

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENOME & COMPANY,
Petitioner,

v.

THE UNIVERSITY OF CHICAGO,
Patent Owner.

PGR2019-00002
Patent 9,855,302 B2

Before SHERIDAN K. SNEDDEN, SUSAN L.C. MITCHELL, and
JOHN E. SCHNEIDER, *Administrative Patent Judges*.

SCHNEIDER, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 328(a)

I. INTRODUCTION

This is a Final Written Decision in a post-grant review challenging the patentability of claims 1–29 (“the challenged claims”) of U.S. Patent 9,855,302 B2 (“the ’302 patent,” Ex. 1001). We have jurisdiction under 35 U.S.C. § 6, and enter this Decision pursuant to 35 U.S.C. § 328(a) and 37 C.F.R. § 42.3. For the reasons set forth below, we determine that Genome & Company (“Petitioner”) has shown, by a preponderance of the evidence, that the challenged claims are unpatentable. *See* 35 U.S.C. § 326(e) (2012).

A. Background

Petitioner filed a Petition requesting post-grant review of claims 1–29 of the ’302 patent. Paper 1 (“Pet.”). The University of Chicago (“Patent Owner”) filed a Preliminary Response. Paper 6 (“Prelim. Resp.”).

On April 15, 2019, pursuant to 35 U.S.C. §324(a), we instituted trial to determine whether any of the challenged claims is unpatentable on the grounds raised in the petition. Paper 8 (“Inst. Dec.”).

Patent Owner filed a Request for Rehearing of our Decision to Institute. Paper 11. On January 9, 2020, we denied Patent Owner’s request. Paper 34.

Patent Owner filed a Patent Owner’s Response on August 1, 2019. Paper 17 (“PO Resp.”). Petitioner filed a Reply on November 11, 2019.

Paper 23 (“Pet. Reply”). Patent Owner filed a Sur-Reply on December 17, 2019. Paper 29 (“PO Sur-Reply”).

On oral hearing was held on January 15, 2020. A copy of the transcript has been made part of the record. Paper 37, 38 (Corrected) (“Tr.”).

B. Real Parties in Interest

Petitioner identifies itself, Genome & Company, as the real party in interest. Pet. 3. Patent Owner identifies itself, the University of Chicago, as the real part in interest and Evelo Biosciences, Inc. as an additional real party in interest. Paper 4, 5

C. Related Matters

The parties assert that there are no related matters involving the ’302 patent. Pet. 3; Paper 4, 5

D. The ’302 Patent

The ’302 patent, titled “Treatment of Cancer by Manipulation of Commensal Microflora” issued on January 2, 2018, from U.S. Patent Application No. 15/170,284 filed on June 1, 2016. Ex. 1001, [54], [45], [21], [22]. The ’302 patent claims priority to U.S. Provisional Application No. 62/169,112 filed on June 1, 2015, and U.S. Provisional Application No. 62/248,741 filed on October 30, 2015. *Id.* at [60].

The ’302 patent teaches the treatment or prevention of cancer through the manipulation of commensal microflora either alone or in combination with one or more co-treatments. Ex. 1001, Abstr.

The '302 patent discloses that aco-treatment can be the administration of an immune checkpoint inhibitor (“CPI”).¹ Ex. 1001, col. 5, ll. 7–8. The CPI used in the practice of the invention disclosed in the '302 patent can be a protein of a peptide, an antibody or fragment thereof, or an interfering nucleic acid molecule. *Id.* at col. 5, ll. 7–20.

The '302 patent discloses that one of the microflora that can be used in practice of the disclosed invention is bacteria of the genus *Bifidobacterium*. *Id.* at col. 3, ll. 10–29.

E. Illustrative Claim

Of the challenged claims, claims 1 is the sole independent claim and reads as follows:

1. A method of treating cancer in a human subject comprising co-administering to the subject an immune checkpoint inhibitor and a bacterial formulation comprising bacteria of the genus *Bifidobacterium*.

Ex. 1001, col. 41, ll. 61–64.

F. Evidence

Petitioner relies on the following references:

Korman et al., US 2009/0217401 A1, published Aug. 27, 2009 (“Korman”) (Ex. 1003).

¹Immune checkpoint inhibitors are described as follows: “We have learned over the last decade that powerful immunologic effector cells may be blocked by inhibitory regulatory pathways controlled by specific molecules often called ‘immune checkpoints.’ These checkpoints serve to control or turn off the immune response when it is no longer needed to prevent tissue injury and autoimmunity.” Ex. 1016, Abstr. Drugs that inhibit these pathways are called checkpoint inhibitors and their use is seen as a potential new strategy for treating cancer. *Id.*

Singh et al., *Bifidobacterium longum*, a lactic acid-producing intestinal bacterium inhibits colon cancer and modulates intermediate biomarkers of cancer carcinogenesis, 18 Carcinogenesis 833 (1997) (“Singh”) (Ex. 1004).

Dong et al., *The role of intestinal bifidobacteria on immune system development in young rats*, 86 Early Human Devel. 51 (2010) (“Dong”) (Ex. 1005).

van der Waaij et al., *The influence of antibiotics on gut colonization*, 18 J. Antimicrobial Chemotherapy 155 (1986) (“van der Waaij”) (Ex. 1010).

Topalian et al., *Survival, Durable Tumor Remission, and Long-Term Safety in Patients with Advanced Melanoma Receiving Nivolumab*, 32 J. Clinical Oncol. 1020 (2014) (“Topalian”) (Ex. 1006).

Kohwi et al., *Anti-tumor Effects of Bifidobacterium infantis in Mice*, 69 Gann. 613 (1978) (“Kohwi”) (Ex. 1007).

Mohania et al., *Modulation of expression of Programmed Death-1 by administration of probiotic Dahi in DMH-induced colorectal carcinogenesis in rats*, 84 Acta Biomed. 102 (2013) (“Mohania”) (Ex. 1008).

Prakash et al., US 2010/028449 A1, published Feb. 4, 2010 (“Prakash”) (Ex. 1009).

Petitioner also relies on the Declarations of Jonathan Braun, M.D., Ph.D. (Exs. 1002, 1043). Patent Owner relies on the Declaration of Sridhar Mani, M.D. (Ex. 2007).

G. Prior Art and Asserted Grounds

Petitioner asserts that claims 1–29 would have been unpatentable on the following grounds:

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–29	112	Enablement

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–9, 12–17, 19–25, 27, 28	103(a) ²	Korman, Singh, Dong
10, 11, 26	103(a)	Korman, Singh, Dong, van der Waaij
18, 19	103(a)	Korman, Singh, Dong, Topalian
1–4, 7–9, 12–17, 19–25, 27, 28	103(a)	Korman, Kohwi
5, 6, 23, 24	103(a)	Korman, Kohwi, Singh
10, 11, 26	103(a)	Korman, Kohwi, van der Waaij
18, 29	103(a)	Korman, Kohwi, Topalian
1–9, 12–17, 19–25, 27, 28	103(a)	Korman, Mohania, Prakash
10, 11, 26	103(a)	Korman, Mohania, Prakash, van der Waaij
18, 29	103(a)	Korman, Mohania, Prakash, Topalian

II. ANALYSIS

A. Legal Standards

1. Enablement

“Section 112 requires that the patent specification enable those skilled in the art to make and use the full scope of the claimed invention without undue experimentation [S]ee also *In re Goodman*, 11 F.3d 1046, 1050 (Fed. Cir. 1993) (‘[T]he specification must teach those of skill in the art how to make and how to use the invention as broadly as it is claimed.’).”

² The Leahy-Smith America Invents Act (“AIA”) Pub. Law. No. 112-29, 125 Stat. 284, 287–288 (2001) amended 35 U.S.C. § 103(a). Because the application from which the ’302 patent issued was filed before March 16, 2013, the effective date of the relevant amendment, the pre-AIA version of section 103 applies.

Invitrogen Corp. v. Clontech Labs. Inc., 429 F.3d 1052, 1070–71 (Fed. Cir. 2005) (internal quotes omitted).

Some experimentation, even a considerable amount, is not “undue” if, e.g., it is merely routine, or if the specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 736–37 (Fed. Cir. 1988). “Factors to be considered in determining whether a disclosure would require undue experimentation . . . include (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.” *Id.* at 737. “Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.” *Id.*

2. *Obviousness*

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 skill in the art, and (4) where in evidence, so-called secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). If the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains, the claim is unpatentable under 35 U.S.C. § 103(a). *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

An invention

composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.

KSR, 550 U.S. at 418.

B. Level of Ordinary Skill in the Art

The level of ordinary skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham*, 383 U.S. at 17–18; *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Dr. Braun, Petitioner's proffered expert, defines a person of ordinary skill in the art as having an advanced degree or its substantial equivalent in the biological sciences, including specifically in the fields of immunology, microbiology and the microbiome, and oncology, coupled with research experience in those fields. Ex. 1002 ¶ 40. Patent Owner does not contest Petitioner's definition of a person of ordinary skill in the art. *See generally*, PO Resp. We determine that Petitioner's description of the level of ordinary skill in the art is supported by the current record. For purposes of this Decision, therefore, we adopt Petitioner's description.

We also note that the applied prior art reflects the appropriate level of skill at the time of the claimed invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

C. Claim Construction

In a post-grant review filed before November 13, 2018, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 100(b) (2018);³ *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to trial proceeding before the USPTO.). Under that standard, and absent any special definitions, we generally give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

We determine that it is unnecessary to expressly construe any claim terms for purposes of this Decision. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (“[C]laim terms need only be construed ‘to the extent necessary to resolve the controversy.’”) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

³ The Office recently changed the claim construction standard to be employed in a post-grant review for petitions filed on or after November 13, 2018. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (October 11, 2018) (amending 37 C.F.R. § 42.100(b) effective November 13, 2018) (now codified at 37 C.F.R. § 42.100(b) (2019)). Based on the filing date of the Petition in this proceeding, however, the applicable claim construction standard remains the broadest reasonable construction as set forth in 37 C.F.R. § 42.100(b) (2016).

D. Lack of Enablement

Petitioner contends that the specification of the '302 patent fails to adequately enable one skilled in the art to make and use the disclosed invention for the full scope of the claims. Pet. 36. Petitioner argues that when the *Wands* factors are properly considered, the factors lead to the conclusion that undue experimentation would be required to practice the full scope of the claims. *Id.*

Patent Owner contends undue experimentation is not required to practice the invention as “all cancer types were known to be susceptible to immune system attack [and] the checkpoint inhibitors known at the time had been shown to work across a wide variety of cancer types and mutational loads.” PO Resp. 4. Patent Owner also contends that Petitioner has failed to present any credible evidence “of functional heterogeneity among *Bifidobacterium* strains or species.” *Id.*

With respect to the *Wands* factors, Patent Owner contends that Petitioner’s arguments “boils down to a sheer numbers argument,” which is insufficient to show non-enablement. *Id.* at 37.

As noted above, our reviewing court has outlined seven different factors which should be considered in determining if undue experimentation is needed to practice the claimed invention. No one factor is determinative, rather the determination should be made after weighing all the factors. *Wands*, 858 F2d at 736. Mindful of this guidance, we consider each of the factors in turn.

1. Nature of the Invention

One of the factors to be considered in the *Wands* analysis is the nature of the invention. Petitioner contends that the invention is directed to treating cancer in a human subject by administering both a CPI and a bacterial

formulation comprising *Bifidobacterium*. Pet. 36. Petitioner contends that the claims are not limited to a specific form of cancer nor to a specific species of *Bifidobacterium*. *Id.* Petitioner also points out that the broader challenged claims do not specify the CPI to be used. *Id.*

Petitioner relies on the Declaration of Dr. Braun to support these contentions concerning the breadth of the challenged claims. *Id.* (citing Ex. 1002 ¶¶ 129–31). In the paragraphs of Dr. Braun’s Declaration cited in the Petition, Dr. Braun cites to earlier portions of his Declaration where he discusses the teachings of the ’302 patent. Ex. 1002 ¶ 131 (citing to ¶¶ 59–63). Dr. Braun discusses the examples in the ’302 patent and explains how the teachings of the examples are very limited. Ex. 1002 ¶¶ 59–63.

Patent Owner does not address this factor other than to contend that Petitioner’s analysis presents this factor as a subsidiary point to support Petitioner’s argument with regards to the quantity of experimentation required. PO Resp. 37–38.

We have considered the positions of the parties and the evidence of record and conclude that Petitioner’s analysis of the nature of the invention is correct. The invention is directed to a method for treating any cancer using a combination of a CPI and a bacteria from the species *Bifidobacterium*. *See, e.g.*, Ex. 1001, col. 41, ll. 61–64 (Claim 1).

2. *Level of Ordinary Skill in the Art*

Another factor to be considered is the level of ordinary skill in the art. Petitioner argues that the level of skill in the art is high, an assessment with which we agree on this record. Pet. 37; *see supra* Section II B. Petitioner contends that the ordinarily skilled artisan would have a specialized knowledge of cancer, immunology, and microbiota. Petitioner contends that

this specialized training is necessary as developing a cancer therapeutic is difficult, complicated, and highly unpredictable. *Id.*

In support of these contentions, Petitioner points to the Declaration of Dr. Braun. *Id.*; Ex. 1002 ¶¶ 132–134. In these paragraphs of his Declaration, Dr. Braun cites to earlier paragraphs in his Declaration where he discusses in detail the support for his opinion as to the level of skill required to develop a cancer therapeutic. *Id.* at ¶ 133 (citing ¶¶ 93–109).

Patent Owner has not contested the definition of a person of ordinary skill in the art advanced by Petitioner and has not contested Petitioner’s contentions as to this factor. *See generally*, PO Resp.

For purposes of this decision, we agree with Petitioner that the level of ordinary skill is high in developing a cancer therapeutic as evidenced by the prior art of record here and that such a skilled artisan would have a specialized knowledge of cancer, immunology, and microbiota. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art itself can reflect the appropriate level of ordinary skill in the art).

3. *The Breadth of the Claims*

Petitioner contends that the claims are very broad in that they cover “thousands of different combinations of cancers, immune checkpoint inhibitors and genera of *Bifidobacterium*.” Pet. 38. Petitioner contends that the claims are directed to any type of cancer and that the Specification of the ’302 patent lists more than 165 types of cancer that can be treated. *Id.* Petitioner also contends that the broader claims do not specify which CPI is to be used and that CPIs include a broad class of agents, such as proteins, including antibodies and fragments thereof, and nucleic acids. *Id.*

In support of these contentions, Petitioner cites to the Declaration of Dr. Braun. *Id.* at 38–41 (citing Ex. 1002 ¶¶ 136, 138–141, 143–146). In the

cited paragraphs, Dr. Braun cites to an earlier discussion in his Declaration where he describes in detail different types of cancer and explains how each is treated by different methods. Ex. 1002 ¶ 138 (citing ¶¶ 95–96). In this earlier discussion, Dr. Braun cites to additional references that support his opinions. *See, e.g.* Ex. 1002 ¶ 95 (citing to Kandoth⁴); Ex. 1021.

Dr. Braun also discusses the different types of CPIs in general and how they have been effective in treating a limited number of cancers and only for a limited subset of patients affected by those cancers. Ex. 1002 ¶¶ 100–103. In support of his opinions, Dr. Braun cites to Pardoll,⁵ which discusses CPIs and their use in treating cancer. *Id.*

Patent Owner does not dispute the issue of the breath of the claims, but appears to agree that the claimed method encompasses any CPI combined with any *Bifidobacterium* to treat any cancer. *See* PO Resp. 6–9.

The Specification of the '302 patent teaches that a CPI may comprise a protein or peptide, an antibody or antigen binding fragment thereof, or an interfering nucleic acid molecule. Ex. 1001, col. 5, ll. 7–20. Additionally, the Specification lists over 165 different cancers that can be treated and lists dozens of species of *Bifidobacterium* that can be used. *Id.* at col. 2, l. 61–col. 4, l. 55. We conclude from the language of the claims when read in light of the Specification of the '302 patent that the scope of the claims is broad encompassing a broad range of CPIs and any genus or strain of *Bifidobacterium* to treat a broad range of cancers.

⁴ Kandoth, et al., *Mutational landscape and significance across 12 major cancer types*, 502 NATURE 333 (2013) (“Kandoth”) (Ex. 1021).

⁵ D. Pardoll, *The blockade of immune checkpoints in cancer immunotherapy*, 12 NAT. REV. CANCER 252 (2012) (“Pardoll”) (Ex. 1026).

4. *Presence of Working Examples*

Petitioner contends that the examples in the '302 patent are limited to two specific types of cancer, melanoma and bladder, and one CPI. Pet. 41. With respect to the *Bifidobacterium* used in the examples, Petitioner contends that the '302 patent only used mouse feces, which contains one unidentified species of *Bifidobacterium* and other gut bacteria and another composition comprising a mixture of four different species of *Bifidobacterium*. *Id.* at 41–42. Petitioner also notes that the data presented in the '302 patent are limited to mouse data and that no human data are discussed. *Id.* at 42.

In support of these contentions, Petitioner relies on the Declaration of Dr. Braun. *Id.* As noted above, Dr. Braun discusses the limited nature of the experiments reported in the examples citing various passages in the '302 patent. Ex. 1002 ¶¶ 59–63, 147–149.

Again, Patent Owner does not offer any specific argument regarding this factor except to argue that, as presented by Petitioner, this factor is subsidiary to the factor addressing the amount of testing required. PO Resp. 37–39.

After considering the arguments presented by the parties and the evidence of record, we conclude that while there are working examples in the Specification, the examples give little guidance to one skilled in the art about how to practice the broad scope of the claimed invention. The examples are based on a single CPI, an antibody against PD-L1. Ex. 1001, col. 34, ll. 23–25; col. 36, l. 56–col. 37, l. 9. The *Bifidobacterium* use was limited to an unspecified species of *Bifidobacterium* present in mouse feces and a mixture of four different species of *Bifidobacterium*. *Id.* at col. 34, ll. 13–25, 57–61. The CPI and *Bifidobacterium* were used against only two

types of cancer, melanoma and bladder cancer. Ex. 1001, col. 33, ll. 44–58. Thus, we agree with Dr. Braun that the working examples are limited when compared to the broad scope of most of the claims, which are directed to treatment of any cancer with any species of *Bifidobacterium* using any CPI.

5. *Amount of Guidance in the Specification*

Petitioner contends that the '302 patent provides no guidance as to which CPI to select to treat a specific cancer. Pet. 42. Petitioner contends that the only guidance in the examples is limited to two types of cancer and one CPI. *Id.* Petitioner contends that given the scope of the claims and the unpredictable nature of the technology, the guidance given in the '302 patent is inadequate. *Id.* at 43.

Petitioner relies on the Declaration of Dr. Braun to support these contentions. *Id.* As described above, Dr. Braun discusses the examples provided in the '302 patent and the guidance given in the rest of the Specification. Ex. 1002 ¶¶ 41–63, 150–151.

Once again, Patent Owner does not address this factor except to contend that this factor is subsidiary to the amount of testing required. *See* PO Resp. 37–38.

We have considered the arguments of the parties and the evidence of record and conclude that the guidance in the Specification of the '302 patent as to how to practice the broad claims is limited. While the Specification defines CPI broadly as including a protein or polypeptide that binds an immune checkpoint as well as an interfering nucleic acid molecule, the CPIs listed in the Specification are almost exclusively antibodies, with the exception of AMP-224, which is a fusion protein containing a fragment of an antibody. Ex. 1001, col. 5, ll. 8–26; Exs. 2034, 1195, 2006. Although encompassed within the broad claims as evidenced by their express

inclusion as a CPI in the Specification of the '302 patent, no discussion of other CPIs such as interfering nucleic acid molecules can be found in the Specification.

With respect to selection of *Bifidobacterium*, while the Specification only contains the limited examples discussed above, the Specification does teach how to identify bifidobacteria that can be used to practice the invention. *See* Ex. 1001, col. 36, l. 43–col. 37, l. 37. Although the Specification appears to provide sufficient guidance to determine which *Bifidobacterium* to use, we find that there is insufficient guidance with respect to the CPI to use or which cancers to treat.

6. *Predictability of the Art.*

Petitioner contends that the art relating to the claimed invention is highly unpredictable. Pet. 43. Petitioner lists several different factors in support of this contention, including:

- Cancer is a term that embraces a variety of specific diseases with different etiologies, outcomes, and therapies;
- There are a limited number of CPIs that have been shown to work for a limited number of cancers, and for only a limited subset of patients with those cancers;
- The properties of *Bifidobacterium* are species and sometimes strain specific; and
- Only certain species of *Bifidobacterium* have been shown to be effective against cancer.

Pet. 43.

Petitioner contends that cancer therapy is an unpredictable art. Pet. 44. Petitioner contends that cancers develop in different ways and can require different methods of treatment. *Id.*

In support of these contentions, Petitioner cites to the Declaration of Dr. Braun. *Id.* Dr. Braun provides a detailed analysis supporting his conclusion that the art of treating cancer is unpredictable. Ex. 1002 ¶¶ 93–109, 152–155. In support of his conclusions, Dr. Braun cites to Kandoth and Kumar⁶ for the proposition that there are a variety of different cancer types and different methods for treating cancers. Ex. 1002 ¶¶ 95–97. Dr. Braun cites to Pardoll to support his conclusions regarding the limited effectiveness of CPIs, and cites to DiMasi⁷ for the proposition that development of a cancer therapy is difficult and complicated. *Id.* at ¶¶ 100–104.

With respect to the action of *Bifidobacterium*, Petitioner contends that the art demonstrates that different species and strains of the genus affect the immune system in different and unpredictable ways. Pet. 32, 44. Petitioner contends that this unpredictability makes the use of the bacteria unpredictable. *Id.* at 44–45.

Petitioner supports its contentions with respect to the unpredictability of *Bifidobacterium* with the declaration of Dr. Braun, the O’Mahony published patent application, and articles by Lopez⁸ and Dong, which describe the variability between species and strains of *Bifidobacterium*. Pet. 29–31, 44–45; Ex. 1002 ¶ 155; Ex. 1005; Ex. 1017; Ex. 1038.

Patent Owner responds by contending that CPIs are known to be effective against cancer. PO Resp. 4. Patent Owner contends that “Cancers

⁶ Kumar et al., *Drug Targets for Cancer Treatment: An Overview*, 5 MED. CHEM. 115 (2015) (“Kumar”) (Ex. 1022).

⁷ DiMasi and Grabowski, *Economic of New Oncology Drug Development*, 25 J. CLINICAL ONCOL. 209 (2007) (“DiMasi”) (Ex. 1027).

⁸ Lopez et al., *Distinct Bifidobacterium strains drive different immune responses in vitro*, 138 INTERN. J. FOOD. MICROBIO. 157 (2010) (“Lopez”) (Ex. 1038)

from all manners of tissue types and of all degrees of mutational burden have been shown to respond to CPI therapy.” *Id.* at 6. In support of this contention, Patent Owner cites the testimony of Dr. Mani wherein he describes the current understanding as to how CPIs promote an immunological response to treat cancer. PO Resp. 6–9 (citing Ex. 2007 ¶¶ 23–28; Exs. 2023–2028, 2033).

Patent Owner also contends that the evidence of record shows that that cancer representative of all cancer types respond to CPIs. PO Resp. 9–13. Patent Owner again relies on the testimony of Dr. Mani as well as several articles which report various clinical trials using CPIs. *Id.* (citing Exs. 2007 ¶¶ 39, 40, 42–45; Exs. 1021, 2029, 2030, 2055, 2056).

Patent Owner offers the following chart to summarize the results of the clinical trials reported at the time the ’302 patent was filed. PO Resp. 10.

Exhibit	Cancer Type	CPI	Response rate	Ref. no. in figures
2037	Chronic lymphocytic leukemia	Pidilizumab	2/3	1
2038	Glioblastoma	Nivolumab	7/10	2
2039	Glioblastoma	Ipilimumab	4/6	3
2040	Pancreatic	Ipilimumab	2/15	4
2041	B-cell lymphoma; Multiple myeloma	Nivolumab	7/11; 18/27	5
2042	Prostate	Ipilimumab	12/30	6
2043	Ovarian	Nivolumab	3/13	7
1030	Renal; Colorectal; Melanoma	Nivolumab	5/39 (all types)	8
2044	Hepatic	Nivolumab	2/39	9
2045	Head and neck	Pembrolizumab	18.2%	10
2046	Head and neck	Durvalumab	12%	11
1031/2047 ³	Colorectal; Endometrial	Pembrolizumab	4/28; 1/2	12
2048	Lung small cell	Nivolumab	1/20	13
2049	Bladder	Atezolizumab	26%	14
2050	Lung non-small cell	Nivolumab	9/63	15
2051	Lung non-small cell	Pembrolizumab	22%	16
1006	Melanoma	Nivolumab	30.8%	17
2052	Melanoma	Ipilimumab	10.9%	18
2053	Melanoma	Lambrolizumab	49%	19
2054	Melanoma	Pembrolizumab	41%	20

PO Resp. 10 (chart showing summary of clinical trials of CPIs).

Patent Owner contends that CPIs are considered effective even though they may have a low response rate in treating a cancer. PO Resp. 13–16. Patent Owner contends that in the area of treating cancer, a 100% response rate is not required and that low response rates are often considered acceptable given the dire need for cancer treatments. Patent Owner supports these contentions with the testimony of Dr. Mani and the exhibits cited by Dr. Mani. *Id.* (citing Ex. 2007 ¶¶ 46–53; Ex. 1006; Ex. 1029; Ex. 1030; Ex. 2037; Ex. 2058–2061, 2064).

Patent Owner contends that the use of several different cancer treatments before settling in on one that provides a satisfactory result is not an indication that such treatments are unpredictable requiring extensive testing. PO Resp. 16–18. Patent Owner contends that at the time the present application was filed, clinical trials on various CPIs had shown efficacy across a wide range of cancers at all levels of mutational load⁹, and with response rates sufficient to persuade the FDA to begin approving them. *Id.* at 18 (citing Ex. 2007 ¶¶ 42–47). This fact, coupled with the oncologist’s normal practice of trying several drugs, meant that, for one of ordinary skill at the time, testing multiple CPIs to find the best fit for a patient’s cancer was simply routine. *Id.* (citing Ex. 2007 ¶¶ 52–54).

With respect to the immunological effects of *Bifidobacterium*, Patent Owner contends that the references cited by Petitioner, namely O’Mahony and Lopez are not credible and do not support Petitioner’s contentions. *See* PO Resp. 19–30. Patent Owner argues that, “[a]mong other problems, neither reference provides sufficient data or statistical analysis to have justified one of ordinary skill in the art to reach the conclusions Petitioner ascribes to it.” PO Resp. 20 (citing Ex. 2007 ¶¶ 55–56).

In reply, Petitioner argues that Patent Owner improperly relies on third party publications to address deficiencies in the present Specification. Pet. Reply 7–8. Petitioner contends that the knowledge of a person of

⁹ Mutational load when used in conjunction with cancer cells is a measure of the number of mutations within a tumor genome. It can be used to predict responses to certain cancer immunotherapies. Normanno, *Tumor Mutational Load: ESMO Biomarker Factsheet*, <https://oncologypro.esmo.org/education-library/factsheets-on-biomarkers/tumour-mutational-load>, last accessed April 7, 2020.

ordinary skill in the art cannot serve as a substitute for enabling information missing in a specification. *Id.* Petitioner contends

Here, the '302 specification is missing key information, not the least of which is its failure to provide a POSITA guidance concerning the selection of which of the multiple CPIs (which includes countless numbers of proteins, antibodies, antibody fragments or interfering nucleic acids) to co-administer with which of the 36 *Bifidobacterium* species or strains thereof, to treat which of the 165 cancers listed in the '302 patent.

Id. at 8.

Petitioner contends that Patent Owner's assertion that O'Mahony is unreliable is contradicted by Patent Owner's arguments during prosecution of the '302 patent and statements in the Specification. Pet. Reply 9. Petitioner contends that during prosecution Patent Owner stated that the *Bifidobacterium* strains disclosed in O'Mahony suppressed immune response, whereas the specification teaches that the same species is immunostimulatory. *Id.* (citing Ex. 1014, 57–65, 123–132; Ex. 1001, col. 38, ll. 36–58, col. 39, l. 12–col. 40, l. 54).

With regards to Lopez, Petitioner contends that Lopez tested twelve different strains of *Bifidobacterium* from four different species and concluded that the results showed “species and strain specific effects. *Id.* at 10 (citing Ex. 1038, 164). With respect to the reliability of the data reported in Lopez, Petitioner points out that Lopez has been cited in a peer reviewed article stating that Lopez showed that different strains of *Bifidobacterium* showed different immunological effects. *Id.* at 10–11 (citing Ex. 1044)

With respect to O'Mahony, Patent Owner again contends that O'Mahony presents no meaningful statistical analysis of the data presented calling into question the reliability of the data presented. PO Sur-Reply 9–

10. Patent Owner also contends that it did not represent in prosecution of the '302 patent that O'Mahony taught strain 1714 was immunosuppressive, but that it merely cited those passages to show that O'Mahony would have led one skilled in the art away from the combination proposed by the Examiner. *Id.*

Patent Owner reiterates its contention that one skilled in the art would not have relied on the teachings of Lopez because of the insufficiency of Lopez's statistical analysis. *Id.* at 10–11. Patent Owner contends that the citation to Lopez in a subsequent article does not establish the correctness of Lopez's conclusion. *Id.*

Petitioner also contends that Patent Owner's expert admitted that the properties of each strain of *Bifidobacterium* cannot be predicted and that each strain must be tested. Pet. Reply 11 (citing Ex. 1042, 138.)

Petitioner also contends that immunotherapy is very complex and involves more than targeting checkpoints. *Id.* at 12.

Petitioner contends that the data advanced by Patent Owner only addresses a limited set of cancers and only for a limited set of cancer patients. *Id.* at 13. Petitioner points out that none of the reported clinical trials involve the use of antibody fragments or interfering nucleic acids. *Id.* at 14.

In its Sur-Reply, Patent Owner contends that the data it has put forth supports its contention that CPIs have been shown to be effective against a broad range of cancer types, and Petitioner has not shown why the data is not representative of all cancer types. PO Sur-Reply 4.

With respect to CPIs, Patent Owner contends that Petitioner has not offered any evidence that CPIs in classes other than antibodies do not exist or that one skilled in the art would not know how to use them in the present

invention. *Id.* at 5. Patent Owner cites to *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052, 1070–71 (Fed. Cir. 2005) for the proposition that “[e]nablement does not require the inventor to foresee every means of implementing an invention at pains of losing his patent franchise.” *Id.* (quoting *Invitrogen*, 429 F.3d at 1070).

Patent Owner contends that while the response levels are low, the levels are consistent indicating that there is no uncertainty that CPIs work for cancer patient populations. PO Sur-Reply 6. Patent Owner also contends that it is typical for an oncologist to try several different therapies before finding the one that provides the best possible result for a given patient. *Id.* at 7.

We have considered the arguments presented by the parties and the evidence of record and conclude that the unpredictability of the art weighs in favor of finding non-enablement with respect to CPIs in general.

While we agree with Patent Owner that CPIs can be effective in treating some cancers, the Specification and the evidence of record show that all of the effective CPIs are antibodies. For example, all of the CPIs listed in the chart of page 10 of Patent Owner’s Response are antibodies. Tr. 39. We find nothing in the record, other than attorney argument that one skilled in the art would know how to make of use other CPIs, such as an interfering nucleic acid molecule, in the claimed method. For example, as Petitioner points out, Patent Owner’s expert did not consider CPIs other than antibodies, in reaching his conclusions regarding enablement. Pet. Reply, 4; Ex. 1042, 19–29.

The record also does not support the contention that one skilled in the art could predict the action of non-antibody CPIs based on the action of an antibody CPI. The art and the Specification identify one non-antibody CPI,

AMP-224, a fusion protein comprising the extracellular domain of PD-L2 and the Fe region of human IgG. Ex. 1001, col. 5, ll. 20–23; Ex. 2034, 206. At the time the '302 patent was filed, studies of this potential CPI indicated that it acted differently than antibody CPIs and that efficacy was lacking compared to other CPIs. *Id.* This evidence supports Petitioner's contention that the use of CPIs, especially non-antibody CPIs, was unpredictable at the time the '302 patent was filed.

We also agree with Petitioner that the selection of *Bifidobacterium* was unpredictable. The evidence of record supports Petitioner's contention that the immunostimulatory activity of *Bifidobacterium* varies from strain to strain, even within the same species. Pet. 44–45. O'Mahony teaches that *Bifidobacterium longum* strain AH1714 is immunosuppressive while another strain of *B. longum* exhibits immunostimulatory activity. Ex. 1017 ¶¶ 103–109. Similarly, Lopez evaluated 12 strains of four different species of *Bifidobacterium* and concluded that the properties exhibited by *Bifidobacterium* varied among the strains. Ex. 1038, Abstr.

Patent Owner's arguments regarding the credibility of O'Mahony and Lopez are unpersuasive. Patent Owner made specific representations to the Examiner on several occasions that strain AH1714 disclosed in O'Mahony was immunosuppressive to support Patent Owner's argument that one would not combine an immunosuppressive agent with an immunostimulatory agent. *See, e.g.* Ex. 1014, 8–9. Patent Owner suggests that it was not asserting that the statements in O'Mahony were accurate, but merely argues that those statements would have led away from making the combination proposed by the Examiner. PO Sur-Reply 10. This argument fails in its logic. If one skilled in the art upon reading O'Mahony would have recognized the alleged errors in O'Mahony's teachings and disregarded them as Patent Owner now

urges, then why would those same teachings have led away from the combination advanced by the Examiner in prosecution as Patent Owner argued.

With respect to Lopez, Lopez states unambiguously that the immune effects of Bifidobacteria are species and strain specific. Petitioner has advanced evidence that those skilled in the art accepted these conclusions, citing Lopez in subsequent articles. Pet. Reply 10–11 (citing Ex. 1044). Moreover, the present inventors found Lopez to be sufficiently credible to incorporate the teachings of Lopez in their entirety into the instant Specification of the '302 patent. Ex. 1001, col. 37, l. 62–col. 38, l. 4.

7. Amount of Experimentation

Petitioner contends that it would require an undue amount of experimentation to practice the full scope of the claims of the '302 patent. Pet. 45. Petitioner argues that it would require more than 100,000 experiments to test all the disclosed CPIs with all the disclosed species of *Bifidobacterium* to test their effectiveness against the range of cancers recited in the '302 patent. *Id.* at 46. Petitioner contends that the number of experiments required is actually even greater as the patent does not give any specific guidance as to the routes of administration. Petitioner contends that the sheer volume of experiments required coupled with the limited guidance in the '302 patent compels the conclusion that undue experimentation is required to practice the full scope of the invention. *Id.* at 48.

Petitioner supports these contentions with the Declaration of Dr. Braun. *Id.* (citing Ex. 1002 ¶¶ 165–166). Dr. Braun bases his opinion that undue experimentation would be required on his analysis of the '302 patent. Ex. 1002 ¶¶ 156–165.

Patent Owner contends that Petitioner's argument with regard to enablement is essentially predicated on the number of experiments needed and that the number of experiments alone is insufficient to establish undue experimentation. PO Resp. 37–40. Patent Owner asserts that a large number of experiments is not undue experimentation if the experiments are of a routine nature. *Id.* Patent Owner asserts that Petitioner has failed to put forth any evidence with regard to the nature of the experiments required let alone show that the experiments are not routine. *Id.*

While we agree with Patent Owner that the number of experiments needed is not determinative by itself, the amount of experimentation Dr. Braun asserts would be necessary to enable the full scope of the broad challenged claims is worthy of note. Petitioner has, through the testimony of Dr. Braun, presented evidence that a significant number of experiments would be need to be conducted to practice the full scope of the claimed method. Ex. 1002 ¶¶ 156–165. While Patent Owner has not acquiesced to this assertion of the number of required experiments, Patent Owner has not presented any evidence to rebut Petitioner's evidence concerning such amount other than to assert that Petitioner has not presented evidence regarding the nature of the experiments needed. PO Resp. 40–41.

8. *Analysis*

We have considered the arguments presented by the parties and the evidence of record and conclude that applying the all the *Wands* factors, Petitioner has demonstrated by a preponderance of the evidence that claims 1–17 and 19–28 are not enabled. In reviewing the evidence of record, we find that the nature of the invention that involves very broad claims, the high level of skill required in such an unpredictable art, and the dearth of working examples and lack of specific guidance on the full range of CPIs and cancers

that are commensurate in scope with the claims, all establish that these challenged claims are not enabled. Because claims 18 and 29 require known CPIs, however, we find that Petitioner has failed to show that these claims are not enabled.

“Section 112 requires that the patent specification enable those skilled in the art to make and use the full scope of the claimed invention without undue experimentation. . . . [S]ee also *In re Goodman*, 11 F.3d 1046, 1050 (Fed. Cir. 1993) (‘[T]he specification must teach those of skill in the art how to make and how to use the invention as broadly as it is claimed.’).” *Invitrogen*, 429 F.3d at 1070–71 (internal quotes omitted).

Claim 1 recites a method for treating cancer using a CPI with bacteria from the genus *Bifidobacterium*. Ex. 1001, col. 41, ll. 61–64. The Specification teaches that a CPI may comprise a protein or peptide such as an antibody or an antigen binding fragment thereof, or the CPI may comprise an interfering nucleic acid. *Id.* at col. 5, ll. 7–20. The Specification also lists agents which can act as CPIs, which include antibodies and a fusion protein. *Id.*; Ex. 2034, 1995. The examples of the ’302 patent use an antibody as a CPI. Ex. 1001, col. 34, ll. 23–25. The additional references cited by Patent Owner concerning the use of CPIs all refer to CPIs that are either antibodies or fusion proteins. Tr. 34; Ex. 2034, 1995.

We find nothing in the present record that, at the time the invention was made, shows the use of antibody fragments or interfering nucleic acids as CPIs. Other than the mention of these molecules as possible CPIs, the Specification of the ’302 patent does not provide any guidance as to how to construct such molecules or how they can be used as CPIs.

Given that non-antibody CPIs were virtually unknown at the time the '302 patent was filed, it is a given that the action of those molecules was also unknown. While Patent Owner asserts that one skilled in the art would expect all CPIs to act in a similar manner, the evidence of record does not support this contention. The evidence suggests that the sole non-antibody CPI known at the time the '302 patent was filed acted differently than antibody CPIs and was not as effective as antibody CPIs. Ex. 2034, 2006. Patent Owner's expert, Dr. Mani conceded that his enablement analysis did not include non-antibody CPIs such as antibody fragments and interfering nucleic acids. Ex. 1042, 19–29.

Patent Owner's reliance on *Invitrogen* is misplaced. In *Invitrogen*, the claims were directed to genetically engineered reverse transcriptase. *Invitrogen*, 429 F.3d at 1070. The court found that the claims were enabled even though the Specification taught only one method for making the reverse transcriptase. *Id.* The court distinguished the claims from those in *Nat'l Recovery Techs, Inc., v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190 (Fed. Cir. 1999), which were directed to a method and not a compound. *Id.* at 1072.

In the present case, the claims are directed to a method of co-administering both a CPI and bacterial formulation comprising bacteria from the genus *Bifidobacterium*. Like the claims in *Nat'l Recovery*, the Specification gives no guidance as to how to select a CPI that, other than those recited in the Specification, is useful in the practice of the invention. *Nat'l Recovery*, 166 F.3d at 1196. As with *Nat'l Recovery*, a person of ordinary skill in the art reading the '302 patent, would have been required to engage in undue experimentation before reaching a means of practicing the claimed method as it pertains to the use of a CPI. As Dr. Braun has testified,

given the broad scope of the claims, the limited guidance in the Specification, the unpredictable nature of CPIs and cancer treatment in general, and the large number of experiments which would be needed, a person of ordinary skill in the art “would have to engage in undue extensive experimentation to even attempt to practice the full scope of claims 1–29 of the ‘302 patent.” Ex. 1002 ¶ 166.

We find the opposite to be true for the selection of *Bifidobacterium*. While we agree with Petitioner that the immunological activity of *Bifidobacterium* can vary by species or strain, the Specification provides guidance sufficient to aid one skilled in the art in determining which species or strain to use. *See* Ex. 1001, col. 36, l. 43–col. 37, l. 37.

Claims 18 and 19 recite the use of specific antibodies as CPIs including nivolumab, BMS-936558, and BMS-936559. Ex. 1001, col. 42, ll. 58–63. The evidence of record shows these antibodies were known in the art to act as CPIs. Ex. 1006; Ex. 2043. Given that the antibodies were known, we find that these claims were enabled with respect to the use of the specific antibodies recited in the claims.

With respect to the treatment of different cancers, we agree with Patent Owner that one skilled in the art would have been able to determine the effectiveness of a combination of a CPI and bacteria once a CPI had been selected. As the evidence of record demonstrates, the processes for determining the effectiveness of various cancer treatments is well known. *See, e.g.* Ex. 2043. While the process of selecting an appropriate cancer therapy may be a long process, we agree with Patent Owner that it is not necessarily undue. The same applies to determining the method for administration.

Based on the foregoing analysis, we conclude that Petitioner has established by a preponderance of the evidence that claims 1–17 and 19–28 are not enabled as they encompass CPIs other than antibody CPIs. We conclude Petitioner has not demonstrated that claims 18 and 29 are not enabled as they embrace known CPIs.

E. Grounds 2–4 – Obviousness based on Combinations Including Korman, Singh, and Dong.

Petitioner contends that claims 1–9, 12–17, 19–25, 27, and 28 would have been rendered obvious by the teachings of Korman combined with Singh, and Dong. Pet. 50–57. Petitioner also alleges that claims 10, 11, and 26 are rendered obvious by the teachings of Korman, Singh, Dong, and van der Waaij. Pet. 57–58. Petitioner contends that claims 18 and 29 are rendered obvious over Korman, Singh, Dong, and Topalian. Pet. 58–59.

Because these grounds all turn on similar issues, we will address these three grounds together.

1. Korman

Korman relates to the use of human monoclonal antibodies to treat cancer. Ex. 1003, Abstr. Korman teaches the use of anti-PD-1 antibodies and anti-CTLA-4 antibodies to treat cancer. *Id.* Korman teaches that these antibodies act as CPIs as they bind to the respective proteins thereby enhancing the immune response to cancer cells. Ex. 1003 ¶¶ 498, 501. Korman teaches that the antibodies can be effective against colorectal cancer cells and SA1/N fibrosarcoma cells. *Id.*

2. Singh

Singh reports a study to determine the effectiveness of *Bifidobacterium longum* to treat cancer. Ex. 1004, 833, 839. Singh teaches

that oral administration of *Bifidobacterium longum* exerts strong anti-tumor activity. *Id.* Singh teaches that daily oral administration of lyophilized cultures of *B. longum* resulted in “significant suppression of colon cancer incidence, tumor multiplicity and reduced tumor volume.” *Id.*

3. Dong

Dong reports a study on the effect of intestinal bifidobacteria on the development of immunity during development. Ex. 1005, Abstr. Dong teaches that administration of bifidobacteria “promoted dendritic cell maturation in Peyer’s Patches, up-regulated IL-12, IL-10, interferon- γ mRNA and the interferon- γ /IL-4 ratio in intestinal mucosa, increased interferon- γ gene expression in cultured PBMCs, and raised immunoglobulin-M secretion in cultured PBMCs.” *Id.* Dong teaches intestinal bifidobacteria can affect “the development of both gut and systemic immunity in early life.” *Id.*

4. Analysis

Petitioner contends that Korman teaches a method for treating cancer in humans by administering CPIs, such as anti-PD-1 and anti-CTLA-4 antibodies that bind to their respective immune checkpoint proteins. Pet. 50. In support of this position, Dr. Braun testifies that “Korman ‘401 showed that that intraperitoneal injection of anti PD-1 and anti CTLA-4 antibodies both alone and in combination reduced tumor growth in MC38 colorectal cancer cells and SA1/N fibrosarcoma cells.” Ex. 1002 ¶ 168.

Petitioner contends that Singh teaches that oral administration of *Bifidobacterium longum* exerts strong anti-tumor activity. Pet. 50. In support of this position, Petitioner’s expert testifies that “Singh showed that daily oral administration of ‘[l]yophilized cultures of *B. longum* ... equivalent to 4 x 10¹⁰ live cells/g diet’ (*Id.* at p. 2, 2nd col.) resulted in

‘significant suppression of colon tumor incidence, tumor multiplicity, and reduced tumor volume.’” Ex. 1002 ¶ 169 (quoting Ex. 1004, Abstr.).

Petitioner contends that Dong teaches that *Bifidobacterium longum* is immunostimulatory. Pet. 50. In support of this position, Dr. Braun testifies that “Dong showed that *Bifidobacterium longum* induced maturation in dendritic cells characterized by increased expression of CD86, IL-12, and IFN- γ , and that such induced maturation of dendritic cells would favor a T-helper cell response of the body in a Th1 type.” Ex. 1002 ¶ 170.

Petitioner contends that it would have been obvious to one skilled in the art to combine the teachings of Korman and Singh to treat cancer in a human subject. Pet. 51. Petitioner contends that one skilled in the art would have been motivated to combine the teachings of the references as the CPIs of Korman and the *Bifidobacterium* of Singh are both shown to be effective in treating colon cancer and are both immunostimulatory. *Id.*

With respect to claims 10, 11, and 26, which call for the administration of an antibiotic before the administration of bifidobacteria, Petitioner contends that this limitation is taught by van der Waaij. Pet. 57. Petitioner contends that van der Waaij teaches that administration of an antibiotic helps reduce the microflora population in a subject and that subsequent repopulation with bifidobacteria will increase the population of bifidobacteria in the patient. *Id.* (citing Ex. 1010). Administering the antibiotic before the bacterial formulation, Petitioner contends, would have been simply routine optimization. *Id.*

Petitioner contends that claims 18 and 29 would have been obvious over the combined teachings of Korman, Singh, Dong, and Topalian. Pet. 58. Claims 18 and 29 further limit claim 1 to specific CPIs including nivolumab, BMS-936558, and BMS-936559. Ex. 1001, col. 42, ll. 58–63;

col. 44, ll. 19–14. Petitioner contends that Topalian teaches the use of those antibodies as CPIs. Pet. 59 (citing Ex. 1006, 1021 and 1026.) Petitioner contends that it would have been obvious to one skilled in the art to substitute the CPIs of Topalian for the CPI in Korman. *Id.*

Patent Owner responds that one skilled in the art would not have been motivated to use the bifidobacteria of Singh with the CPIs of Korman as the *Bifidobacterium* used in Singh and Dong are immunosuppressive and not immunostimulatory. Prelim. Resp. 7.¹⁰ Patent Owner contends that one skilled in the art would not use an immunosuppressive agent in combination with an immunostimulatory agent, and therefore, would not have combined Singh’s purportedly *immunosuppressive Bifidobacterium* with Korman’s *immunostimulatory* CPIs. *Id.*

In support of this contention, Patent Owner points to the teaching in Singh that the administration of *Bifidobacterium longum* upregulated the production of IL-10, which is described in the art as anti-inflammatory. Prelim. Resp. 7 (citing Ex. 1005, 7). Patent Owner contends that one skilled in the art would not have considered *Bifidobacterium longum* to be immunostimulatory as Dong teaches that the bacteria has both an anti-inflammatory and pro-inflammatory effect. Prelim. Resp. 7–8. Patent

¹⁰ Patent Owner asserts that during prosecution, it overcame an obviousness rejection by arguing that the *Bifidobacterium* species taught by that art is immunosuppressive “and that combining an immunosuppressive *Bifidobacterium* with an immunostimulatory checkpoint inhibitor would have been antithetical to one of ordinary skill.” Prelim. Resp. 6. Petitioner does not appear to dispute Patent Owner’s contention that an ordinarily skilled artisan would have avoided co-administration of an immunosuppressive *Bifidobacterium* species with an immunostimulatory CPI. *See* Pet. 2, note 1, 13–16.

Owner also contends that the conclusions in Dong are tentative and would not have led one skilled in the art to conclude that the *Bifidobacterium* used in Dong were immunostimulatory. *Id.*

Patent Owner also contends that Singh and Dong only suggest that *B. Longum* might have anti-tumor activity and are immunostimulatory. PO Resp. 45. Patent Owner contends that Singh suggests that the activity observed might be due to anti-carcinogen activity and not anti-tumor activity. *Id.* Patent Owner also contends that flaws in Dong's experimental design prevent drawing a conclusion as to whether *B. Longum* is immunostimulatory. *Id.*

Petitioner responds that one skilled in the art would interpret Singh as demonstrating that the *B. longum* used exhibited anti-tumor activity. Pet. Reply 18. In support of this contention, Petitioner points to subsequently published articles, which cite Singh for that proposition. *Id.* (citing Exs. 1050–1053.) Similarly, Petitioner contends that one skilled in the art would interpret Singh as teaching that the bifidobacteria used were immunostimulatory. *Id.* at 18–19. Again, Petitioner supports this contention by citing to a subsequent article, which cites Singh for that proposition. *Id.* at 19–20 (citing Ex. 1011, 6.) Petitioner also contends that Dong teaches that *B. Longum* is immunostimulatory. *Id.* at 20.

With respect to the motivation to combine the references, Petitioner contends that one skilled in the art would have been motivated to use the CPI of Korman with the bifidobacteria of Singh as both have an anti-tumor effect. *Id.* at 20. Petitioner contends that one skilled in the art would have had a reasonable expectation of success in that Singh employed an established cancer model that is translatable to humans. *Id.* at 21 (citing Ex. 1004, 834; Ex. 1043 ¶ 82)

With respect to the dosing schedule recited in claims 9, Petitioner contends that based on the teachings of the references and the knowledge of one skilled in the art, a practitioner would have arrived at the claimed schedule through routine optimization. *Id.* at 21.

In response, Patent Owner contends in its Sur-Reply that Singh acknowledges that the effects observed might be due to an anti-carcinogen effect and not an anti-tumor effect. PO Sur-Reply 14. Similarly, Patent Owner contends that Singh is equivocal about whether the bifidobacteria used was immunostimulatory. *Id.* at 14–15. Patent Owner also contends that the model used by Singh has been criticized in the art because it cannot distinguish between an anti-tumor effect and an anti-carcinogen effect. PO Resp. 48.

In our Decision to Institute, we concluded that, based on the record before us then, Petitioner had not demonstrated that it was likely to prevail in showing that the challenged claims were obvious over the references cited in grounds 2–4. Dec. 20. We agree with the Patent Owner that one skilled in the art would not have combined an immunostimulatory agent with an immunosuppressive agent and that the evidence supported the conclusion that the CPI of Korman was immunostimulatory and that the bifidobacteria of Singh was immunosuppressive. *Id.*

In its Reply, Petitioner points to additional evidence to support its contention that the bifidobacteria used in Singh was immunostimulatory. Pet. Reply 19–20. In addition to Dong cited in the Petition as teaching that *B. longum* is immunostimulatory, Petitioner also offers Lee¹¹, which cites

¹¹ Lee, et al., *Anti-proliferative effects of BifidoBacterium adolescentis SPM0212 extract on human colon cancer cell lines*, 8 BMC Cancer 310 (2008) (“Lee”) (Ex. 1011).

Singh for the proposition that *Bifidobacterium* stimulate immune function and anti-tumor effects. *Id.* In addition, Petitioner points out that Singh itself teaches that the bifidobacteria used are immunostimulatory. *Id.*

Patent Owner contends that Dong and Singh, at best, suggest that the bifidobacteria used in Singh might be immunostimulatory. PO Resp. 45. Patent Owner has not produced any independent evidence to support this contention except to challenge Dong's experimental design. *Id.* Patent Owner also argues that Lee's citation to Singh stating that *Bifidobacterium* stimulate immune function and anti-tumor effects does not make the statement true and does not correct the failure of Singh to teach that the bifidobacteria is immunostimulatory. PO Sur-Reply 16–17.

We have considered the parties arguments and find that, based on the full record before us, Petitioner has shown that the bifidobacteria used in Singh is immunostimulatory. Singh expressly teaches that the *B. longum* used acts as an immunomodulatory. Ex. 1004, 838. Dong teaches that “supplementation with bifidobacteria promoted dendritic cell maturation in Peyer's Patches, up-regulated IL-12, IL-10, interferon- γ mRNA and the interferon- γ /IL-4 ratio in intestinal mucosa, increased interferon- γ gene expression in cultured PBMCs, and raised immunoglobulin-M secretion in cultured PBMCs.” Ex. 1005, Abstr. Dr. Braun testifies that this demonstrated that the bifidobacteria was immunostimulatory. Ex. 1002 ¶ 170. Finally, Lee cites Singh along with other references for the proposition that bifidobacteria are immunostimulatory. Ex. 1011, 283.¹²

¹² Our citations are to the original page numbers of the references rather than the page number assigned by the parties.

Patent Owner contends that experimental design flaws preclude any reasonable conclusion that *B. longum* is immunostimulatory. PO Resp. 45, 52–59. We do not find this argument persuasive. The '302 patent incorporates the teachings of Dong, in its entirety, into the Specification. Ex. 1001, col. 37, l. 62–col. 38, l. 1. As with Lopez discussed above, we find it hard to believe that if the teachings of Dong were as flawed as Patent Owner contends, the inventors would have recognized this fact and not have incorporated Dong's teachings in total into the Specification especially with respect to the "interactions between bifidobacteria and the host immune system." *Id.*

Similarly Patent Owner contends that the citation of Singh in Lee does not prove that the bifidobacteria is immunostimulatory. PO Resp. 50. While this may be true, is it strong evidence that the authors of Lee interpreted the teachings of Lee as supporting the proposition that bifidobacteria is immunostimulatory.

We are not persuaded by Patent Owner's arguments that one skilled in the art would not have interpreted Singh as teaching that the bifidobacteria used had an anti-tumor effect. PO Resp. 45–52. Singh affirmatively states that the data "suggests that the oral administration of probiotic *B. longum* exerts strong anti-tumor activity as indicated by mediation of intermediate biomarkers, and consequently reduced tumor outcome." Ex. 1004, 833. Singh also states "regardless of the mechanism involved, data demonstrate that dietary *B. longum* modulates the process of selective amplification of ras-p21 in AOM-induced colon carcinogenesis." *Id.* at 839. Dr. Braun's testimony also supports the conclusion that the bifidobacteria used in Singh was immunostimulatory. *See* Ex. 1002 ¶ 172

While we agree with Patent Owner that there has been criticism of the AOM cancer model, as Petitioner points out, subsequent to these criticisms, authors have cited to Singh for the proposition that *B. longum* exhibits an anti-tumor effect. For example, Uccello¹³ reports “Singh et al [85] demonstrated that *B. longum* resulted in a significant suppression of colon tumor incidence and tumor multiplicity.” Ex. 1050, 5. Boopathy¹⁴ reports “*Bifidobacterium longum* has significant suppression of colon tumor incidence, tumor multiplicity and tumor volume.” Ex. 1052, 7505. Additional references cite to Singh as describing *B. Longum* as exhibiting anti-tumor activity. See, e.g., Exs. 1052, 1053. Dr. Braun has testified that the statements in the recited articles are “consistent with Singh’s stated purpose of the paper: to ‘evaluate the colon tumor inhibitory properties of dietary B.longum in the established colon cancer model.’” Ex. 1043 ¶ 80 (quoting Ex. 1004, Abstr.).

Claim 9 calls for the administration of two or more doses of bifidobacteria where the doses are separated by at least one week. Ex. 1001, col. 42, ll. 34–35. Petitioner contends that the subject matter of this claim would have been obvious over Korman combined with Singh and Dong. Pet. 50. Dr. Braun testifies that administration of two or more doses of bifidobacteria at least one week apart would have been arrived at through routine optimization. Ex. 1002 ¶ 179.

¹³ Uccello et al., *Potential role of probiotics on colorectal cancer prevention*, 12 BMC Surgery 535 (2012) (“Uccello”) (Ex. 1050).

¹⁴ Boopathy et al., *Effect of Mangrove Tea Extract from *Ceriops decandra* (Griff.) Ding Hou. On Salivary Bacterial Flora of DMBA induced Hamster Buccal Pouch Carcinoma*, 51 Indian J. Microbiol. 338 (2011) (“Boopathy”) (Ex. 1052).

Patent Owner contends that Petitioner did not refer to any reference that teaches this limitation but instead relies on the opinion of its expert that the dosing schedule would have been arrived at through routine optimization. PO Resp. 60. Patent Owner contends that Dr. Braun's testimony cannot serve as a substitute for disclosure in a prior art reference. *Id.* at 60–61.

In reply, Petitioner contends that Dr. Braun's opinion regarding claim 9 was based on the teachings of the references and the general knowledge of one skilled in the art. Pet. Reply 21. Petitioner contends that the disclosure in the present Specification of the '302 patent supports the contention that dosing would be determined through routine optimization. *Id.* (citing Ex. 1001, col. 6, ll. 5–20).

We have considered the arguments presented by the parties and the evidence of record and conclude that the subject matter of claim 9 would have been obvious. “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456 (CCPA 1955).

The references here describe the general conditions of claim 9, which is the administration of two or more doses of bifidobacteria over a period of time. Singh teaches that “Male F344 rats were fed a modified diet AIN-76A diet containing 0 or 2% lyophilized cultures of *B. longum* and s.c. administer azoxymethane (AOM) dissolved in normal saline at a dose of 15 mg/kg body wt, once weekly for 2 weeks.” Ex. 1004, Abstr. Thus, Singh teaches administration of at least two doses spaced apart. Ex. 1043 ¶ 83. As discussed above, Singh also teaches that the administration of bifidobacteria has an anti-tumor effect.

Given that Singh teaches the general conditions, we agree with Dr. Braun that one skilled in the art would have developed the claimed treatment schedule through routine optimization. Ex. 1002 ¶ 179. Our conclusion is further supported by the testimony of Dr. Mani, which we credit, who stated that it is routine for a physician to try different therapies to identify the treatment that elicits the greatest clinical response to prolong patient survival. Ex. 2007 ¶ 46.

With respect to Grounds 3 and 4, Patent Owner has not contested Petitioner's contentions with respect to the teachings of van der Waaij and Topalian, with which we agree. See PO Resp. 61.

Based on the foregoing, we conclude that Petitioner has established by a preponderance of the evidence that claims 1–9, 12–17, 19–25 and 27–28 are unpatentable over Korman combined with Singh and Dong; claims 10, 11, and 26 are unpatentable over Korman combined with Singh, Dong, and van der Waaij; and claims 18 and 29 are unpatentable over Korman combined with Singh, Dong, and Topalian.

F. Obviousness Based on Combinations of Korman and Kohwi

Petitioner contends that claims 1–4, 7–9, 12–17, 19–25, 27, and 28 are rendered obvious by the teachings of Korman combined with Kohwi. Pet. 59–67. Petitioner also alleges that claims 5, 6, 23, and 24 are rendered obvious by the teachings of Korman, Kohwi and Singh. Pet. 67–68. Petitioner contends that claims 10, 11, and 26 are rendered obvious over Korman, Kohwi and van der Waaij. Pet. 68. Petitioner contends that claims 18 and 29 are rendered obvious over Korman, Kohwi, and Topalian. Pet. 68–69.

Because these grounds turn on similar issues, we shall consider these grounds together.

1. *Kohwi*

Kohwi describes a study into the possible anti-tumor effects of *Bifidobacterium infantis* and *Bifidobacterium adolescentis* in mice. Ex. 1007, 1. Kohwi teaches “[t]wo strains of *Bifidobacterium* isolated from a human exhibited a remarkable anti-tumor effect to Meth-A sarcoma cells transplanted into BALB/c mice.” Ex. 1007, 617. Kohwi suggests that this anti-tumor response may be due to involvement of a host-mediated immunological response to the tumor, at least to some extent, together with the nonspecific local reaction. *Id.* Kohwi goes on to teach “[t]aken together, destruction of part of tumor cells by the local reaction induced by the bacteria and following immunological stimulation with the tumor may account for the anti-tumor mechanism of the bacteria.” *Id.*

2. *Analysis*

Petitioner contends that Korman teaches a method for treating cancer in humans by administering CPIs such as anti-PD-1 and anti-CTLA-4 antibodies that bind to their respective immune checkpoint proteins. Pet. 59–60. In support of this position, Dr. Braun testifies that “Korman ‘401 showed that that intraperitoneal injection of anti PD-1 and anti CTLA-4 antibodies both alone and in combination reduced tumor growth in MC38 colorectal cancer cells and SA1/N fibrosarcoma cells.” Ex. 1002 ¶ 181.

Petitioner contends that Kohwi teaches that *Bifidobacterium infantis* and *Bifidobacterium adolescentis* exhibit a remarkable anti-tumor effect on Meth-A sarcoma cells. Pet. 60. Petitioner also contends that Kohwi teaches that the anti-tumor effect shown by the bacteria was due to the bacteria being immunostimulatory. *Id.* In support of this contention Dr. Braun cites to these teachings in Kohwi. Ex. 1002 ¶¶ 182–184 (citing Ex. 1007, Abstr., 617).

Petitioner contends that it would have been obvious to one of ordinary skill in the art to combine the CPIs of Korman with the *Bifidobacterium* of Kohwi to treat cancer. Pet. 61. Petitioner contends that one skilled in the art would have been motivated to co-administer the *Bifidobacterium* of Kohwi with the CPIs of Korman as both have been shown to be effective against cancers such as SA1/N fibrosarcoma cells and both are immunostimulatory. *Id.*

With respect to claims 18 and 19, Petitioner contends that Topalian teaches that antibodies nivolumab, BMS-936558, and BMS936559 act as CPIs. Pet. 58–59 (citing Exs. 1006, 1021, 1026). Petitioner contends that it would have been obvious to substitute the CPIs described in Topalian for the CPI disclosed in Korman. *Id.*

Patent Owner contends that one skilled in the art would not have concluded from Kohwi that the bifidobacteria used were immunostimulatory as there are serious shortcomings in Kohwi’s analysis. PO Resp. 62. Patent Owner also contends that there are alternate explanations for the results observed in Kohwi. *Id.* Specifically, Patent Owner contends that Kohwi does not teach that the immunological response is related to the administration of the bifidobacteria. *Id.* at 67–68.

With respect to claim 9, Patent Owner contends that Petitioner has failed to properly explain how the references teach the claimed dosing interval. *Id.* at 69.

With respect to claims 5, 6, 23, and 24, Patent Owner contends that neither Korman nor Kohwi teach oral or rectal administration. *Id.* at 69–72.

Patent Owner contends that claims 10, 11, and 26 are patentable as Petitioner has not explained how reducing gut microflora with an antibiotic would affect subcutaneous or peritoneal treatments. *Id.* at 72–74.

In reply, Petitioner contends that subsequent articles have cited Kohwi for the proposition that the bifidobacteria used exert anti-tumor effects demonstrating that those skilled in the art do not discount Kohwi's teachings because of alleged analytical errors. Pet. Reply 21–22. Petitioner also contends that any alleged errors with respect to the data reported in figure 1 of Kohwi are outweighed by the unequivocal statements in Kohwi regarding the effectiveness of bifidobacteria used and the fact that the data in the rest of the article was subject to appropriate statistical analysis and supports the conclusion that at least *B. infantis* was effective. *Id.* at 22–23.

With respect to the bifidobacteria being immunostimulatory, Petitioner points to our Decision to Institute where we found Kohwi teaches that the bifidobacteria used was immunostimulatory. *Id.* at 23.

Petitioner contends that Patent Owner's argument that Kohwi speculated that the bifidobacteria was not involved in the immune response to the tumor is without merit. *Id.* Petitioner contends that Kohwi clearly teaches that the bifidobacteria augments the host's immune response. *Id.* (citing Ex. 1007, 617). Petitioner contends that this is supported by the subsequent articles, which cite to Kohwi. *Id.* at 24.

Petitioner contends that claim 9 is obvious for the reasons discussed with respect to Ground 2 above. *Id.* Petitioner also contends that even if Kohwi is viewed as not teaching that the bifidobacteria used was immunostimulatory, there is no evidence that the bacteria was immunosuppressive. *Id.*

With respect to claims 5, 6, 23, and 24, Petitioner contends that it was known in the art that bifidobacteria can achieve detectable blood levels and systemic dissemination when administered through the intestine. *Id.* (citing Exs. 1056, 1057). Petitioner also contends that one skilled in the art would

have known to administer the bacteria orally as this is the route taught by Singh. *Id.*

Petitioner contends that the use of antibiotics to decrease microflora population and to repopulate it with bifidobacteria would have been obvious. *Id.* at 25.

In its Sur-Reply, Patent Owner reiterates its argument that the data reported in Kohwi is irreproducible and unreliable. PO Sur-Reply 20.

We have considered the arguments presented by the parties and the evidence of record and conclude that for claims 1–9, 12–25 and 27–29, Petitioner has shown by a preponderance of the evidence that the claims are unpatentable over Korman combined with Kohwi, Singh, and Topalian. We conclude that Petitioner has not shown that claims 10, 11, and 26 are unpatentable over Korman combined with Kohwi and van der Waaij.

Korman teaches the use of anti-PD-1 antibodies as a treatment for cancer. Ex. 1003 ¶ 1. Kohwi teaches that “two strains of Bifidobacterium of human origin exhibited a marked anti-tumor effect.” Ex. 1007, 613. Given the teachings of the reference that both the antibodies of Korman and the bifidobacteria of Kohwi exhibit an anti-tumor effect, we agree with Petitioner that it would have been obvious to combine the two agents to treat cancer. Ex. 1002 ¶ 185. “The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR*, 550 U.S. at 416.

Patent Owner argues that the data in Kohwi was flawed to the extent that no one skilled in the art could have drawn a reasonable conclusion from the data. PO Resp. 62. We are not persuaded by this argument. Subsequent to Kohwi, at least two sets of authors have cited to Kohwi as teaching that the stains of bifidobacteria used had an anti-tumor effect. For example,

Yin¹⁵ states “*Bifidobacterium* itself has been proven to have anticancer functions” citing to Kohwi. Ex. 1054, 485. Similarly, Singh states “Kohwi et al. (65) have demonstrated that repeated intralesional injections of viable or killed *Bifidobacterium* inhibited the growth of Meth-A tumor cells.” Ex. 1004, 838. Thus, any flaws in the data presented in Kohwi did not dissuade others in the field from relying on the conclusions stated in Kohwi.

We are similarly unpersuaded by Patent Owner’s argument that Kohwi does not teach that the bifidobacteria used was immunostimulatory. PO Resp. 62. Dr. Braun has testified that the bifidobacteria used in Kohwi was immunostimulatory. Ex. 1002 ¶ 184 (quoting Ex. 1007, 4 (relying on Kohwi’s statement that part of tumor cells were destroyed by local reaction *induced by the bacteria and the following immunological stimulation* with the tumor)). In addition, Kohwi teaches that the bifidobacteria stimulated that host’s immune response. Ex. 1007, 617.

Even if we were to accept Patent Owner’s argument that the evidence did not support the conclusion that the bifidobacteria were immunostimulatory, as we pointed out in our Decision to Institute, the evidence shows that for *Bifidobacterium adolescentis*, the bacteria is either immunostimulatory or shows no stimulatory effect. Dec. 24. Given that the claims do not call for the bifidobacteria to exhibit an immunostimulatory effect and the reason to combine is based on the anti-tumor effect, we conclude that any lack of an immunostimulatory effect does not negate the motivation to combine advanced by Petitioner concerning the anti-tumor effect.

¹⁵ Yin et al, *Therapeutic efficacy of Bifidobacterium longum-mediated human interleukin-2 with endostatin or TRAIL in implanted tumors in mice*, 3 Exp. Therap. Med. 481 (2012) (“Yin”) (Ex. 1054).

With respect to claims 10, 11, 25, and 26, while van der Waaij teaches that the administration of an antibiotic will affect the population of microflora in the gut, we find no teaching or suggestion in any of the references with regard to repopulating the gut with bifidobacteria. Ex. 1010.

With respect to claims 5, 6, 23, and 24, for the reasons stated above in Section II E, we agree with Petitioner that the subject matter of these claims would have been obvious.

With respect to claims 18 and 29, we agree with Petitioner that these claims would have been obvious. Topalian teaches that Nivolumab, BMS - 936558, and BMS936559 act as CPIs. Exs. 1006, 1021, 1026. Korman teaches the use of PD-1 antibodies as CPIs for treating cancer. Ex. 1003 ¶¶ 647, 480; Ex. 1002 ¶ 167. We agree with Petitioner that it would have been obvious to substitute the CPIs of Topalian for the CPI of Korman to treat cancer. It would have been obvious to those skilled in the art to substitute one known equivalent for another. *See In re Omeprazole Patent Litigation*, 483 F.3d 1364, 1374 (Fed. Cir. 2007) (“[T]his court finds no . . . error in [the] conclusion that it would have been obvious to one skilled in the art to substitute one ARC [alkaline reactive compound] for another.”).

G. Obviousness based on Combinations of Korman, Mohania and Prakash

Petitioner contends that claims 1–9, 12–17, 19–25, 27, and 28 are rendered obvious by the teachings of Korman combined with Mohania and Prakash. Pet. 69–78. Petitioner also alleges that claims 10, 11, and 26 are rendered obvious by the teachings of Korman, Mohania, Prakash, and van der Waaij. Pet. 79. Petitioner contends that claims 18 and 29 are rendered obvious over Korman, Mohania, Prakash, and Topalian. Pet. 79–80.

Because these grounds turn on similar issues, we will address these three grounds together.

1. Mohania

Mohania reports a study of the effect of the probiotic Dahi as a chemoprotective agent for colorectal cancer. Ex. 1008, 102. Dahi is a fermented milk product comprising a mixture of bacteria including *Bifidobacterium bifidum*. Ex. 1008, 103. Mohania teaches that oral administration of Dahi to rats reduced expression of PD-1 and that “Dahi can be used as an effective chemoprotective agent in the management of colorectal cancer.” Ex. 1008, Abstr.

2. Prakash

Prakash is directed to an oral preparation comprising bacteria and fermented milk for treating gastrointestinal disorders. Ex. 1009, Abstr. Prakash teaches that various species of *Bifidobacterium* including *Bifidobacterium bifidum*, can be used to treat cancer including colorectal cancer. Ex. 1009 ¶¶ 25, 30, 79.

3. Analysis

Petitioner contends that it would have been obvious to one of ordinary skill in the art to co-administer a CPI of Korman with the *Bifidobacterium bifidum* of Mohania to treat colon cancer. Pet. 70. Petitioner contends that a person of ordinary skill in the art would have been motivated to combine the CPIs of Korman and the *Bifidobacterium bifidum* of Mohania as both have been shown to be effective against colorectal cancer. *Id.* at 70–71. Petitioner also contends that one skilled in the art would have been motivated to combine the two agents as both the anti-PD-1 antibody of Korman and the *Bifidobacterium bifidum* of Mohania act to minimize the function of PD-1 and their effects are additive. *Id.* at 71.

Petitioner supports these contentions with the testimony of its declarant, Dr. Braun, who testifies that the antiPD-1 antibody blocks the PD-

1 receptor from being activated and *Bifidobacterium bifidum* downregulates the PD-1 receptor's expression making the effect of the two agents additive. Ex. 1002 ¶ 203.

Petitioner also cites to the prosecution history of the child application of the '302 patent, USSN 15/718,735 ("735 Appln."). Pet. 72. During prosecution of the '735 Application, the Examiner responded to Patent Owner's argument that the probiotic of Mohania and the anti-PD-1 antibody of Korman acted through "mutually counter productive [sic] mechanisms" by finding that the compositions of Korman, Mohania and Prakash work to inhibit or decrease the function of PFD-1 and are not counter-productive. Ex. 1015, 68.

With respect to claims 10, 11, and 26, Petitioner contends that van der Waaij teaches administration of an antibiotic to reduce microflora population followed by repopulation of the microflora. Pet. 79 (citing Ex. 1002 ¶ 207, Ex. 1010). Petitioner contends that from the teachings of van der Waaij, Mohania and Parkash, one skilled in the art would have administered an antibiotic before administering the bifidobacteria. *Id.*

With respect to claims 18 and 19, Petitioner contends that Topalian teaches the use of antibodies nivolumab, BMS-936558, and BMS936559 as CPIs. *Id.* at 79 (citing Ex. 1002 ¶ 209). Petitioner contends that it would have been obvious to substitute one CPI for another. *Id.* at 79–80.

Patent Owner contends that the data reported in Mohania does not necessarily support Petitioner's contention that the bifidobacteria present in the Dahi had an anti-tumor effect. PO Resp. 76. Patent Owner contends that, like the experiments in Singh, the effect observed may have been caused by the inhibition of the carcinogen rather than action against the tumor. *Id.* Patent Owner also contends that while Mohania teaches that

there was reduction in PD-1 expression, there is nothing in Mohania that shows an actual anti-tumor effect. *Id.* at 77–78. Patent Owner also contends that one skilled in the art would not have any confidence in Mohania’s data because the method used to analyze the data is subjective. *Id.* at 78–79. Patent Owner contends that the data reported in Mohania does not support Petitioner’s contention that the bifidobacteria used by Mohania cause downregulation of PD-1. *Id.* at 79–82. Patent Owner contends that Petitioner’s expert admitted that the results reported in Mohania were not related to PD-1 expression in T Cells. *Id.* at 82–84.

With respect to Prakash, Patent Owner contends Prakash does not teach that bifidobacteria has an anti-tumor effect. *Id.* at 84. Patent Owner supports this contention by pointing to data, which show yogurt containing *Lactobacillus* alone performed the same as yogurt containing both *Lactobacillus* and bifidobacteria. *Id.* at 85. Patent Owner contends that Prakash concluded that the use of bifidobacteria did not add to the anti-tumor effect of using *Lactobacillus*. *Id.* at 87–88. Patent Owner contends that this refutes Petitioner’s contention that the bifidobacteria possessed anti-tumor activity. *Id.* at 87.

In its Reply, Petitioner contends that Mohania did not conclude that the effect observed was due to an anti-carcinogen effect alone but concluded that several factors were at play including immunomodulatory effects. Pet. Reply 25 (citing Ex. 1008, 106). Petitioner also contends that the data reported in Mohania was sufficient to draw the conclusion that the administration of bifidobacteria caused a reduction in PD-1 expression. *Id.* at 26–27. With respect to Prakash, Petitioner contends that Prakash unequivocally states that *Bifidobacterium bifidum* and a few other species of

Bifidobacterium can be administered orally to treat a number of cancers, including colorectal cancer. *Id.* at 27 (citing Ex. 1009 ¶¶ 25, 30, 79.)

Patent Owner responds in its Sur-Reply by contending that Petitioner has not established that the bifidobacteria did not have an anti-carcinogenic effect. PO Sur-Reply 21. Patent Owner also contends that Petitioner is relying on new evidence regarding the PD-1 reduction effect of the bifidobacteria used in Mohania. *Id.* at 21–22. Patent Owner contends that Dr. Braun’s new interpretation of Mohania’s Figure 2 is new evidence and should not be considered as Patent Owner has not had a chance to reply to that opinion and Dr. Braun does not provide a detailed analysis to support his conclusions. *Id.* at 21–22. With respect to Prakash, Patent Owner contends that one skilled in the art would have discounted Prakash’s broad statements regarding the effect of bifidobacteria given that the bacteria did not reduce the number of tumors formed. *Id.* at 22–23.

We have considered the arguments presented by the parties and the evidence of record and conclude that Petitioner has established by a preponderance of the evidence that the subject matter of claims 1–9, 12–17, 19–25, 27, and 28 is rendered obvious by the teachings of Korman combined with Mohania and Prakash. We conclude that Petitioner has established by a preponderance of the evidence that the subject matter of claims 10, 11, and 26 is rendered obvious by the teachings of Korman, Mohania, Prakash, and van der Waaij. Pet. 79. We also conclude that Petitioner has established by a preponderance of the evidence that the subject matter of claims 18 and 29 is rendered obvious over Korman, Mohania, Prakash, and Topalian. Pet. 79–80.

As discussed above, Korman teaches the use of an antibody CPI to treat cancer. *See* Section II.E above. Patent Owner does not contest this fact.

Mohania teaches that “probiotic Dahi can be used as an effective chemopreventative agent in the management of colorectal cancer.” Ex. 1008, Abstr. One of the Dahi mixtures used by Mohania contained both *L. acidophilus* and *B. bifidum*. *Id.* at 103. The data obtained showed that Dahi, with or without bifidobacteria reduced the expression of PD-1 and that PD-1 is related to tumor development. *Id.* at 107–108.

Prakash teaches the use of an oral formulation for the treatment of human diseases and disorders such as cancer. Ex. 1009 ¶¶ 25, 28, 30. The oral formulation comprises a bacteria selected from any member of the genera *Lactobacillus* or *Bifidobacterium*. *Id.* at ¶ 79.

We agree with Petitioner that, given that Korman, Mohania, and Prakash all relate to the treatment or prevention of cancer, one skilled in the art would have been motivated to use either the Dahi of Mohania or the *Bifidobacterium* of Prakash in combination with the CPI of Korman to treat or prevent cancer. Pet. 71–72.

We are not persuaded by Patent Owner’s argument that Mohania suggests that the effect reported in Mohania may be due to an anti-carcinogen effect rather than an anti-tumor effect. As Dr. Braun testified, Mohania teaches that the administration of bifidobacteria caused several effects including immunomodulatory effects. Ex. 1043 ¶ 94 (citing Ex. 1008, 278–279.)

Similarly, we are unpersuaded by Patent Owner’s argument concerning the bifidobacteria not causing down regulation of PD-1. As Dr. Braun testified, the conclusion that the administration of bifidobacteria

results in a reduction of PD-1 expression is borne out from an analysis of the data and discussion presented in connection with Figure 2 of Mohania, which shows a reduction of PD-1 expression in tissue treated with bifidobacteria. Ex. 1043 ¶ 97 (citing Ex. 1008, 105).

Patent Owner's complaint that Dr. Braun's testimony presents new evidence is not well taken. The additional opinions offered by Dr. Braun were based on the teachings of Mohania, which was already of record, and were in response to Patent Owner's assertions concerning the teachings of Mohania. Ex. 1043 ¶ 97. Moreover, the supplemental opinions offered by Dr. Braun are consistent with the positions he took in his original declaration. *See* Ex. 1002 ¶¶ 198–199.

We are similarly unpersuaded by Patent Owner's arguments regarding Prakash. While examples of Prakash may suggest that bifidobacteria itself does not produce an anti-tumor effect, the present claims only can produce an anti-tumor effect for administration of a bacterial formulation comprising bacteria of the genus *Bifidobacterium*. Ex. 1001, col. 41, ll. 63–64. Nowhere does the claim call for the *Bifidobacterium* itself to have any specific effect. Moreover, the examples do not negate the overall teaching of Prakash regarding the use of an oral formulation comprising bifidobacteria to treat cancer. Ex. 1009 ¶¶ 25, 30, 79.

As discussed more fully above, we agree with Petitioner that it would have been obvious to substitute the CPIs of Topalian for the CPI in Korman to treat cancer.

III. CONCLUSION¹⁶

We conclude that Petitioner has established by a preponderance of the evidence that claims 1–17 and 19–28 are unpatentable under 35 U.S.C.

§112, first paragraph for lack of enablement.

We conclude that Petitioner has not established that claims 18 and 29 are unpatentable under 35 U.S.C. §112, first paragraph for lack of enablement.

We conclude that Petitioner has established by a preponderance of the evidence that claims 1–9, 12–17, 19–25, 27, and 28 are unpatentable under 35 U.S.C. § 103(a) over Korman combined with Singh and Dong.

We conclude that Petitioner has established by a preponderance of the evidence that claims 10, 11, and 26 are unpatentable under 35 U.S.C. § 103(a) over Korman combined with Singh, Dong, and van der Waaij.

We conclude that Petitioner has established by a preponderance of the evidence that claims 18 and 29 are unpatentable under 35 U.S.C. § 103(a) over Korman combined with Singh, Dong, and Topalian.

We conclude that Petitioner has established by a preponderance of the evidence that claims 10, 11, and 26 are unpatentable under 35 U.S.C. § 103(a) over Korman combined with Singh, Dong, and van der Waaij.

¹⁶ Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. See 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. See 37 C.F.R. § 42.8(a)(3), (b)(2).

We conclude that Petitioner has established by a preponderance of the evidence that claims 18 and 29 are unpatentable under 35 U.S.C. § 103(a) over Korman combined with Singh, Dong, and Topalian.

We conclude that Petitioner has established by a preponderance of the evidence that claims 1–4, 7–9, 12–17, 19–25, 27, and 28 are unpatentable under 35 U.S.C. § 103(a) over Korman combined with Kohwi.

We conclude that Petitioner has established by a preponderance of the evidence that claims 5, 6, 23, and 24 are unpatentable under 35 U.S.C. § 103(a) over Korman combined with Kohwi and Singh.

We conclude that Petitioner has not established by a preponderance of the evidence that claims 10, 11, and 26 are unpatentable under 35 U.S.C. § 103(a) over Korman combined with Kohwi and van der Waaij.

We conclude that Petitioner has established by a preponderance of the evidence that claims 18 and 29 are unpatentable under 35 U.S.C. § 103(a) over Korman combined with Kohwi and Topalian.

We conclude that Petitioner has established by a preponderance of the evidence that claims 10, 11, and 26 are unpatentable under 35 U.S.C. § 103(a) over Korman combined with Singh, Dong, and van der Waaij.

We conclude that Petitioner has established by a preponderance of the evidence that claims 1–9, 12–27, 19–25, 27, and 28 are unpatentable under 35 U.S.C. § 103(a) over Korman combined with Mohania and Parkash.

We conclude that Petitioner has established by a preponderance of the evidence that claims 10, 11, and 26 are unpatentable under 35 U.S.C. § 103(a) over Korman combined with Mohania, Prakash, and van der Waaij.

We conclude that Petitioner has established by a preponderance of the evidence that claims 18 and 29 are unpatentable under 35 U.S.C. § 103(a) over Korman combined with Mohania, Prakash, and Topalian.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, based on the preponderance of the evidence that claims 1–29 of the '302 patent are unpatentable;

FURTHER ORDERED, because this is a final decision, the parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. §90.2

In summary:

Claims	35 U.S.C. §	Reference(s)/Basis	Claims Shown Unpatentable	Claims Not shown Unpatentable
1–29	112	Enablement	1–17, 19–28	18, 29
1–9, 12–17, 19–25, 27, 28	103(a)	Korman, Singh, Dong	1–9, 12–17, 19–25, 27, 28	
10, 11, 26	103(a)	Korman, Singh, Dong, van der Waaij	10, 11, 26	
18, 29	103(a)	Korman Singh, Dong, Topalian	18, 29	
1–4, 7–9, 12–17, 19–25, 27, 28	103(a)	Korman, Kohwi	1–4, 7–9, 12–17, 19–25, 27, 28	
5, 6, 23, 24	103(a)	Korman, Kohwi, Singh		5, 6, 23, 24
10, 11, 26	103(a)	Korman, Kohwi, van der Waaij		10, 11, 26
18, 29	103(a)	Korman, Kohwi, Topalian	18, 29	
1–9, 12–17, 19–25, 27, 28	103(a)	Korman, Mohania, Prakash	1–9, 12–17, 19–25, 27, 28	
10, 11, 26	103(a)	Korman, Mohania, Prakash, van der Waaij	10, 11, 26	
18, 29	103(a)	Korman, Mohania, Prakash, Topalian	18, 29	
Overall Outcome			1–29	

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