content=&utm_medium=email&utm_name=&utm_source=govdelivery&utm_term=.

> setting), and/or (2) produced, prepared, purified, and/or manufactured by the hand of man. Isolated bacteria may be separated from at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or more of the other components with which they were initially associated. In some embodiments, isolated bacteria are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. As used herein, a substance is "pure" if it is substantially free of other components.
>
> The term "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 bacteria population, and a purified bacterium or bacterial population may contain other materials up to about 10%, about 20%, about 30%, about 40%, about 50%, about 60% about, 70%, about 80%, about 90% or above about 90% and still be considered "isolated." In some embodiments, purified bacteria and bacterial populations are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. In the instance of bacterial compositions provided herein, the one or more bacterial types present in the composition can be independently purified from one or more other bacteria produced and/or present in the material or environment containing the bacterial type. Bacterial compositions and the bacterial components thereof are generally purified from residual habitat products.

Ex. 1001, 28:40–29:11.

In reviewing the express definitions of "isolated" and "purified," it is not surprising that the two similar terms, "isolated" and "purified," may have

overlapping definitions. We agree with Patent Owner that such overlap does not mean the definitions lack "reasonable clarity, deliberateness, and precision" that would inform a POSA with reasonable certainty about the scope of claim 1. We also agree with Patent Owner that a POSA would understand the two parts of the definition of "isolated" set forth above.

We note that the test for indefiniteness requires a reasonable certainty, not absolute certainty, concerning the scope of the claims. Therefore, we also determine a POSA would have reasonably understood the meaning of "bacteria belonging to the family Ruminococcaceae."

2. Conclusion

We therefore determine that Petitioner has not demonstrated that is more likely than not that Petitioner will prevail in showing that claims 1–19 of the '838 patent are unpatentable as indefinite.

G. Prior Art Challenges

Petitioner asserts that claims 1–3 and 5–19 would have been obvious over Honda and Gajewski. Pet. 29, 60–84. Petitioner also asserts that claim 4 would have been obvious over Honda, Gajewski, and Miguel. Pet. 29, 60–84. Because we find that Petitioner has not shown sufficiently why a POSA would have a reason to combine Honda with Gajewski to arrive at the claimed invention, we determine that Petitioner has not shown that it is more likely than not that it would prevail in its prior art challenges as to any of the challenged claims 1–19.

1. Parties' Assertions

Petitioner relies on Honda for teaching "a method of reducing or delaying growth of a skin cancer tumor in a subject in need thereof" because

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 . . . " Pet. 72 (citing Ex. 1011 ¶ 1, claims 2, 12). Petitioner asserts Honda does not exclude skin cancer from the type of cancers that could be treated, therefore "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 skin cancer tumor." Pet. 72 (citing Ex. 1003 ¶ 188).

Petitioner also points to Gajewski's teaching 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,'" which, Petitioner asserts, would encompass "reducing or delaying growth" of skin cancer tumor cells. Pet. 73 (citing Ex. 1012, 21:31–23:31). Petitioner also relies on Gajewski's teaching that the disclosed commensal bacterial compositions were useful for treating skin cancers such as malignant melanoma, basal cell carcinoma, and Kaposi's carcinoma. Pet. 73 (citing Ex. 1012, 5:13–6:5, 40:27, 41:15–20).

Petitioner also relies on Honda for teaching "administering to the subject a composition comprising an isolated or purified population of bacteria belonging to the family Ruminococcaceae." Pet. 74–75. Petitioner points to Honda's teaching of "specific methods for 'isolating or purifying' the desired intestinal commensal bacteria." Pet. 74 (citing Ex. 1011 ¶¶ 23,

63). Petitioner also relies on Gajewski to cure any alleged deficiencies in Honda's disclosure. Pet. 75–76.

Petitioner offers several reasons why a POSA would have reason to combine the teachings of Honda, Gajewski, and Miguel to arrive at the claimed inventions. Pet. 68–72. For instance, Petitioner asserts that a POSA would have reason to combine the teachings of Honda and Gajewski because both pertain to bacteria such as Ruminococcaceae for addressing cancer in a subject. Pet. 68 (citing Ex. 1003 ¶ 181). Petitioner states:

> 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.

Pet. 68–69 (alterations in original).

Petitioner describes additional reasons to combine Honda and Gajewski stating that a POSA would also have been "motivated to employ the specific processing procedures of Honda to the fecal bacterial samples

disclosed in Gajewski," would have been motivated "to employ the composition comprising Ruminococcaceae bacteria with other adjuvant cancer therapies, such as immune checkpoint inhibitors, as taught in Gajewski," and would be motivated to modify the teachings of Honda with Gajewski and Miguel's teaching concerning *Faecalibacterium prausnitzii*. Pet. 69–71. Finally, Petitioner asserts that a POSA would 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." Pet. 69.

Patent Owner responds that "Petitioner fails to establish that a POSA would have started with Honda's 'Th17-inducing bacterial compositions' when the art taught that Th17 cells *promote* tumor growth—the opposite of what Petitioner alleged a POSA would have sought to achieve." Prelim. Resp. 40 (citing Ex. 2021, Abst.; Ex. 2022, 10113; Ex. 2003, 927; Ex. 2001 ¶¶ 42–44); *see also* Ex. 2022, 10112 (stating "the presence of Th17 cells in tumors has been associated with both favorable and unfavorable prognoses"); Ex. 2021, Abst, Fig. 1, 1459 (stating "Th17 cells can promote tumor growth" of melanoma in mice); Ex. 2006, 10–11 (stating Th17 responses can *enhance carcinogenesis*); Ex. 2003, 927 (finding IL-17 promotes tumor development in human nonmelanoma skin cancer).

Patent Owner also asserts that Petitioner ignores teaching in Gajewski that the presence or increased level of bacteria such as *Ruminococcus* "***potentiates*** cancer/tumor growth, spread (e.g., malignancy)." Prelim. Resp. 41 (citing Ex. 1012, 22:6–9); Ex. 2001 ¶¶ 45–46. Patent Owner also asserts that "Petitioner also ignores Gajewski's teaching 'modulating levels of one

or more commensal microbes,' which includes *Ruminococcus*, by '***decreasing*** levels' of the microbe." Prelim. Resp. 41 (Ex. 1012, 2:14–15; Ex. 2001 ¶ 46). Patent Owner concludes that "[i]n ignoring these teachings altogether, Petitioner fails to consider the reference for all that it teaches, and fails to establish that a POSA would have had a reason to administer *Ruminococcaceae* to reduce or delay tumor growth." *Id*.

Patent Owner also asserts that Petitioner employs impermissible hindsight to arrive at the claimed inventions. For instance, Petitioner does not explain sufficiently why a POSA would have chosen *Ruminococcus* from Gajewski's list of 51 taxa that were associated with an anti-tumor response. Prelim. Resp. 42 (citing Ex. 1012, 49:3–5; Ex. 2001 ¶ 47). As Patent Owner notes, when selecting elements from a large list in a reference, there must be a reason to make the combination and a reasonable expectation of success for the combination. *Id*. (citing *In re Stepan Co.*, 868 F.3d 1342, 1346 n.1 (Fed. Cir. 2017)). Finally, Patent Owner states "Petitioner also fails to show why a POSA would have chosen to administer *Ruminococcus* to reduce or delay skin cancer tumor growth, when Gajewski concludes that of the 51 potential anti-skin cancer taxa identified, only *Bifidobacterium* 'showed a positive association with anti-tumor T cell responses.'" Prelim. Resp. 42 (citing Ex. 1012, 42:7–9, Figs. 8A–D; Ex. 2001 ¶¶ 48–49).

2. Principles of Law

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to

which the claimed invention pertains. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art "to combine . . . known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016). "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *see also see Sensonics Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996) ("To draw on hindsight knowledge of the patented invention, when the prior art does not contain or suggest that

knowledge, is to use the invention as a template for its own reconstruction—an illogical and inappropriate process by which to determine patentability." (internal citation omitted).

An obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418; *see In re Translogic Tech, Inc.*, 504 F.3d 1249, 1259 (Fed. Cir. 2007). In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a POSITA:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421. "*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established functions.'" *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

3. Honda (Ex. 1011)

Honda describes "a composition of human-derived bacteria that induces proliferation of T helper 17 (Th17) cells and which comprises, as an

active component, human-derived bacteria, preferably (a) one or more bacteria isolated and cultured form the ampicillin-resistant bacterial fraction of a fecal sample or, (b) a culture supernatant of one or more bacteria of (a)." Ex. 1011 ¶ 1. Honda also describes using this bacterial composition to treat or prevent a disease responsive to induction of Th17 cells, such as an infectious disease, "by oral administration of the bacterial composition alone or in combination with an antigen to an individual in need thereof." *Id*. Honda also states that this bacterial composition may be used to treat cancer. *See id*. ¶ 17, claim 12.

Honda describes the bacterial composition that induces proliferation, accumulation, or both of Th17 cells as comprising an active component of at least one or more organisms selected from the group consisting of *Clostridium symbiosum, Clostridium hathewayi, Clostridium citroniae, Clostridium bolteae, Ruminococcus sp. M-1, Ruminococcus gnavus, Blautia sp. canine oral taxon 143, Anaerostipes caccae, Clostridium lactatifermentans, Coprobacillus cateniformis, Clostridium ramosum, cf. Clostridium sp. MLG055, Clostridium innocuum, Eubacterium desmolans, Clostridium orbiscindens, Ruminococcus sp. 16442, Anaerotruncus colihominis, Bacteroides dorei, Bifidobacterium pseudolongum subsp. Pseudolongum, and Bifidobacterium breve*. Ex. 1011 ¶ 6, claim 9.

As Petitioner admits, Honda does not expressly state any specific types of cancer the bacterial composition will treat. *See* Pet. 68 (stating "[w]hile 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").

4. Gajewski (Ex. 1012)

Gajewski teaches treating or preventing cancer by manipulation of commensal microflora. Ex. 1012, 2:5–6. Gajewski describes an embodiment of a method for treating or preventing cancer in a subject as:

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

Ex. 1012, 2:10–19.

Gajewski focuses on *Bifidobacterium* as a bacteria associated with anti-tumor effects. Ex. 1012, 21:24–28. Gajewski states:

> T cell infiltration of solid tumors is associated with favorable patient outcomes, yet the mechanisms underlying variable endogenous immune responses between individuals are not well understood. Experiments were conducted during development of embodiments described herein to examine potential effects of microbial composition on spontaneous anti-tumor immunity. B16 melanoma growth was compared in C57BL/6 mice having distinct commensal microbiota. The two populations of mice showed robust versus weak spontaneous anti-tumor immunity. This phenotypic difference was eliminated upon cohousing or following fecal transfer. 16S rRNA sequencing identified *Bifidobacterium* as associated with the anti-tumor effects. Oral administration of *Bifidobacterium* alone or in combination with systemic αPD-L1 in tumor-bearing mice markedly improved tumor control in a $CD8^+$ T

> cell-dependent manner. Mechanistically, the effect was mediated by augmented dendritic cell function leading to more robust antigen-specific $CD8^+$ T cell priming and markedly increased accumulation of activated T cells in the tumor microenvironment. These data, for example, demonstrate advantages manipulating commensal microbes as a cancer therapeutic.

Ex. 1012, 21:18–32.

Gajewski does note that in some embodiments, "the presence or increased level of one or more microbes (e.g., one or more types of bacteria) in a subject potentiates cancer/tumor growth, spread (e.g., malignancy), and/or evasion of treatment/immune response." Ex. 1012, 22:6–8.

Gajewski provides a "non-limiting" laundry list of cancers, including skin cancers, "that may be treated with compositions and methods described here." Ex. 1012, 37:21–43:19; *see id.* at 4:13–6:5.

Gajewski provides an example using mice with subcutaneous B16.S1Y melanoma growth "to test whether differences in the specific composition of the normal microbiota influence the immune response to a growing tumor in vivo." Ex. 1012, 47:9–53:14. Gajewski states:

> To directly test the role of commensal bacteria in regulating anti-tumor immunity, JAX fecal suspensions or control TAC fecal suspensions were transferred into TAC recipients by oral gavage prior to tumor implantation (Figure 5A). Strikingly, it was found that prophylactic transfer of FAX fecal material into TAC recipients was sufficient to delay tumor growth (Figure 2A) and enhance induction and infiltration of tumor-specific $CD8^+$ T cells (Figure 2B–C and 5B), supporting a microbe- or microbial product-derived effect. Reciprocal transfer of TAC fecal material into JAX recipients resulted in only a minimal increase in tumor growth rate and did not significantly alter anti-tumor T cell responses (Figure 2A–C and Figure 5B).
>
> * * *

> Comparative analysis of specific bacterial taxa showed that 97 taxa were significantly more abundant in JAX mice relative to TAC mice (FDR<0.05) (Figure 8B), and 51 taxa were significantly increased in JAX-fed TAC mice relative to TAC-fed TAC mice ($p<0.05$). Only 32 taxa overlapped between these two comparisons, such that they were of greater abundance in both JAX mice and JAX-fed TAC mice. A significant association was observed for *Bifidobacterium*, which showed a positive association with anti-tumor T cell responses and increased in relative abundance over 400-fold in JAX-fed TAC mice (Figure 8C).

Ex. 1012, 47:29–49:9.

5. Analysis

We agree with Patent Owner that Petitioner employed impermissible hindsight in combining the teachings of Honda, Gajewski, and Miguel to arrive at the claimed inventions. Thus, we determine that Petitioner has not demonstrated that it is more likely than not that it will prevail in showing that claims 1–19 of the '838 patent are unpatentable.

Honda discloses treating cancer generically, but does not identify treating skin cancer specifically. *See* Ex. 1003 ¶ 189. Petitioner has not shown sufficiently a rationale as to why a POSA would choose a *Ruminococcus* from the list of possible bacteria set forth in Honda to treat skin cancer specifically with any reasonable expectation of success. We are also not persuaded that Gajewski fills this gap in Honda's teaching to arrive at the claimed invention.

Dr. Robinson testifies:

> To the extent that [Patent Owner] argues that Honda does not expressly discloses "skin" cancer, Gajewski teaches "A method of treating or preventing cancer in a subject" by "administering a beneficial microbes to the subject" selected "from the genera *Ruminococcus*." EX-1012 Claims 1–4. Moreover, Gajewski demonstrated that "the presence or increased level of one or

> more . . . types of bacteria in a subject," including bacteria belonging to the genus *Ruminococcus*, "discourages cancer/tumor growth, spread, and/or evasion of treatment/immune response." P.21, ll. 31–p.23, ll.31. A POSA understood that the methods of "discourage[ing] cancer/tumor growth [or] spread" in Gajewski to encompass "reducing or delaying growth" of skin cancer tumor cells.

Ex. 1003 ¶ 189 (alterations in original).

As Dr. Garrett points out and as set forth above in the description of Gajewski's teaching, "Gajewski does *not* teach that *Ruminococcus* is beneficial for reducing or delaying growth of skin cancer tumor." Ex. 2001 ¶ 45. First, Gajewski's focus and conclusion is that *Bifidobacterium* is associated with anti-tumor effects. *See* Ex. 1012, 21:25–28; 49:7–9; *see generally id*. at 47:9–14 (Example 2 – Results). Gajewski concludes:

> Experiments conducted during development of embodiments herein demonstrate an unexpected role for commensal microflora (e.g., *Bifidobacterium*) in enhancing anti-tumor immunity. These data support the idea that one source of inter-subject heterogeneity with regard to spontaneous anti-tumor immunity and therapeutic effects of antibodies targeting the PD-1/PD-L1 axis may be the specific composition of gut microbes, which can be manipulated for therapeutic benefit.

Ex. 1012, 53:9–14.

Gajewski recognizes that the composition of gut microbes can be manipulated for therapeutic benefit, but that manipulation, Gajewski states, involves modulating the levels of one or more commensal microbes by *increasing and/or decreasing* levels of the microbes or bacteria such as those from the genera *Ruminococcus*. *See* Ex. 1012, 2:14–19, claim 3. Gajewski further states that the presence or increased level of one or more types of bacteria, which may include *Ruminococcus*, in a subject "potentiates

cancer/tumor growth, spread (e.g., malignancy), and/or evasion of treatment/immune response." Ex. 1012, 22:6–8.

The teachings of Gajewski do not support Petitioner's conclusion that a POSA would have reason to select *Ruminococcus* from the list of bacteria genera to treat skin cancer. The teachings of Gajewski tie *Bifidobacterium*, not *Ruminococcus*, to the enhancement of anti-tumor immunity in mice with melanoma. At best, Gajewski provides equivocal statements that modulating the level of commensal bacteria in the gut for enhanced immune response may include either increasing *and/or* decreasing levels of bacteria from the bacterial genera including *Ruminococcus*. Such statements would not provide sufficient reason for a POSA to select *Ruminococcus* from the list of bacteria genera to be administered to a subject to treat skin cancer.

6. Conclusion

We determine that Petitioner has not demonstrated that it is more likely than not that Petitioner will prevail in showing that claims 1–19 of the '838 patent are unpatentable.

III. CONCLUSION

For the foregoing reasons, we conclude that the information presented in the Petition does not establish that it is more likely than not that Petitioner will prevail in showing that challenged claims 1–19 of the '838 patent are unpatentable.[7] Accordingly, we do not institute a post-grant review of these challenged claims.

[7] Patent Owner requested that we exercise our discretion to deny institution under 35 U.S.C. § 325(d). *See* Prelim. Resp. 11–49. Because we determine on the merits that no post-grant review should be instituted, we will not address Patent Owner's arguments concerning Section 325(d).

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is denied; and

FURTHER ORDERED that the requested post-grant review is not instituted with respect to any claim of the '838 patent.

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