UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENOME & COMPANY,
Petitioner,

v.

THE UNIVERSITY OF CHICAGO,
Patent Owner.

Case PGR2019-00002

U.S. Patent No. 9,855,302 B2

PETITION FOR POST GRANT REVIEW
UNDER 35 U.S.C. §§ 321-329 AND 37 C.F.R. § 42.200

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

Other Authorities

TABLE OF EXHIBITS

Exhibit	Description
1001	U.S. Patent No. 9,855,302
1002	Declaration of Jonathan Braun, M.D., Ph.D.
1003	U.S. Publication No. 2009/027401 to Korman *et al.*
1004	Jagveer Singh *et al.*, *Bifidobacterium longum, a lactic acid-producing intestinal bacterium inhibits colon cancer and modulated the intermediate biomarkers of colon carcinogenesis*, Carcinogenesis (1997)
1005	Ping Dong *et al.*, *The role of intestinal Bifidobacteria on immune system development in young rats*, Early Human Development (2010)
1006	Suzanne L. Topalian *et al.*, *Survival, Durable Tumor Remission, and Long-Term Safety in Patients With Advanced Melanoma Receiving Nivolumab*, Journal of Clinical Oncology (Apr. 1, 2014)
1007	Yoshinori Kohwi *et al.*, *Antitumor effect of Bifidobacterium Infantis in Mice*, Gann (Oct. 1978)
1008	Dheeraj Mohania *et al.*, *Modulation of expression of Programmed Death-1 by administration of probiotic Dahi in DMH-induced colorectal carcinogenesis in rats*, Acta Biomed (2013)
1009	U.S. Publication No. 2010/0028449 to Prakash *et al.*
1010	D. van der Waaij *et al.*, *The Influence of antibiotics on gut colonization*, Journal of Antimicrobial Chemotherapy (1986)
1011	Do Kyung Lee *et al.*, *Anti-proliferative effects of Bifidobacterium adolescentis SPM0212 extract on human colon cancer cell lines*, BMC Cancer, (Oct. 2008)
1012	U.S. Provisional Patent Application No. 62/169,112
1013	U.S. Provisional Patent Application No. 62/248,741
1014	File History of U.S. Patent No. 9,855,302
1015	File History of U.S. Patent Application No. 15/718,735
1016	Elad Sharon *et al*, *Immune checkpoints in cancer clinical trials*, Chinese Journal of Cancer (2014)
1017	U.S. Publication No. 2012/0276143 to O'Mahony *et al.*
1018	U.S. Publication No. 2007/0258953 to Duncan *et al.*
1019	Mosby's Medical dictionary 8th ed. (2009)

Exhibit	Description
1020	Dorland's Illustrated Med Diction 31st ed. (2007)
1021	Cyriac Kandoth *et al.*, *Mutational landscape and significance across 12 major cancer types*, Nature (Oct. 17, 2013)
1022	Shashank Kumar *et al.*, *Drug Targets for Cancer Treatment: An Overview*, Medicinal Chemistry (2015)
1023	*Targeted Cancer Therapies*, National Cancer Institute, https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-factsheet
1024	Andrew M. Scott *et al.*, *Monoclonal antibodies in cancer therapy*, Cancer Immunity Commentary (May 1, 2012)
1025	Henrique Neves *et al.*, *Recent advances in the field of anti-cancer immunotherapy*, BBA Clinical (2015)
1026	Drew M. Pardoll, *The blockade of immune checkpoints in cancer immunotherapy*, Nature Reviews Cancer (Apr. 2012)
1027	Joseph A. DiMasi *et al.*, *Economics of New Oncology Drug Development*, Journal of Clinical Oncology (Jan. 10, 2007)
1028	Satheesh Thungappa *et al.*, *Immune checkpoint inhibitors in lung cancer: the holy grail has not yet been found…*, ESMO Open (2017)
1029	Naiyer A. Rizvi *et al.*, *Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer*, Science (2015)
1030	Julie R. Brahmer *et al.*, *Phase I Study-Agent Anti-Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates*, Journal of Clinical Oncology (July 1, 2010)
1031	D. T. Le *et al.*, *PD-1 Blockade in Tumors with Mismatch-Repair Deficiency*, The New England Journal of Medicine (2015)
1032	Jocelyn Kaiser, *Why a powerful cancer drug only helps some patients*, Science(Mar. 12, 2015)
1033	Alexandra Snyder *et al.*, *Genetic basis for clinical response to CTLA-4 blockade in melanoma*, The New England Journal of Medicine (2014)
1034	Ivaylo I. Ivanov *et al.*, *Intestinal commensal microbes as immune modulators*, Cell Host & Microbe (2012)
1035	Lora V. Hooper *et al.*, *Interactions between the microbiota and the immune system*, Science (June 8, 2012)

Exhibit	Description
1036	Kenya Honda *et al.*, *The Microbiome in Infection Disease and Inflammation*, Annual Review of Immunology (2012)
1037	Paul B. Eckburg *et al.*, *Diversity of the human intestinal microbial flora*, Science (June 10, 2005)
1038	Patricia Lopez *et al.*, *Distinct Bifidobacterium strains drive different immune responses in vitro*, International Journal of Food Microbiology (2010)
1039	U.S. Publication No. 2008/0193373 to Stritzker *et al.*
1040	Bandaru S. Reddy *et al.*, *Inhibitory effect of Bifidobacterium longum on Colon, Mammary, and Liver Carcinogenesis Induced by 2-Amino-3-methylimidazo[4,5-f]quinolone, a Food Mutagen*, Cancer Research (Sept. 1, 1993)

I. INTRODUCTION

U.S. Patent No. 9,855,302 is an invalid patent having breathtakingly broad cancer treatment claims inadequately supported by a predominantly prophetic disclosure. The claims cover methods of treating any and all cancers in a human subject by co-administering the combination of any and all immune checkpoint inhibitors and any and all species of *Bifidobacterium*. Notably, the predominantly prophetic disclosure of the '302 patent provides laundry lists of over 165 types of cancer, tens of "immune checkpoint inhibitors," including any protein or protein fragment (whatever that may be) that binds to an immune checkpoint protein, and 36 different genera of *Bifidobacterium*, including "*Bifidobacterium sp*" – any yet to be discovered species of *Bifidobacterium.*

In stark contrast to the nearly limitless scope of the cancer treatment claims, the actual experimental evidence reported in the '302 patent is miniscule. The '302 specification describes a few mouse experiments involving a couple types of cancer (melanoma and bladder), one immune checkpoint inhibitor (αPD-L1), and a few species of *Bifidobacterium*. That is it.

In light of the highly unpredictable nature of cancer treatment, highly unpredictable nature of immune checkpoint inhibitors to treat cancer, and highly unpredictable nature of the immunological and anti-cancer properties of various

species and strains of *Bifidobacterium*, the claims of the '302 patent are undisputedly not enabled.

The sheer breadth of the '302 claims also renders them obvious. Prior art not before the Examiner reported experiments in not just mice, but also rats, demonstrating that some strains of *Bifidobacterium* inhibited the growth and/or decreased the size of colon and sarcoma tumors. The prior art also showed that these strains of *Bifidobacterium* were immunostimulatory. Accordingly, a POSITA would have been motivated to combine administering these immunostimulatory strains of Bifidobacterium[1] demonstrating anti-cancer properties with a known checkpoint inhibitor, also having known immunostimulatory and anti-cancer properties against certain types of cancer, including colon cancer. A POSITA would have also possessed a reasonable expectation of success for treating those types of cancers already proven to be responsive to immune checkpoint inhibitors, including colon cancer. Accordingly, claims 1-29 of the '302 patent are also invalid as being rendered obvious by the prior art.

[1] The case was allowed based on applicant's arguments that the cited prior art described immunosuppressive *Bifidobacterium*, and therefore, a POSITA would not have been motivated to co-administer it with an immune checkpoint inhibitor which is immunostimulatory.

For the foregoing reasons and as discussed in detail below, Petitioner requests post-grant review ("PGR") and cancellation of claims 1-29 of the '302 patent. 35 U.S.C. § 324(a).

II. MANDATORY NOTICES

As set forth below and pursuant to 37 C.F.R. § 42.8(a)(1), the following mandatory notices are provided as part of this petition.

A. Real Parties in Interest

Pursuant to 37 C.F.R. § 42.8(b)(1), Genome & Company is identified as the real party in interest. Genome & Company is not controlled by any other entity.

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

There are no related matters.

C. Lead and Backup Counsel (37 C.F.R. §§ 42.8(b)(3) and 42.10(a))

Petitioner designates the following individuals as its lead counsel and back-up lead counsel:

Lead Counsel	**Back Up Counsel**
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D. Service Information (37 C.F.R. § 42.8(b)(4))

Please address all correspondence to the lead and backup counsel at the above address.

E. Payment of Fees

Pursuant to 37 C.F.R. §§ 42.203 and 42.15(b), the requisite filing fee of $52,925 (request fee of $16,000, post-institution fee of $22,000 and excess claims fee of $11,550) for a Petition for Post Grant Review is submitted herewith. Claims 1-29 of the ‘302 patent are being reviewed as part of this Petition. The undersigned further authorizes payment from Deposit Account No. 50-0311 for any additional fees or refund that may be due in connection with the Petition.

F. Time for Filing Petition

The ‘302 patent issued on January 2, 2018 and the instant Petition was timely filed no later than the date that is nine months after the date of the grant of a patent. 35 U.S.C. § 321(c); 37 C.F.R. § 42.202.

III. ADDITIONAL REQUIREMENTS FOR POST-GRANT REVIEW

A. Grounds for Standing (37 C.F.R. § 42.204(a))

Petitioner hereby certifies that the ‘302 patent is available for Post Grant Review and that Petitioner is not barred or estopped from requesting Post Grant Review challenging the claims of the ‘302 patent on the grounds identified herein. Petitioner further certifies that the prohibitions of 35 U.S.C. § 325(a) are inapplicable.

The earliest possible effective filing date for the '302 Patent is June 1, 2015, the filing date of the first provisional application (serial no. 62/169,112). Thus, the '302 Patent is subject to AIA and eligible for Post Grant Review.

IV. IDENTIFICATION OF CHALLENGE AND RELIEF REQUESTED (37 C.F.R. § 42.204(B) AND 37 C.F.R. § 42.22(A)(1))

The precise relief requested by Petitioner is that Claims 1-29 are found unpatentable and cancelled from the '302 Patent.

A. Claims for which Post-Grant Review is Requested (37 C.F.R. § 42.204(b)(2))

Petitioner requests Post Grant Review of Claims 1-29 of the '302 Patent.

B. Specific Statutory Grounds on which the Challenge is Based (37 C.F.R. § 42.204(b)(2))

The specific statutory grounds for the challenge are as follows:

Ground	Reference(s)	Basis	Claims Challenged
1		35 U.S.C. §112(a) Lack of enablement	1-29
2	Korman '401 (Ex. 1003), Singh (Ex. 1004), and Dong (Ex. 1005)	35 U.S.C. §103(a)	1-9, 12-17, 19-25, 27-28
3	Korman '401, Singh, Dong, and van der Waaij (Ex. 1010)	35 U.S.C. §103(a)	10, 11, 26
4	Korman '401, Singh, Dong, and Topalian (Ex. 1006)	35 U.S.C. §103(a)	18, 29
5	Korman '401, Kohwi (Ex. 1007)	35 U.S.C. §103(a)	1-4, 7-9, 12-17, 19-25, 27-28
6	Korman '401, Kohwi, Singh	35 U.S.C. §103(a)	5-6, 23-24
7	Korman '401, Kohwi, and van der Waaij	35 U.S.C. §103(a)	10, 11, 26

8	Korman ‘401, Kohwi, Topalian	35 U.S.C. §103(a)	18, 29
9	Korman ‘401, Mohania (Ex. 1008), Prakash ‘449 (Ex. 1009)	35 U.S.C. §103(a)	1-9, 12-17, 19-25, 27-28
10	Korman ‘401, Mohania, Prakash ‘449, and van der Waaij	35 U.S.C. §103(a)	10, 11, 26
11	Korman ‘401, Mohania, Prakash, and Topalian	35 U.S.C. §103(a)	18, 29

V. THE ‘302 PATENT (EXHIBIT 1001)

A. Summary of the ‘302 Patent

The ‘302 patent issued from U.S. application serial no. 15/170,284, filed June 1, 2016 and titled “Treatment of Cancer by Manipulation of Commensal Microflora.” The ‘302 patent claims priority to provisional application 62/169,112, filed on June 1, 2015 (Ex. 1012) and provisional application 62/248,741, filed on October 30, 2015 (Ex. 1013).

The ‘302 patent purports to describe methods of treating or preventing cancer in humans by manipulating levels of commensal microbes found in the gut, including commensal bacteria, to facilitate co-treatment with a “immune checkpoint inhibitor” – a known therapeutic agent to treat cancer. Ex. 1002 at ¶ 42.

While the ‘302 patent lists a broad range of bacteria spanning many different genera that may be used for the co-treatment (Ex. 1001 at 2:13-19), nearly all of the data reported in the ‘302 patent pertains to a single genus of bacteria, i.e.,

Bifidobacterium, and more specifically, to a few species of *Bifidobacterium.* Ex. *1002 at* ¶ 43.

The claims of the '302 patent claim a method of treating cancer in a human subject by co-administering to the subject an immune checkpoint inhibitor and a bacterial formulation comprising bacteria of the genus *Bifidobacterium*. Claim 1, the only independent claim of the '302 patent, recites:

> 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 at 41:62-64. The issued claims of the '302 patent thus recite three essential elements. Ex. 1002 at ¶ 44.

The first element of the claims is "treating cancer." Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. Ex. 1002 at ¶ 45.

The '302 patent lists 165 disorders and 22 broad categories of cancers and describes them as "[n]on-limiting examples of cancers that may be treated with the compositions and methods described herein." Ex. 1001 at 28:54-32:44. Ex. 1002 at ¶ 46.

The second element of the issued claims is the administration of an "immune checkpoint inhibitor." "Immune Checkpoint inhibition broadly refers to inhibiting

the immune checkpoints that cancer cells can produce to prevent or downregulate an immune response." Ex. 1001 at 24:18-20. Ex. 1002 at ¶ 47.

Immune checkpoints can be proteins such as "CTLA4, PD-1, PD-L1, PD-L2, A2AR, B7-H3, B7-H4, BTLA, KIR, LAG3, TIM-3 or VISTA." Ex. 1001 at 5:11-13. Ex. 1002 at ¶ 48.

An immune checkpoint inhibitor can be "a protein or polypeptide that binds an immune checkpoint" (Ex. 1001 at 5:8-10), including "antibodies or antigen binding fragments that bind to and inhibit an immune checkpoint protein." *Id*. at 24:23-25. The immune checkpoint inhibitor may also be "an interfering nucleic acid molecule" including "an shRNA molecule or an antisense RNA molecule." *Id*. at 5:17-20. Ex. 1002 at ¶ 49.

The '302 patent lists twelve immune checkpoint proteins as potential targets and 17 immune checkpoint inhibitors. Ex. 1001 at 24:16-30; *see also* 5:7-26. Ex. 1002 at ¶ 50.

The third element of the issued claims is the administration of a bacterial formulation comprising bacteria of the genus *Bifidobacterium*. The specification lists 36 species of *Bifidobacterium*. It also lists *Bifidobacterium* sp. – a reference to any yet to be discovered bacterium that would qualify as a *Bifidobacterium*. Ex. 1001 at 3:10-29. Ex. 1002 at ¶ 51.

Independent claim 1 and nearly all of the dependent claims[2] do not provide any restrictions on the route of administration for either the immune checkpoint inhibitor or the *Bifidobacterium* bacterial formulation. Moreover, the predominantly prophetic specification includes an extremely broad selection of administration routes. Ex. 1002 at ¶ 52.

With respect to the immune checkpoint inhibitor, the '302 patent provides a multitude of routes, including via injection, orally, topically, and via aerosol. Ex. 1001 at 28:30-34. Ex. 1002 at ¶ 53.

With respect to the *Bifidobacterium* bacterial formulation, the '302 patent similarly provides a multitude of routes: vaginal, oral, nasal, intrapulmonary, topical, and injection. Ex. 1001 at 4:56-60 and 19:19-24. Ex. 1002 at ¶ 54.

Independent claim 1 and nearly all of the dependent claims do not provide any restrictions on the dosage of either the immune checkpoint inhibitor or the

[2] Claim 29 limits the immune checkpoint route of administration to "intravenous injection, intramuscular injection, intratumoral injection or subcutaneous injection." Claims 5, 6, 23 and 24 limit the route of administration of the *Bifidobacterium* to oral or rectal administration.

Bifidobacterium bacterial formulation.[3] The predominantly prophetic specification provides an extremely broad selection of dosages. Ex. 1002 at ¶ 55.

With respect to the bacterial formulations, the '302 specification lists doses ranging from 10 to 10^{14} Colony Forming Units (CFUs). Ex. 1001 at 20:27-37 and 21:44 to 27:53. Ex. 1002 at ¶ 56.

With respect to the immune checkpoint inhibitor, the '302 specification does not provide any specific dosage information. Ex. 1002 at ¶ 57.

Independent claim 1 and nearly all of the dependent claims do not provide any restrictions on the frequency of administration of either the immune checkpoint inhibitor or the *Bifidobacterium* bacterial formulation.[4] The predominantly prophetic specification teaches a very broad range spanning from every minute to days. Ex. 1001 at 21:20-27, 21:37-44, and 27:8-17. Ex. 1002 at ¶ 58.

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[3] Claims 7 and 20 claim administering at least 5 x 10^6 CFU of *Bifidobacterium*.

[4] Claims 8 and 25 require administration of at least 2 doses of the bacterial formulation. Claim 9 requires the two or more doses to be separated by at least 1 week.

B. The Only Data in the '302 Patent Is Mouse Data

The experimental studies described in the '302 patent are limited to mouse experiments involving only two types of cancer (melanoma and bladder), one immune checkpoint inhibitor (αPD-L1 antibody), mouse feces containing *Bifidobacterium* and other gut bacteria that happen to be present in the feces, and a *Bifidobacterium* "cocktail" comprising a few different commercially available species of *Bifidobacterium*. Ex. 1001 at 33:37-40:62. Ex. 1002 at ¶ 58.

More specifically, in C57BL/6 mice obtained from two different sources that were known to have distinct gut microbiota, Jackson Laboratory ("JAX") and Taconic Farms ("TAC"), B16 melanoma growth was assayed. The JAX mice showed a robust anti-tumor immunity whereas the TAC mice showed a weak anti-tumor immunity. Ex. 1001 at 16:38-41. Upon further analysis of the microbiota of the JAX and TAC mice, the patentee identified the bacteria *Bifidobacterium* as being associated with the JAX anti-tumor effects. Ex. 1001 at 16:41-44. Ex. 1002 at ¶ 60.

The inventors tested the transfer of JAX-fecal material alone or in combination with αPD-L1 antibody on established tumors in TAC mice. They found JAX-fecal matter alone slowed tumor growth, increased tumor-specific T-cell, and increased infiltration of antigen-specific T-cells into the tumor. The JAX-fecal transfer in combination with intraperitoneally administered αPD-L1 antibody immune checkpoint inhibitor had an additive effect on slowed tumor growth and

increased tumor-specific T-cells, but not on infiltration of antigen-specific T cells into the tumor. Ex. 1001 at 36:56-37:9. Ex. 1002 at ¶ 61.

Since the patentee identified the bacteria *Bifidobacterium* as being associated with the JAX anti-tumor effects, they then tested in mice an orally administered *Bifidobacterium* cocktail of four different species *(B. bifidium, B. longum, B. lactis, and B. breve)* alone as well as in combination with the intraperitoneally administered αPD-Ll antibody that functions as an immune checkpoint inhibitor by targeting the immune checkpoint ligand PD-L1. The inventors reported that oral administration of the *Bifidobacterium* cocktail alone or in combination with the intraperitoneally administered αPD-Ll antibody immune checkpoint inhibitor improved tumor volume reduction and that the combination resulted in an additive effect. Ex. 1001 at 38:12-35. Ex. 1002 at ¶ 62.

The inventors also reported that the commercially available cocktail of four strains of *Bifidobacterium* stimulated the immune system, and more specifically, dendritic cell function, resulting in an increase in activated cytolytic T cells whose function is to kill tumor cells. Ex. 1001 at 40:34-53. Ex. 1002 at ¶ 63.

C. Prosecution of the ‘302 Patent and a Continuing Application of the ‘302 Patent

1. Prosecution of US Patent Application 15/170,284 Which Issued as the ‘302 Patent

The ‘302 patent was filed on June 1, 2016 and given application serial no. 15/170,284. Ex. 1014. The application set forth 30 claims, of which claims 1 and 20 were independent. Claim 1 is recited below.

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

Ex. 1014 at 1455-1458.

A first Office Action issued on November 4, 2016 in which the claims were rejected on §103 grounds. Ex. 1014 at 1302-1310. The Examiner alleged that Sharon *et al.* (Chin. J. Cancer. 2014. 33(9):434-444; (“Sharon;” Ex. 1016)) in view of O’Mahony *et al.* (US Patent Application 2012/0276143; (“O’Mahony;” Ex. 1017) rendered pending claims 1-30 obvious. According to the Examiner, Sharon taught a method of treating cancer comprising administering to the subject an immune checkpoint inhibitor such as PD-1 and PD-L1 targeting agents. O’Mahony taught *Bifidobacterium* strains may be significantly immunomodulatory following oral consumption in humans and *Bifidobacterium* strains could be used in the prophylaxis and/or treatment of gastrointestinal cancer(s). Thus, according to the Examiner, it would have been obvious to incorporate O’Mahony’s *Bifidobacterium* into Sharon’s

method for treating cancer with an immune checkpoint inhibitor because it was already known that such a bacterial species was known to treat cancer. *Id.* at 1307. Ex. 1002 at ¶ 65.

On February 6, 2017, applicant filed a response and argued there was no suggestion to co-administer the immune checkpoint inhibitor of Sharon and *Bifidobacterium of O'Mahony*. Applicant argued that Sharon's administration of its immune checkpoint inhibitor promoted an immune response by inhibiting the immune checkpoint controls whereas O'Mahony's administration of its *Bifidobacterium* to treat cancer suppressed an immune response by exhibiting anti-inflammatory properties. Ex. 1014 at 123-134. Ex. 1002 at ¶ 66.

On March 28, 2017, the Examiner issued a Final Office Action (Ex. 1014 at 101-114) and maintained the outstanding rejection. The Examiner asserted that it would have been obvious to co-administer the immune checkpoint inhibitor of Sharon and *Bifidobacterium of O'Mahony* because both had been suggested as agents to treat cancer. Further, a POSITA would have possessed a reasonable expectation of success by combining both components because the prior art combination therapy was well known to produce beneficial and even synergistic results. *Id. at* 106. Ex. 1002 at ¶ 67.

On June 28, 2017, Applicant filed an amendment (Ex. 1014 at 87-95) and amended claim 1 to emphasize that the *Bifidobacterium* was immunostimulatory and that it would enhance the immune response. The amended claim reads:

> 1.(currently amended) A method of treating cancer in a human subject comprising administering to the subject an immune checkpoint inhibitor and an immunostimulatory bacteria of the genus ~~a bacterial formulation comprising bacteria of the genera~~ *Bifidobacterium*, such that the bacteria enhance immune response in the subject to treat the cancer.

Ex. 1014 at 88. Ex. 1002 at ¶ 69.

Applicants argued, once again, "…that [a POSITA] would not combine Sharon *et al.* with O'Mahony *et al.*… [because' Sharon *et al.* describes promoting an immune response while O'Mahony *et al.* describes the suppression of immune response." Ex. 1014 at 92. Ex. 1002 at ¶ 70.

On July 19, 2017, the Examiner issued an Advisory Action in which the proposed amendments were not entered because they raised new issues. Ex. 1014 at 74. Ex. 1002 at ¶ 71.

On September 18, 2017, Applicant submitted a response (Ex. 1014 at 57-65) and asserted, once again, that a POSITA would not be motivated to combine Sharon and O'Mahony because O'Mahony describes inhibition of the immune response whereas Sharon describes stimulation of the immune response. Ex. 1002 at ¶ 74.

On September 29, 2017, the Examiner issued a Notice of Allowance (Ex. 1014 at 29-36), presumably on the basis of applicant's repeated assertions that a POSITA

would not have been motivated to combine Sharon with O'Mahony because Sharon describes promoting an immune response whereas O'Mahony describes the suppression of an immune response.

Applicant's assertion that O'Mahony teaches suppression of an immune response, however, is incomplete and misleading. O'Mahony shows that while *Bifidobacterium longum* strain 1714 exhibited immnosuppressive properties, *Bifidobacterium longum* strain UCC356624 exhibited immunostimulatory properties. Ex. 017. at [0103-0109]. Indeed, O'Mahony states that the properties of *Bifidobacterium longum* are "strain specific." Id. at [109] Thus, contrary to assertions of applicant, O'Mahony did teach immunostimulatory *Bifidobacterium* longum strains. In addition, other prior art apparently not before the Examiner showed various species and/or strains of *Bifidobacterium* possessing immunostimulatory properties. Ex. 1002 at ¶ 77.

D. Prosecution of Child US Patent Application 15/718,735

Pending U.S. patent application 15/718,735 ("735 application;" Ex. 1015) is a continuation of U.S. patent application 15/170,284, which issued as the '302 patent. The filed claims were directed to a method of treating cancer comprising administering an immune checkpoint inhibitor and a bacteria formulation comprising a bacteria of the genus *Bifidobacterium*. Ex. 1015 at pp. 262-263.

A first Office Action issued on November 15, 2017 (Ex. 1015 at 126-137). The claims were rejected under §103 for being rendered obvious by Korman *et al.* (US Patent publication 2009/01217401 (Korman '401; Ex. 1003)) in view of Mohania *et al.* "Modulation of expression of Programmed Death-1 by Administration of Probiotic Dahi in DMH-Induced Colorectal Carcinogenesis in Rats," ACTA BIOMED, 84:102-109, 2013 ("Mohania;" Ex. 1008), and Prakash *et al.* (US Patent publication 2010/0028449 ("Prakash; Ex. 1009"). The Examiner asserted that Korman taught methods of treating cancer using anti-PD-1 antibodies. Mohania taught the oral consumption of probiotic Dahi (fermented milk with *Lactobacillus acidophilus* LaVK2 and *Bifidobacterium bifidus* BbVK3) decreased expression of PD-1 antigen and could be used as an effective chemopreventative agent in the management of colorectal cancer. Prakash taught a method of treating a patient suffering from cancer with an oral formulation of *Bifidobacteria*. Therefore, according to the Examiner, it would have been *prima facie* obvious to incorporate the ***Bifidobacteria*** of Mohania and Prakash into Korman's method of administering an immune checkpoint inhibitor to treat cancer in a human subject. Ex. 1015 at 129-133. Ex. 1002 at ¶ 79.

On December 13, 2017, Applicant filed an amendment, canceled all pending claims, and added new claims 20-49. Ex. 1015 at 111-117. Dropping all references to *Bifidobacterium*, the newly submitted claims recite a method of treating cancer in

a human subject by co-administering an immune checkpoint inhibitor and a bacterial formulation comprising bacteria of the genus … *Lactobacillus*. *Id.* at 112-116. Ex. 1002 at ¶ 80.

On January 8, 2018, the Examiner issued a second Office Action. (Ex. 1015 at 89-102) and rejected claims 20-39 based on the same previously cited references. The Examiner asserted that Korman taught methods of treating cancer using anti-PD-1 antibodies. Mohania and Prakash taught oral compositions comprising *Lactobacillus* in the treatment of cancer. Therefore, according to the Examiner, it would have been obvious to incorporate the ***Lactobacillus*** of Mohania and Prakash into Korman's method of administering an immune checkpoint inhibitor to treat cancer in a human subject. *Id.* at 92-97. Ex. 1002 at ¶ 81.

Claims 40-49 were also rejected on obviousness grounds. Claim 40-49 were similar to claims 20-39, except for the genus of bacteria administered. Claims 40-49 claimed co-administering a bacterial formulation comprising bacteria of the genus *Rikenella, Alistipes, Marinilabilia,* or *Anaerostipes*. Ex. 1002 at ¶ 82.

The Examiner asserted that Korman in view of Mohania and Prakash as applied to claims 20-39 in further view of Duncan (US Patent Publication 2007/0258953 ("Duncan; Ex. 1018)) rendered claims 40-49 obvious. The Examiner asserted that Duncan taught a prophylactic method of reducing the incidence or severity of colorectal cancer in a mammal by administering the bacteria

Anaerostipes caccae, and thus, it would have been obvious to incorporate Duncan's *Anaerostipes caccae* bacteria to treat colorectal cancer to the method of Korman, Mohania, and Prakash. Ex. 1015 at 97-100. Ex. 1002 at ¶ 83.

On March 8, 2018, Applicant submitted a response (Ex. 1015 at 75-84) and asserted that Korman '401 mediates its effect by having an anti-PD-1 antibody bind to PD-1. Thus, Korman '401 requires the presence of PD-1. Mohania mediates its effect by downregulating PD-1, i.e., by inducing the absence of PD-1. Therefore, according to Applicant, a POSITA would not have been motivated to combine the teachings of Korman and Mohania because they taught opposing mechanisms of action. Ex. 1015 at 81-84. Ex. 1002 at ¶ 84.

A Final Rejection was issued on April 30, 2018 in which the Examiner maintained the obviousness rejections. Ex. 1015 at 56-72. The Examiner expressly rejected applicant's argument, explaining that the PD-1 checkpoint inhibitor of Korman '401 and *Lactobacillus* of *Mohania* both reduce PD-1 activity, and therefore, the combination would be expected to be useful to treat cancer. Therefore, the claims were obvious. Ex. 1015 at 58-72. Ex. 1002 at ¶ 85.

On June 29, 2018, Applicant filed a response amending the claims. Ex. 1015 at 45-52. Apparently conceding that Korman in view of Mohania and Prakash rendered obvious the administration of *Lactobacillus* or *Anaerostipes* in combination with an immune checkpoint inhibitor to treat cancer in a human subject,

applicant amended the claims to exclude sole administration of *Lactobacillus* or *Anaerostipes* in combination with an immune checkpoint inhibitor. Applicant then argued that the amendments overcame the §103 rejection as the cited art did not teach or suggest, individually or in combination, the subject matter of the amended claims. Ex. 1015 at 45-51. Ex. 1002 at ¶ 86.

On July 20, 2018, the Examiner issued an Advisory Action refusing entry of the amendments, asserting that the proposed amendments required further search. Ex. 1015 at 38-39. Ex. 1002 at ¶ 87.

On July 24, 2018, Applicant submitted an RCE and presented the same claims and arguments it presented in the June 29, 2018 response. Ex. 1015 at 20-39. Ex. 1002 at ¶ 88.

On August 24, 2018, a Non-final Office Action issued. Ex. 1015 at 1-16. The Examiner withdrew the §103 rejection of claims 20-49 under Korman ‘401, in view of Mohania and Prakash and proffered a new rejection. Claims 20-49 were rejected under §103 as being unpatentable over Stritzker *et al.* (US Patent Publication 2008/0193373 (Stritzker ‘373; Ex. 1039) in view of Korman ‘401. The Examiner asserted that Stritzker taught methods of treating cancer using a combination comprising *Nissle* bacterium and an anti-tumor or anti-cancer agent. Stritzker also taught use of other bacteria employed in the methods including *E. coli*, *Bacteriodes, Eubacterium, Fusobacterium, Lactococcus*, and/or *Lactobacillus*. Korman ‘401

taught methods of treating cancer using anti-PD-1 antibodies. The Examiner asserted that it would have been *prima facie* obvious to incorporate the Korman '401 anti-cancer immune checkpoint inhibitors with Stritzker's method of treating cancer with a bacterial formulation when it was already known to treat cancer with bacterial formulations in combination with anti-cancer therapies. Ex. 1015 at 1-15. Ex. 1002 at ¶ 89.

VI. THE STATE OF THE ART

A. It Was Known At The Time Of The Invention That Cancer Is A Term Covering A Variety Of Specific Diseases With Disparate Etiologies, Outcomes, And Therapies And that Cancer Treatment Is Highly Unpredictable

Cancer is a complex set of diseases caused by the abnormal, unregulated growth of cells. Abnormal, unregulated growth can develop in tissues when an injured or aberrant cell does not follow the natural process of cell death, and the cell is able to reproduce in an uncontrolled manner. These growths are tumors. Ex. 1002 at ¶ 93.

Tumors can be benign or malignant. *See* Mosby's Medical dictionary 8th edition at 204, (2009) (Ex. 1019). The difference between them is a benign tumor does not invade the tissue around it while a malignant tumor is associated with the capacity to invade neighboring tissues and metastasize (move) to different sites in the body. *Id.* at 1136, 1180. The term cancer is associated with these malignant

characteristics. Dorland's Illustrated Med. Diction. 31st ed. at 284, (2007), Ex. 1020. Ex. 1002 at ¶ 94.

There are many different kinds of cancers, including carcinomas, sarcomas, lymphomas, leukemias, and germ cell tumors. The most common cancers are carcinomas, which are cancers derived from the epithelium—skin, glands, or other lining elements and organs in our bodies. Ex. 1020 at 295-297. Breast cancer, lung cancer, and prostate cancer are categorized as epithelial tumors (carcinoma), but they are very different diseases. Even within each tissue type, many different subtypes can occur, each displaying a different morphology, sub-type treatment plans, and prognosis. In addition, there are inter- and intra-individual heterogeneity of particular cancer subtypes, with distinct combinations of driver and modifier gene mutants and signaling pathways, and concordant treatments targeting those genes and pathways. Kandoth, C., *et al.* (2013), "Mutational landscape and significance across 12 major cancer types." Nature 502(7471): 333-339, Ex. 1021. The granularity of cancer typing is evidence of the diverse nature of cancer. Ex. 1002 at ¶ 95.

Because the types of cancers and ways in which they develop are so varied, each cancer type requires different treatment approaches. For example, cancer therapy can involve radiation, surgery, and/or chemical or biological agents. Chemical/biological agents can have diverse targets such as DNA synthesis,

microtubules, cell surface receptors, or intracellular signaling molecules. *See* Kumar *et al.*, "Drug Targets for Cancer Treatment: An Overview," Med. Chem. 5(3), 115–123 (2015), Ex. 1022. Some cancers are treated with multiple therapies, where each therapy attacks the cancer using a different mechanism of action. Ex. 1002 at ¶ 96.

One class of cancer therapies is small molecule chemotherapeutics, which are compounds with a low molecular weight that affect biological processes. Chemotherapeutics are often agents that interfere with cell division and therefore kill rapidly dividing cells such as cancer cells. Chemotherapeutics often have highly toxic side effects because they can damage normal dividing cells as well. *See* Ex. 1022. Ex. 1002 at ¶ 97.

Targeted therapeutics describe another class of cancer treatment, and are specifically designed to preferentially target cancer cells. These therapies are typically directed to a specific type, or even sub-type of cancer, as compared to small molecule chemotherapeutic treatments, which are often used to treat many types of cancer. Targeted Cancer Therapies, National Cancer Institute, https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-factsheet, Ex. 1023. Ex. 1002 at ¶ 98.

Many targeted therapeutic agents are biologics, which are large molecules that are often, and most typically, antibodies. *See* Scott *et al.*, "Monoclonal antibodies in cancer therapy," Cancer Immunity Commentary (12):14 (2012), Ex. 1024.

Through monoclonal antibody engineering and recombinant antibody engineering, scientists have been able to custom design antibodies to target proteins that are selectively expressed or overexpressed by cancer cells so that those cancer cells can be specifically targeted for a range of therapeutic approaches. *See* Neves *et al.*, "Recent advances in the field of anti-cancer immunotherapy," BBA Clinical. 3:280-288 (2015), Ex. 1025. Ex. 1002 at ¶ 99.

Yet another class of cancer therapeutics is immune checkpoint inhibitors. Immune checkpoints are a normal part of pathways in the immune system. Tumors co-opt certain immune-checkpoint pathways as a mechanism of immune evasion, particularly evading T cells that are specific for tumor antigens. T cells are a type of cell that play a central role in cell-mediated immunity. They have a receptor on their surface called a T cell receptor. This is important in the function of T cells to scan the body for foreign cells or tumor cells. Tumor cells evade T cells by presenting proteins that prevent them from being recognized by T cells. Immune checkpoint inhibitors block these proteins on tumor cells or the proteins on T cells that respond to them. The result is to remove the blinders that prevented T cells from recognizing the cells as cancerous and leading an immune system assault on them. Pardoll, "The blockade of immune checkpoints in cancer immunotherapy," Nat Rev Cancer; 12(4): 252–264. (2012), Ex. 1026. Ex. 1002 at ¶ 100.

There are many immune checkpoint proteins that have been and are still being discovered. These include PD-1, CTLA-4, A2AR, B7-H3, B7-H4, BTLA, KIR, LAG3, TIM-3, VISTA, and IDO. These serve as targets for the development of immune checkpoint inhibitors. *See* Figure 1 and Table 1 of Ex. 1026. Ex. 1002 at ¶ 101.

Two of the most well studied immune checkpoints, CTLA-4 and PD-1 are described, for example, in Figure 3 of Ex. 2016. The cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)-mediated immune checkpoint is induced in T cells at the time of their initial response to antigen. CTLA-4 functions as a signal dampener to maintain a consistent level of T cell activation in the face of widely varying concentrations and affinities of ligand for the TCR. It also reduces effective T cell activity due to its role in induction and maintenance of regulatory T cells. In contrast, the major role of the programmed cell death protein 1 (PD-1) pathway is not at the initial T-cell activation stage but rather to regulate inflammatory responses in tissues by effector T-cells recognizing antigen in peripheral tissues. Activated T-cells upregulate PD-1 and continue to express it in tissues. Inflammatory signals in the tissues induce the expression of PD-1 ligands, which downregulate the activity of T cells, and thus limit collateral tissue damage in response to a microorganism infection in that tissue. Ex. 1002 at ¶ 102.

There are multiple additional immune checkpoints. Ex. 1026 at 2. Because there are many immune checkpoint proteins, there are many potential immune checkpoint inhibitors. There is data on a few that show ability to treat a limited number of cancers and others are still in clinical trials and undergoing basic research analysis. Ex. 1026 at Figure 1. Ex. 1002 at ¶ 103.

Developing a cancer therapy is a very difficult and complicated process for two reasons. First, formidable cell biology and medicinal chemistry must be overcome to create a therapeutic for a particular target. Second, as outlined above, there are many different cancer subtypes and further intra- and inter-individual heterogeneity, reflecting great variability in available treatment targets for an individual patient. Developing a successful treatment requires substantial time and money, and many proposed treatments ultimately fail at some point in the development process. *See* DiMasi *et al.*, "Economics of New Oncology Drug Development," J.Clin. Onc. 25(2), 209–216 (2007), Ex. 1027. Ex. 1002 at ¶ 104.

Cancer and cancer therapy are highly unpredictable. Results seen in one cancer cannot be assumed to occur in another cancer without experimental proof. Ex. 1002 at ¶ 105.

B. It Was Known At The Time Of The Invention That Immune Checkpoint Inhibitors Work Only On A Subset Of Cancers And Are Highly Unpredictable

While immune checkpoint inhibitors have received much attention, their utility as a cancer therapy has only been proven in a limited number of cancers, such as melanoma, bladder cancer, non-small cell lung cancer, and colorectal cancer. In addition, these therapies have only been proven effective in a subset of patients with those specific cancers. In other words, even with data showing an immune checkpoint inhibitor capable of treating non-small cell lung carcinoma, for example, that same immune checkpoint inhibitor does not successfully treat all patients with non-small cell lung carcinoma. Similarly, only a subset of colorectal patients are responsive to immune checkpoint inhibitors. *See e.g.* Thungappa *et al.*" Immune checkpoint inhibitors in lung cancer: the holy grail has not yet been found…." ESMO Open 2017;2 Ex. 1028; Rizvi *et al.* "Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer," Science. 2015 April 3; 348(6230): 124–128. Ex. 1029; Brahmer *et al.* "Phase I Study Of Single-Agent Anti-Programmed Death-1 (MDX-1106) In Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, And Immunologic Correlates." J Clin Onc. 2010; 28: 3167-75, Ex. 1030; D.T. Le *et al.* 2015, May 30, "PD-1 Blockade in Tumors with Mismatch-Repair Deficiency," 372(26): 2509-2520, Ex. 1031. Ex. 1002 at ¶ 106.

Immune checkpoint inhibitors are not interchangeable because they can act on different aspects of the immune checkpoint pathway. Furthermore, not all immune checkpoint inhibitors affect all cancers or even all patients with the same cancer. Ex. 1002 at ¶ 107.

Clinical studies showed that PD-1 inhibitors shrink tumors in only about 20-30% of lung cancer patients. *See* Kaiser, "Why a powerful cancer drug only helps some patients," Science. doi:10.1126/science.aab0310, March 12, 2015. (Ex. 1032). Research showed that patients were more likely to respond to a PD-1 blockade if their tumor had higher levels of nonsynonymous mutations, potentially thereby creating neoantigenic targets for immune attack. *See* Ex. 1029. Studies in malignant melanoma patients showed tumors with elevated neoantigen levels correlated with a strong response to CTLA-4 blockade. *See* Snyder *et al.*, "Genetic basis for clinical response to CTLA-4 blockade in melanoma," NEJM, 371(123):2189-2199. (2014), Ex. 1033. Ex. 1002 at ¶ 108.

The conclusion from these types of studies is that not all patients with a particular cancer respond to a particular immune checkpoint inhibitor. By June 2015 or even June 2016 immune checkpoint inhibitors were relatively new. Only a few had been studied or tested and shown to work on a small subset of cancers. Furthermore, immune checkpoint inhibitors did not work on all patients with those

cancers. In sum, the use of immune checkpoint inhibitors to treat cancers in humans was highly unpredictable as of June 2015 and is still so today. Ex. 1002 at ¶ 109.

C. It Was Known at the Time of the Invention that Gut Microbiota Influence Health and the Immune System in Unpredictable Ways.

It was known that bacteria in the gut ("gut microbiota") influence the immune system in a number of ways and are necessary for the development and maintenance of a healthy immune system. In addition to well-established immune-stimulatory effects of the gut microbiota, the presence of certain species of bacteria with immunomodulatory effects had been described. These organisms are permanent members of the microbiota and affect host immune homeostasis in distinct ways. *See e.g.* Ivanov *et al.* "Intestinal commensal microbes as immune modulators," Cell Host Microbe. 12(4): 496-508 (2012), Ex. 1034; Hooper *et al.* "Interactions between the microbiota and the immune system" Science. 336(6086):1268-1273, June 2012, Ex. 1035; Honda *et al.* "The Microbiome in Infection Disease and Inflammation," Annu Rev. Immunol. 30:759-795. 2012, Ex. 1036. Ex. 1002 at ¶ 110.

The distinct ways the gut microbiota affects the host immune system is on the development and function of various immune cell populations, including IgA-secreting plasma cells, Th17 cells, regulatory T (Treg) cells, invariant natural killer T (iNKT) cells, γδT cells, NK cells, macrophages, dendritic cells (DCs), and innate lymphoid cells (ILCs). *See* Ex. 1036 at 16-24. Ex. 1002 at ¶ 111.

The gut microbiota is a term encompassing all gut bacteria but only four phyla dominate the adult human intestine: Bacteroidetes (including *Bacteroides*); Firmicutes (including *Clostridium*, *Lactobacillus*, and *Bacillus*); Proteobacteria (including *Escherichia*); and Actinobacteria (including *Bifidobacterium*). *See* Eckburg *et al.* "Diversity of the human intestinal microbial flor" Science. 308:1635–-38 2005, Ex. 1037 at 2. Ex. 1002 at ¶ 112.

With respect to *Bifidobacteria*, research showed that intestinal *Bifidobacterium longum* could promote DC maturation and its expression of IL-12 locally in the gut, influence T-cell development in the thymus, favor the T-helper cell response of the body in a Th1 type and ensure of the development of Treg response in the gut, and enhance antibody synthesis by peripheral blood mononuclear cells. Dong *et al.* "The role of intestinal Bifidobacteria on immune system development in young rats," Early Human Dev. 86:51-58. 2010, Ex 1005. Ex. 1002 at ¶ 113.

Additional work in the field showed that distinct *Bifidobacterium* strains drive different immune responses *in vitro*. *See* Lopez *et al.* "Distinct *Bifidobacterium* strains drive different immune responses *in vitro*," Intern.J.Food.Microbio. 138:157-165. 2010, Ex. 1038. The *in vitro* effect of 12 *Bifidobacterium* strains belonging to 4 different species, *Bifidobacterium longum*, *Bifidobacterium breve*, *Bifidobacterium bifidum* and *Bifidobacterium animalis* subsp. *lactis*, on the

maturation pattern of human monocyte-derived dendritic cells (DCs), as well as in their ability to induce cytokine secretion was examined. Ex. 1002 at ¶ 114.

The data showed the *Bifidobacteria* strains were able to induce full DC maturation but there were significant differences in the maturation markers among different strains and in the pattern of cytokine production. For instance, DCs exposed to *B. animalis* subsp. *lactis* and *B. longum* induced in general an elevated IL-12 secretion, very low IL-10/ IL-12 and IL-1β/IL-12 ratios and relatively high TNFα/IL-10 balance. DC maturation with most of the *B. bifidum* strains (IF 10/10, A8 and L22), *B. breve* LMG13208 and *E. coli* induced low IL-12 production, leading to the highest IL-1β/IL-12 and IL-10/IL-12 ratios, a profile that could be suggestive of a Th17 or a Th2/ regulatory T cell differentiation. Ex. 1038 at 162-163. Ex. 1002 at ¶ 115.

O'Mahony showed that *Bifidobacterium longum* subspecies infantis strain UCC356624 was immunostimulatory whereas *Bifidobacterium longum* strain 1714 was immnosuppressive or anti-inflammatory. *Bifidobacterium longum* strain UCC356624 had "quite a different pattern" for immunostimulatory cytokines IL-12, IFNγ and IL-6 than *Bifidobacterium longum* strain 1714. Consistent with those results, O'Mahony states that "the in vivo protection observed was strain specific". *See* Ex. 1017 at [0103-0109], [0108]. Ex. 1002 at ¶ 116.

As shown above, different species of *Bifidobacteria,* and even different strains of the same species of *Bifidobacteria,* affect the immune system in different and unpredictable ways, e.g., some are immunostimulatory whereas others are immunosuppressive. Ex. 1002 at ¶ 117.

D. It Was Known at the Time of the Invention that Some Species and Strains of *Bifidobacterium* Had Anti-Tumor Activity

It was well known by 2015 that some species and strains of *Bifidobacterium* had anti-tumor activity. Ex. 1002 at ¶ 118.

Kohwi *et al.* showed that two strains of *Bifidobacteria*, *Bifidobacterium infantis* and *Bifidobacterium adolescentis,* exhibited "a remarkable antitumor effect on Meth-A sarcoma cells." Kohwi *et al.* "Antitumor effect of *Bifidobacterium Infantis* in Mice" Gan. 69(5):613-8. 1978, ("Kohwi;" Ex 1007), Abstract. Ex. 1002 at ¶ 119.

Mice were injected intraperitoneally or subcutaneously with Meth-A sarcoma cells and with *Bifidobacterium infantis* or *Bifidobacterium adolescentis* or without either. The data showed that after day 8, many of the established tumors underwent complete or partial regression in mice treated with *B. infantis* and *B. adolescentis* while tumors in the control group went on to kill the mice. Ex. 1007. Ex. 1002 at ¶ 120.

Reddy *et al.* showed the inhibitory effect of *Bifidobacterium longum* on colon, mammary, and liver carcinogenesis induced by a quinoline compound known to be

a food mutagen. Experimental rats were fed a high fat diet with or without lyophilized cultures of *B. longum* and with or without IQ (quinoline compound that induces carcinogenesis). The data showed dietary *B. longum* significantly inhibited IQ-induced incidence (percent of animals with tumors) of colon (100%) and liver (80%) tumors in male rats and multiplicity (tumors/animal) of colon, liver, and small intestinal tumors. Multiplicity of mammary tumors was significantly inhibited in female rats fed the diet containing *B. longum*. Reddy *et al.* "Inhibitory effect of *Bifidobacterium longum* on Colon, Mammary, and Liver Carcinogenesis Induced by 2-Amino-3-methylimidazo[4,5-f]quinolone, a Food Mutagen," Cancer Res. 53: 3914-3918, Sept. 1993 ("Reddy;" Ex. 1040). Ex. 1002 at ¶ 121.

Singh *et al.* showed that "oral administration of *Bifidobacterium longum* exerts strong antitumor activity… Singh *et al.* "*Bifidobacterium longum*, a lactic acid-producing intestinal bacterium inhibits colon cancer and modulated the intermediate biomarkers of colon carcinogenesis," Carcinogenesis. 18(4): 8330841, 1997, ("Singh;" Ex. 1004), Abstract. Singh showed that daily oral administration of "lyophilized cultures of B. *longum* … equivalent to 4 x 10^{10} live cells/g diet" (Id at p. 2, 2nd col.) resulted in "significant suppression of colon tumor incidence, tumor multiplicity, and reduced tumor volume. Abstract, p. 1. Ex. 1002 at ¶ 122.

Lee *et al.* showed an extract of *Bifidobacterium adolescentis* SPM0212 (strain) had anti-proliferative effects on human colon cancer cell lines. Cultures of

B. adolescentis SPM0212 were lyophilized, re-suspended, and extracted with a variety of solvents. The n-butanol extracted sample showed suppression activity in a tumor cell proliferation assay. Data showed the extract inhibited proliferation of three colon cancer cell lines. *See* Lee *et al.* “”Anti-proliferative effects of *Bifidobacterium adolescentis* SPM0212 extract on human colon cancer cell lines,” BMC Cancer, 8:310 Oct. 2008 (“Lee;” Ex. 1011). Ex. 1002 at ¶ 123.

Mohania *et al.* tested the effect of a fermented milk product (Dahi) on PD-1 expression in the colorectum of rats having colorectal carcinogenesis induced by 1,2-dimethylhydrazine (DMH). PD-1 expression was shown to be reversed with oral administration of the fermented milk product (Dahi) which contained Lactobacillicus acidophilus (LaVK2) and *Bifidobacterium bifidum* BbVK3). Mohania *et al.* “Modulation of expression of Programmed Death-1 by administration of probiotic Dahi in DMH-induced colorectal carcinogenesis in rats,” ACTA BIOMED, 84:102-109, 2013 (“Mohania;” Ex. 1008). Ex. 1002 at ¶ 124.

Mohania concluded that the study suggests that probiotic Dahi can be used as an effective chemopreventive agent in the management of colorectal cancer. Ex. 1008, Abstract, p 1. Ex. 1002 at ¶ 125.

As shown above, the prior art taught that certain species and/or strains of *Bifidobacterium* species possessed antitumor activity. Ex. 1002 at ¶ 126.

VII. THE CLAIMS OF THE '302 PATENT ARE INVALID

A. (Ground 1) Claims 1-29 Are Invalid for Failing to Meet the Enablement Requirement Under §112(a)

To satisfy the enablement requirement of §112(a), "the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). "Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation." *Wyeth & Cordis Corps. v.Abbott Labs*., 720 F.3d 1380, 1384 (Fed. Cir. 2013). "It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997)

Undue experimentation factors 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." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors are merely illustrative; an individual case must turn on its facts. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

"A patentee who chooses broad claim language must make sure the broad claims are fully enabled." *Sitrick v. Dreamworks, LLC,* 516 F.3d 993, 999 (Fed. Cir. 2008)

In the present case, the specification fails to provide this adequate enablement. The relevant Wands factors all support Petitioner's position that undue experimentation would be required to practice the full scope of the claimed invention, rendering claims 1-29 invalid for lack of enablement under 35 U.S.C. §112(a).

B. Wands Factor Analysis

1. The Nature of the Invention - Treating Cancer In A Human Subject

The invention is drawn to a method of treating cancer in a human subject by administering a combination of an immune checkpoint inhibitor and a bacterial formulation comprising the genus *Bifidobacterium*. Ex. 1002 at ¶ 129.

Claims 1-29 do not limit the type of cancer treated or the genera of *Bifidobacterium* to be administered. Nor do the claims, except for a few, provide any restrictions on the immune checkpoint inhibitor administered. Ex. 1002 at ¶ 130.

The predominantly prophetic '302 specification presents hypotheses that the claimed methods of treatment could work based on a few mouse experiments performed in the laboratory. Ex. 1002 at ¶ 131.

2. The Level of Ordinary Skill in the Art Is High

The level of ordinary skill in the art in the field of this purported invention is high: an ordinary skilled artisan needs specialized knowledge of cancer, immunology, and microbiota. Ex. 1002 at ¶ 132.

Developing and testing a cancer therapeutic is difficult, complicated, and highly unpredictable because there are many different cancers, each with different etiologies, development, and treatment. Only a few immune checkpoint inhibitors had been shown to work. And those that had been shown to work worked only in a small subset of cancers. Further, for some of the cancers, the immune checkpoint inhibitors worked only for a small subset of patients having those cancers. Ex. 1002 at ¶ 133.

Furthermore, there is strain and species specificity as it relates to effects of *Bifidobacteria* on tumors and the immune system. Thus, determining the efficacy of a combination of immune checkpoint inhibitors and a bacterial formulation comprising the genus of *Bifidobacterium* in the treatment of cancer requires a high level of skill. Ex. 1002 at ¶ 134.

3. The Claims Are Extremely Broad - Treating All Cancers With All Immune Checkpoint Inhibitors and All Species of *Bifidobacterium*

The scope of the claims is extremely broad, covering thousands of different combinations of cancers, immune checkpoint inhibitors, and genera of *Bifidobacterium*. Ex. 1002 at ¶ 136.

Claim 1 recites:

> 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*.

Claims 1-29 cover a method of treating cancer. None of the claims specifies the cancer to be treated. Thus, the claims cover treating all types of cancer. The specification provides an exemplary list of more than 165 cancers that are allegedly treatable by the claimed invention. As previously noted, cancers have different etiologies, mechanisms of development, respond differently to cancer therapies, and require different treatment approaches. Ex. 1002 at ¶ 138.

Claims 1-11 and 19-26 cover a method of treating cancer by administering an immune checkpoint inhibitor. None of these claims specifies the immune checkpoint inhibitor to be used. Thus, the claims cover treating all types of cancer with all entities that function as immune checkpoint inhibitors. Ex. 1002 at ¶ 139.

Immune checkpoint inhibitors are a broad class of agents that include proteins, including antibodies and antibody fragments, and nucleic acids, where the

underlying commonality is simply the ability to function as an inhibitor of an immune checkpoint protein. The specification provides an exemplary list of 12 immune checkpoint proteins and 17 immune checkpoint inhibitors. As explained in ¶107, s*upra*, immune checkpoint inhibitors are not interchangeable in their ability to treat cancer. Ex. 1002 at ¶ 140.

Claims 12-18 and 27-29 further define the immune checkpoint inhibitors. Claims 12 and 15, respectively, define the immune checkpoint inhibitor solely by its function, i.e., "a protein or polypeptide that binds to an immune checkpoint protein" or "an antibody or antigen binding fragment thereof that binds to an immune checkpoint protein." These functional dependent claims represent a nearly limitless number of possible immune checkpoint inhibitors. Ex. 1002 at ¶ 141.

Claims 13 and 16 (which depend from claims 12 and 15, respectively) recite, *inter alia*, "…wherein the immune checkpoint protein is CTLA4, PD-1, PD-L1, PD-L2, A2AR, B7-H3, B7-H4, BTLA, KIR, LAG3, TIM-3 or VISTA." Claim 27 recites, *inter alia*, "…wherein the immune checkpoint inhibitor is an antibody or antigen fragment thereof that binds to CTLA4, PD-1, PD-L1, PD-L2, A2AR, B7-H3, B7-H4, BTLA, KIR, LAG3, TIM-3 or VISTA." Because these claims limit claim 1 only by describing the immune checkpoint inhibitor's function, *i.e.*, as a protein or antibody that binds any one of these twelve proteins, these claims still

represent a nearly limitless number of possible immune checkpoint inhibitors. Ex. 1002 at ¶ 143.

Claims 14 and 17 (depending from claims 13 and 16 respectively) recite, *inter alia*, " …wherein the immune checkpoint protein is "PD-1 or PD-L1" Once again, because claims 14 and 17 are functional claims, i.e., they cover any protein, polypeptide, antibody of antigen binding fragment that binds to PD-1 or PD-L1, these claims also represent a nearly limitless number of possibilities. Furthermore, these claims are broad insofar as the type of cancer is not limited nor is the species or strain of *bifidobacterium* limited. Ex. 1002 at ¶ 143.

Claims 18 and 29 recite, *inter alia*, "…wherein the immune checkpoint inhibitor is nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, STI-A1110, TSR-042, RG-7446, BMS-936559, BMS-936558, MK-3475, CT O11, MPDL3280A, MEDI-4736, MSB-0020718C, AUR-012 and STI-A1010." There are 17 specific immune checkpoint inhibitors encompassed by these claims. Furthermore, these claims are broad insofar as the type of cancer is not limited nor is the species or strain of *Bifidobacterium* limited. As previously explained, the utility of these drugs as a cancer therapy have been shown to work in only a small subset of cancers. In addition, these therapies have only been shown to work in a subset of patients with those cancers. Furthermore, the claims cover any one of at least 17 immune checkpoint inhibitors combined with any species of

Bifidobacterium, whose properties are known to be species and/or strain specific. Ex. 1002 at ¶ 144.

Claims 1-3, 5-21, and 23-29 cover a bacterial formulation comprising bacteria of the genus of *Bifidobacterium*. The specification provides no less than 36 specific species of genus *Bifidobacterium*. Furthermore, the claim lists "*Bifidobacterium* sp." which is an indicator for an unnamed species, thus making the list a nearly limitless number of species of *Bifidobacterium*. These claims are also broad with respect to the number of cancers treated, the classes of immune checkpoint inhibitors used for treatment.. Ex. 1002 at ¶ 145.

Claims 4 and 22 claim a bacterial formulation comprising a bacteria species from a list of 35 specific species, plus the claims denotes "*Bifidobacterium* sp." which is an indicator for an unnamed species, thus making the list nearly limitless for species of *Bifidobacterium*. The claims are broad with respect to the number of cancers treated and the classes of immune checkpoint inhibitors used for treatment. Ex. 1002 at ¶ 146.

4. The Working Examples Are Limited To a Few Mouse Experiments Involving Two Types of Cancer, A Single Immune Checkpoint Inhibitor, And A Few Species of *Bifidobacterium*

As previously explained, the experimental studies described in the '302 patent are limited to mouse experiments involving only two types of cancer (melanoma and bladder), one immune checkpoint inhibitor (αPD-L1 antibody), mouse feces

containing *Bifidobacterium* and other gut bacteria that happen to be present in the feces, and a *Bifidobacterium* "cocktail" comprising four species *of Bifidobacterium*: *B. bifidum, B. longum, B. lactis,* and *B. breve.* Ex. 1001 at 33:37-40:62. Ex. 1002 at ¶ 147.

There is no data on any other cancers, any other immune checkpoint inhibitor, or any other species of *Bifidobacterium.* Ex. 1002 at ¶ 148.

Nor is there any human data. Ex. 1002 at ¶ 149.

5. The '302 Patent Provides Nearly No Guidance

There is no direction or guidance provided by the specification as it relates to which of the vast number of cancers are treatable and by which combination of immune checkpoint inhibitors and bacteria species of the genus *Bifidobacterium*. A POSITA would not find direction or guidance from the specification as to which immune checkpoint inhibitor to select from among the broad classes of immune checkpoint inhibitors and which species of *Bifidobacterium* to select from the list of *Bifidobacterium* species disclosed. As noted above, the only "guidance," comes from limited mouse experiments involving two types of cancer, one immune checkpoint inhibitor, and a cocktail of four different *Bifidobacterium* species. Ex. 1002 at ¶ 150.

As such, the '302 patent proposes no more than a hypothesis that all immune checkpoint inhibitor/*Bifidobacterium* species combinations can be used to treat any

cancer in humans. Because of the highly unpredictable nature of cancer treatment in general, combined with the highly unpredictable nature of immune checkpoint inhibitors and different species of Bifidobacterium, all combinations of immune checkpoint inhibitors and *Bifidobacterium* species would have to be tested against each cancer to see if it works. Unquestionably, such testing is burdensome and undue. Ex. 1002 at ¶ 151.

6. Cancer Treatment Employing Immune Checkpoint Inhibitors and Bifidobacterium Is Highly Unpredictable

The state of the prior art is set forth above. As of June 2015 as well as June 2016, it was understood by a POSITA that:

- cancer is a term covering a variety of specific diseases with disparate etiologies, outcomes, and therapies;
- a limited number of immune checkpoint inhibitors had been proven to treat a few cancers and that for some cancers, were only effective in a subset of patients;
- gut microbiota influence health and the immune system; and
- properties of *Bifidobacterium* are species specific, and can also be strain specific;
- certain species and strains of *Bifidobacterium* have been shown to have anti-tumor activity.

Ex. 1002 at ¶ 151.

Cancer therapy is a highly unpredictable art. There are many different types of cancer. They each develop in different ways, and each type can require different treatment approaches. This is evidenced by the vast array of potential therapies – radiation, surgery, chemotherapeutics, and targeted therapeutics – and the use of multiple therapies to treat some cancers. Ex. 1002 at ¶ 153.

Furthermore, the subset of therapies known as immune checkpoint inhibitors is highly unpredictable. The utility of this class of therapeutics has only been proven for a limited number of inhibitors, in a limited numbers of cancers and for some of these cancers, they have only proven effective in a subset of patients. In other words, there is significant unpredictability in the efficacy of a given immune checkpoint inhibitor on a particular cancer without extensive testing. *See* ¶¶106-109*, supra.* Ex. 1002 at ¶ 154.

At the time of the invention, it was understood that *Bifidobacterium* effected the immune system but the effects were species and strain specific. *See* Ex. 1038. Additional research showed while a strains had anti-tumor activity and immunostimulatory (s*ee* Ex. 1005, 1007), other strains were anti-inflammatory (Ex. 1017). The diverse activity and species-specific immune effects of *Bifidobacterium* thus render it unpredictable. In other words, there is significant unpredictability in the efficacy of a given species of *Bifidobacterium* on a particular cancer. A POSITA would have to test each strain in combination with immune checkpoint inhibitors, to

ascertain whether the combination was effective against cancer. Such experimentation is burdensome and undue. Ex. 1002 at ¶ 155.

7. Extensive and Undue Experimentation Is Required To Practice The Full Scope of the Claimed Invention

Practicing the full scope of claims 1-29 requires an extensive amount of experimentation to test for the broad range of any immune checkpoint inhibitor and any *Bifidobacterium* to treat any type of cancer. Ex. 1002 at ¶ 156.

To practice the full scope of the '302 claims, a POSITA would have to test all combinations of immune checkpoint inhibitors and *Bifidobacterium* species against each cancer to know whether the claimed treatment would work. The list of possible immune checkpoint inhibitors, possible species of *Bifidobacterium,* and possible cancer types is nearly limitless for most of the claims. Indeed, claims 1-12 and 19-26 place NO restriction on the type of cancer, immune checkpoint inhibitor, or species of *bifidobacterium*. Ex. 1002 at ¶ 157.

Even if the '302 claims were expressly limited to the cancer types, immune checkpoint inhibitors, and species of *bifidobacterium* expressly listed in the '302 patent – <u>which the claims are not</u> – a POSITA would still have to engage in an extensive and undue amount of experimentation. Ex. 1002 at ¶ 158.

The '302 patent lists 17 immune checkpoint inhibitors (Ex. 1001 at 5:20-26), 35 species of *Bifidobacterium* (Ex. 1001 at 3:10-29), and 165 disorders and twenty-two (22) broad categories of cancers that are described as "[n]on-limiting examples

of cancers that may be treated with the compositions and methods described herein against every cancer." Ex. 1001 at 28:54-56. Thus, testing for these listed cancers, which the patent describes as "non-limiting," would require over 100,000 tests. Ex. 1002 at ¶ 159.

The aforementioned 100,000 tests, however, are only a starting point for determining enablement of the full scope of the '302 claims. Those 100,000 tests assume that the same route of administration and same dosage for both the immune checkpoint inhibitor and *Bifidobacterium* are employed. The claims, however, are not so limited. Indeed, claims 1-18 and 20-29 do not place any restriction on the route of administration or dosage of the immune checkpoint inhibitor. Ex. 1002 at ¶ 160.

The '302 specification lists 7 different administration routes for the immune checkpoint inhibitor, three of which are inoperable: intravenous injection, intramuscular injection, intratumoral injection, subcutaneous injection; **oral administration, topical administration, or via aerosol**. Ex. 1001 at 28:30-34 (emphasis added). Ex. 1002 at ¶ 161.

Administering an immune checkpoint inhibitor that is a protein or a nucleic acid by oral or topical administration, or via an aerosol, presents many biological obstacles. As of June 2015, and even as of today, Petitioner's expert is not aware of any immune checkpoint inhibitor that has been successfully administered by oral or

topical administration, or via an aerosol, to treat cancer. Thus, the claims encompass inoperative embodiuments. Ex. 1002 at ¶ 162.

With respect to the administration of *Bifidobacterium,* claims 1-4, 7-18, 20-22 or 25-29 do not place any restrictions on the route of administration or dosage of the *Bifidobacterium.* Significantly, the '302 specification lists 8 different routes of administration for the *bifidobacterium*: oral, rectal, vaginal, topical, nasal, intrapulmonary, and injection. Ex. 1001 at 19:19-24; *see also* 4:56-60. Moreover, Petitioner's expert is unaware of any clinical use of intrapulmonary bacterial delivery. Ex. 1002 at ¶ 163.

Thus, taking into account the various routes of administration for both the immune checkpoint inhibitor and Bifidobacterium, well over 1,000,000 tests would be needed to be performed to test for the full scope of the claimed invention – *assuming arguendo* – that the claims are expressly limited to the cancer types, immune checkpoint inhibitors and species of *Bifidobacterium* expressly listed in the '302 patent – which the claims are not. Moreover, the claims encompass inoperative embodiments. Ex. 1002 at ¶ 164.

Against this backdrop of needing to engage in extensive testing to test well over 1,000,000 different combinations, the experimental studies described in the '302 patent are limited to mouse experiments involving only two types of cancer (melanoma and bladder), one immune checkpoint inhibitor (αPD-L1 antibody),

mouse feces containing *Bifidobacterium* and other gut bacteria that happen to be present in the feces, and a cocktail comprising four commercially available species of *Bifidobacterium*: *B. breve, B. longum, B. lactis,* and *B. bifidum*. Moreover, the '302 patent does not provide any human testing. Ex. 1002 at ¶ 165.

Based on the analysis of the *Wands* factors set forth hereinabove, and given the broad scope of the '302 claims, the lack of guidance provided in the '302 patent, and the highly unpredictable nature of not only cancer treatment in general, but also the unpredictable nature of immune checkpoint inhibitors and different species of *Bifidobacterium* in particular, a POSITA would have to engage in undue extensive experimentation to even attempt to practice the full scope of claims 1-29 of the '302 patent. Therefore, claims 1-29 of the '302 patent are invalid for lack of enablement. Ex. 1002 at ¶ 166.

VIII. CLAIMS 1-29 OF THE '302 PATENT ARE OBVIOUS

35 U.S.C. §103, provides, in relevant part:

> A patent for a claimed invention may not be obtained…if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The Supreme Court has instructed courts to address the question of obviousness against the "background" of three inquiries: 1) the scope and content of the prior art; 2) differences between the prior art and the claims at issue; and 3) the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966)

A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id*. at 416. "[A] court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. at 417. "[W]hen a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." Id. (quoting *Sakraida v. Ag Pro, Inc*., 425 U.S. 273, 282 (1976)). "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." Id. at 418. It may also be "helpful" to ask whether there was a "teaching, suggestion, or motivation to combine known elements" that would have rendered an invention obvious ("the TSM test"). Id. "Common sense teaches . . . that familiar

items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." Id. at 420.

A. (Ground 2) Korman '401 in View of Singh and Dong Render Obvious Claims 1-9, 12-17, and 19-25, and 27-28

Korman '401 teaches a method of treating cancer in humans by systemically administering immune checkpoint inhibitors such as anti PD-1 and anti CTLA-4 antibodies that bind to their respective immune checkpoint proteins, PD-1 and CTLA-4. Ex. 1003 at [467,480]. Ex. 1002 at ¶ 167.

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. 1003 at [498, 501] and the Figures cited therein. Ex. 1002 at ¶ 168.

Singh reported that "oral administration of *Bifidobacterium longum* exerts strong antitumor activity…" Ex. 1004, p. 1, Abstract. Singh showed that daily oral administration of "[l]yophilized cultures of B. *longum* … equivalent to 4 x 10^{10} live cells/g diet" (*Id* at p. 2, 2nd col.) resulted in "significant suppression of colon tumor incidence, tumor multiplicity, and reduced tumor volume. *Id.*, Abstract, *see also* pp. 2, 4, and 5. Ex. 1002 at ¶ 169.

Dong (Ex. 1005) showed that *Bifidobacterium longum* is immunostimulatory. 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. *Id.*at pp 2-4, and 7. Ex. 1002 at ¶ 170.

It would have been obvious to a POSITA at the time of the '302 patent's purported invention to combine Singh's daily oral administration of *Bifidobacterium longum* with Korman's systemic injection of an immune checkpoint inhibitor such as anti PD-1 and/or anti CTLA-4 antibody to treat cancer in a human subject. Ex. 1002 at ¶ 171.

A POSITA would have been motivated to co-administer the *Bifidobacterium longum* of Singh and immune checkpoint inhibitor of Korman '401 such as an anti PD-1 and/or anti CTLA-4 antibody to treat cancer in a human subject because anti PD-1 and anti CTLA-4 antibody immune checkpoint inhibitors had been shown to possess antitumor activity against a small number cancers, including colon cancer (*see* ¶106-109, *supra*), and *Bifidobacterium longum* had been shown to possess antitumor activity against colon cancer. Furthermore, Dong showed that *Bifidobacterium longum* was immunostimulatory, thus providing motivation to combine the immunostimulatory immune checkpoint inhibitors of Korman '401 with the immunostimulatory *Bifidobacterium longum* of Singh. Ex. 1002 at ¶ 172.

One of ordinary skill in the art would have possessed a reasonable expectation of success that the combined administration of the immune checkpoint inhibitor of

Korman ‘401 and the *Bifidobacterium longum* of Singh would be effective to treat, in humans, cancers known to be responsive to immune checkpoint inhibitors, including colon cancer, because immune checkpoint inhibitors had been shown to possess that activity, and the *Bifidobacterium longum* had also been shown to possess anti-tumor activity against colon tumors and to be immunostimulatory. One of ordinary skill in the art would also have possessed a reasonable expectation of success that the immune checkpoint inhibitor of Korman ‘401 and Bifidobacterium *longum* of Singh would yield an additive anti-cancer effect for treating such cancers because both agents were shown to be immunostimulatory. Ex. 1002 at ¶ 173.

For the foregoing reasons and as shown in more detail in the claim chart below, the combination of Korman ‘401 in view of Singh and Dong render obvious claims 1-9, 12-17, and 19-28. Ex. 1002 at ¶¶ 174, 179. Indeed, passages recited in the claim chart below describe Singh administering multiple oral doses of 4 x 10^{10} CFU of *B.longum,* thus rendering obvious claims 2-9 and 20-25. The passages also show Kormon ‘401 injecting immune checkpoint inhibitor anti PD-1 antibody which binds to immune checkpoint PD-1, thus rendering obvious claims 12-17, 19 and 27-28. *See* Ex. 1002 at ¶¶ 179.

‘302 Patent Claims	**Prior Art**
1. A method of treating cancer in a human subject comprising co-administering to the subject an immune checkpoint inhibitor and a	**Korman ‘401 (Ex. 1003)** **[001]** The present invention relates generally to immunotherapy in the treatment of human disease …[T]he present invention relates to the use of anti-PD-1 antibodies and the use of

‘302 Patent Claims	Prior Art
bacterial formulation comprising bacteria of the genus *Bifidobacterium*.	combination immunotherapy, including the combination of anti-CTLA-4 and anti-PD-1 antibodies, to treat cancer… **[0467] …** The present invention relates to treatment of a subject in vivo using an anti-PD-1 antibody such that growth of cancerous tumors is inhibited. **[0498]** Mouse tumor models (MC38 colon cancer and SAl/N fibrosarcoma) were used to examine the in vivo effect of treating a tumor by combining immunostimulatory therapeutic antibodies anti-CTLA-4 and anti-PD-1… [I]t was found that anti-CTLA-4 antibody treatment alone and anti-PD-1 antibody … treatment alone had a modest effect on reducing tumor growth in the MC38 tumor model (see, e.g., FIGS. 21, 24 and 27). The anti-CTLA-4 antibody alone was quite effective in the SAl/N tumor model (see FIG. 30D), which required a lower anti-CTLA-4 antibody dose for the combination studies in this model. [T]he combination treatment of anti-CTLA-4 antibody and anti-PD-1 antibody showed an unexpected, significantly greater effect on reducing tumor growth as compared to treatment with either antibody alone (see, e.g., FIGS. 21D, 24D, 30F and 33H-J). **[0581]…** The mice were implanted subcutaneously in the right flank with $2x10^6$ SAl/N fibrosarcoma cells…The animals were dosed by intraperitoneal injection with approximately 200 µl of PBS containing antibody or vehicle… The results are shown in FIG. 20. The anti-PD-1 antibody extended the mean time to reaching the tumor end point volume… Thus, treatment with an anti-PD-1 antibody has a direct in vivo inhibitory effect on

'302 Patent Claims	Prior Art
	tumor growth. ***See also*** **[585-611]** reporting the efficacy of individually administered anti-PD-1 and anti CTLA-4 antibodies as well as their combined administration against MC38 colorecal cancer cells and SA1/N fibrosarcoma cells. **Singh (Ex. 1004)** The data demonstrate that dietary administration of lyophilized cultures of *B.longum* resulted in significant suppression of colon tumor incidence and tumor multiplicity and also reduced tumor volume. …Data suggest that oral administration of probiotic *B.longum* exerts strong antitumor activity… **Abstract, p. 1.** It was therefore of interest to evaluate the colon tumor inhibitory properties of dietary *B.longum* in the established colon cancer model. We have analyzed the effect of dietary *B.longum* on AOM-induced colon tumorigenesis in male F344 rats. **p. 2, 1st col.** Lyophilized cultures of *B.longum* at the 2% level, equivalent to 4 x 10^{10} live cells/g diet, were added to the AIN-76A diet at the expense of dextrose. **p. 2, 2nd col.** Dietary administration of *B.longum* cultures significantly inhibited the incidence of colon adenocarcinomas (P < 0.05), and colon tumor multiplicity in terms of tumors/animal (P , 0.001) and tumors/tumor-bearing animal (P , 0.01). **p. 4, 1st col.** As summarized in Table III, dietary *B.longum* significantly suppressed AOM-induced proliferative indices in the lower, middle and upper compartment as well as in the total crypt column (P < 0.01–0.001). This inhibitory effect

'302 Patent Claims	Prior Art
	of *B.longum* on AOM-induced cell proliferation was strongly correlated with tumor outcome. **p. 4, 1st col.** Our experiments demonstrate that whereas AOM administration induces multiple colon tumors in ~77% of treated animals, dietary intake of B *B.longum* significantly suppresses the number as well as the size of these tumors. To our knowledge, this is the first study providing evidence that ingestion of lyophilized cultures of B *B.longum*, a lactic acid-producing bacterium present in the human colon, inhibits tumor incidence and multiplicity in addition to reducing the overall volume of AOM-induced colon tumors. **p. 5, 2nd col.** **Dong (Ex. 1005)** Thus, the SD rats used in the study were fed from birth with sufficient antibiotics per day (bifidobacteria minimisation [(BM)] group) or administrated a daily dose of *Bifidobacterium longum* (bifidobacteria supplementation [(BM)] group) until one, three and six weeks of age, which are equivalent to the neonatal, infant and adolescent period of childhood…**p. 2, 1st Col**, For the level of surface marker CD86 (co-stimulatory molecule) expression increases as DCs mature gradually and thus reflects DC developmental stage [13]. It was found that in [payer patches] PPs and at six weeks, as compared with the control (19.17 (2.32)), the Geo Mean (SD) fluorescence intensity of CD86 in the… BS group had an increased significantly… The results of RT-PCR showed that the BS group had an increased expression of

'302 Patent Claims	Prior Art
	IL-12-mRNA in the intestinal mucosa, both at three weeks and six weeks. **¶ bridging pp. 3-4.** *3.4. The impact of bifidobacteria on the T-helper cell response* The BS group… had upregulated IFN-γ mRNA and IFN-γ/IL-4 ratio in intestinal mucosa both at three weeks and six weeks … as well as increased IFN-γ gene expression in cultured PBMCs at six weeks. **p. 4, 2nd column.** One of the main purposes of our study was to explore the effects of bifidobacteria on the regulation of DCs in vivo; the results indicate that intestinal bifidobacteria induce a pattern of maturation of DCs in PPs characterised by the up-regulated expression of the co-stimulatory molecule CD86 with increased production of IL-12 locally in the gut… The maturation of DCs induced by captured bifidobacteria might facilitate the stimulation of the underlying lymphoid tissues, including the activation of resting CD4+ T cells. We speculate that a specific intracellular signalling cascade may be triggered by the association of bifidobacteria with DCs, which ultimately modulate the phenotype and function of DCs; and the exact mechanisms involved need to be further elucidated **p. 4, 2nd column.** In summary, intestinal bifidobacteria could promote DC maturation and its expression of IL-12 locally in the gut, influence T-cell development in the thymus, favour the T-helper cell response of the body in a Th1 type and meanwhile ensure the development of Treg response in the gut. Moreover, they enhance antibody synthesis by PBMCs, thereby affecting

‘302 Patent Claims	Prior Art
	the development of both the gut and systemic immunity in early life. **p. 7, 2nd col.**

B. (Ground 3) Korman ‘401 in View of Singh and Dong and Further in View of Van der Waaij Render Obvious Claims 10, 11 and 26.

It would have been an obvious to one of ordinary skill in the art to administer an antibiotic prior to the administration of the bacterial formulation to reduce the microflora population in the subject and repopulate the microflora population with the *Bifidobacterium* in order to increase the amount of *Bifidobacterium* in the microflora population. Van der Waaij *et al*., 1986 “The Influence Of Antibiotics On Gut Colonization, J Antimicrob Chemother. 18 Suppl C:155-158 (“Van der Waaij;” (Ex. 1010)). Ex. 1002 at ¶ 175.

Further, administering the antibiotic at least 1 day before the bacterial formulation is administered to the subject would have been considered routine optimization. Accordingly, Korman ‘401 in view of Singh and Dong and further in view of Van der Waaij render obvious claims 10, 11, and 26. Ex. 1002 at ¶ 176.

10. The method of claim 1, further comprising administering to the subject an antibiotic prior to the administration of the bacterial formulation.	**Van der Waaij (Ex. 1010)** Animal and human studies have suggested the concept of “colonization resistance” of the gastro-intestinal tract, which can be decreased by administration of antibiotics that inhibit the anaerobic portion of the normal flora of the gut. **Ex. 1010, p. 1.**

	It has been observed frequently that colonization and infection by nosocomial Gramnegative bacilli are likely to follow administration of broad spectrum antibiotics. **Ex. 1010, p. 1.**
11. The method of claim 10, wherein the antibiotic is administered to the subject at least 1 day before the bacterial formulation is administered to the subject.	*See analysis for claim 10.*

C. (Ground 4) Korman '401 in View of Singh and Dong and Further in View of Topalian Render Obvious Claims 18 and 29

Claims 18 and 29 list known immune checkpoint inhibitors, including anti PD-1 antibodies named nivolumab and BMS-936558. Claims 18 and 29 also list an anti PD-L1 antibody BMS936559. Ex. 1002 at ¶ 177.

Topalian describes immune checkpoint inhibitors to treat cancer in human patients, including anti PD-1 antibodies named nivolumab and BMS-936558 and an anti PD-L1 antibody named BMS936559. As previously explained, Korman '401 teaches a method of treating cancer in humans by systemically administering immune checkpoint inhibitors such as anti PD-1 and anti CTLA-4 antibodies that bind to their respective immune checkpoint proteins, PD-1 and CTLA-4. It would have been obvious to a POSITA to substitute the anti PD-1 and PD-L1-immune checkpoint inhibitor antibodies described in Topalian for the immune checkpoint

inhibitor antibodies Korman ‘401. Accordingly, Korman ‘401 in view of Singh and Dong and further in view of Topalian renders obvious claims 18 and 29. Ex. 1002 at ¶ 178, see also ¶ 179.

18. The method of claim 1, wherein the immune checkpoint inhibitor is nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, STI-A1110, TSR-042, RG-7446, BMS-936559, BMS-936558, MK-3475, CT O11, MPDL3280A, MEDI-4736, MSB-0020718C, AUR-012 and STI-A1010.	**Topalian (Ex. 1006)** In the first-in-human study of the PD-1 immune checkpoint inhibitor nivolumab (BMS-936558, MDX-1106, ONO-4538)… **p. 1021, 1st col. 1.** This dose-escalation, cohort expansion study evaluated the antitumor activity and safety of nivolumab, a fully human immunoglobulin G4 monoclonal antibody blocking PD-1 in patients with advanced cancers, including melanoma and non–small-cell lung, kidney, colorectal, and castration resistant prostate cancer… **p. 1021, 1st col. 1.** The critical role of the PD-1 pathway in suppressing antitumorimmunity, first revealed in laboratory models, has now been validated in clinical studies. Monotherapy with drugs blocking PD-1 (nivolumab, MK-3475 [lambrolizumab])[15,19] or its major ligand PD-L1 (BMS936559, MPDL3280A)[20,21] can mediate rapid and durable regressions in patients with advanced treatment–refractory solid tumors **p. 1026, 1st col. 1.**

D. (Ground 5) Korman ‘401 in View of Kohwi Renders Obvious Claims 1-4, 7-9, 12-17, 19-25, and 27-28

Korman ‘401 teaches a method of treating cancer in humans by systemically administering immune checkpoint inhibitors such as anti PD-1 and anti CTLA-4

antibodies that bind to their respective immune checkpoint proteins, PD-1 and CTLA-4. Ex. 1003 at [467, 480]. Ex. 1002 at ¶ 180.

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. 1003 at [498, 501] and the Figures cited therein. Ex. 1002 at ¶ 181.

Kohwi *et al.* (Ex. 1007) showed that two strains of *Bifidobacteria*, *Bifidobacterium infantis* and *bifidobacterium adolescentis,* exhibited "a remarkable antitumor effect on Meth-A sarcoma cells." *Id.*, p. 5. Ex. 1002 at ¶ 182.

Mice were injected intraperitoneally or subcutaneously with Meth-A sarcoma cells and with *Bifidobacterium infantis* or *Bifidobacterium adolescentis* or without either. The data showed that after day 8, many of the established tumors underwent complete or partial regression in mice treated with *B. infantis* and *B. adolescentis* while tumors in the control group went on to kill the mice. Ex. 1007 at p. 1-3. Ex. 1002 at ¶ 183.

Kohwi suggested that the anti-tumor activity of the *Bifidobacterium* was due to it being immunostimulatory. Kohwi states, "[t]aken together, destruction of a part of tumor cells by the local reaction i**nduced by the bacteria and the following immunological stimulation** with the tumor may account for the antitumor mechanism of the bacteria." Ex. 1007, p. 4, (emphasis added). Ex. 1002 at ¶ 184.

It would have been obvious to a POSITA at the time of the '302 patent's purported invention to combine Kowhai's administration of *Bifidobacterium infantis* or *Bifidobacterium adolescentis* with Korman's systemic injection of an immune checkpoint inhibitor such as anti PD-1 and/or anti CTLA-4 antibody to treat cancer in a human subject. Ex. 1002 at ¶ 185.

A POSITA would have been motivated to co-administer the *Bifidobacterium infantis* or *Bifidobacterium adolescentis* of Kohwi and immune checkpoint inhibitor of Korman '401 such as an anti PD-1 and/or anti CTLA-4 antibody to treat cancer in a human subject because the anti PD-1 and anti CTLA-4 antibody immune checkpoint inhibitors had been shown to possess antitumor activity against a small number cancers, including SA1/N fibrosarcoma cells, and the *Bifidobacterium infantis* and *Bifidobacterium adolescentis* had been shown to possess antitumor activity against Meth A sarcoma cells. Furthermore, Kohwi taught that *Bifidobacterium infantis* and *Bifidobacterium adolescentis* were immunostimulatory, thus providing motivation to combine the immunostimulatory immune checkpoint inhibitor of Korman '401 with the immunostimulatory *Bifidobacterium infantis* and *Bifidobacterium adolescentis* of Kohwi. Ex. 1002 at ¶ 186.

One of ordinary skill in the art would have possessed a reasonable expectation of success that the combined administration of the immune checkpoint inhibitor of

Korman ‘401 and the *Bifidobacterium infantis or Bifidobacterium adolescentis* of Kohwi would be effective to treat, in humans, cancers known to be responsive to immune checkpoint inhibitors because immune checkpoint inhibitors had been shown to possess that activity, and the *Bifidobacterium infantis or Bifidobacterium adolescentis* had also been shown to possess anti-tumor activity and to be immunostimulatory. One of ordinary skill in the art would also have possessed a reasonable expectation of success that the immune checkpoint inhibitor of Korman ‘401 and *Bifidobacterium infantis or Bifidobacterium adolescentis* of Kohwi would yield an additive anti-cancer effect for treating such cancers because both agents were shown to be immunostimulatory. Ex. 1002 at ¶ 187.

For the foregoing reasons and as explained in more detail in the claim chart appearing below, the combination of Korman ‘401 in view of Kohwi render obvious claims 1-4, 7-9, 12-17, 19-25, and 27 of the 302 patent. Ex. 1002 at ¶ 188, 195 Indeed, passages recited in the claim chart below describe Kowhi repeatedly injecting administering multiple doses of 10^9 CFU of *B.Infantis or B. adolescentis,* thus rendering obvious claims 2-4, 7-9, 20-22, and 25. The passages also show Kormon ‘401 injecting immune checkpoint inhibitor anti PD-1 antibody which binds to immune checkpoint PD-1, thus rendering obvious claims 12-17, 19 and 27-28. *See* Ex. 1002 at ¶195.

‘302 Patent Claims	Prior Art
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.*	**Korman ‘401 (Ex. 1003)** **[001]** The present invention relates generally to immunotherapy in the treatment of human disease …[T]he present invention relates to the use of anti-PD-1 antibodies and the use of combination immunotherapy, including the combination of anti-CTLA-4 and anti-PD-1 antibodies, to treat cancer… **[0467] …** The present invention relates to treatment of a subject in vivo using an anti-PD-1 antibody such that growth of cancerous tumors is inhibited. **[0498]** Mouse tumor models (MC38 colon cancer and SAl/N fibrosarcoma) were used to examine the in vivo effect of treating a tumor by combining immunostimulatory therapeutic antibodies anti-CTLA-4 and anti-PD-1… [I]t was found that anti-CTLA-4 antibody treatment alone and anti-PD-1 antibody … treatment alone had a modest effect on reducing tumor growth in the MC38 tumor model (see, e.g., FIGS. 21, 24 and 27). The anti-CTLA-4 antibody alone was quite effective in the SAl/N tumor model (see FIG. 30D), which required a lower anti-CTLA-4 antibody dose for the combination studies in this model. [T]he combination treatment of anti-CTLA-4 antibody and anti-PD-1 antibody showed an unexpected, significantly greater effect on reducing tumor growth as compared to treatment with either antibody alone (see, e.g., FIGS. 21D, 24D, 30F and 33H-J). **[0581]…** The mice were implanted subcutaneously in the right flank with $2x10^6$ SAl/N fibrosarcoma cells… The animals were dosed by intraperitoneal injection with

‘302 Patent Claims	Prior Art
	approximately 200 µ1 of PBS containing antibody or vehicle…The results are shown in FIG. 20. The anti-PD-1 antibody extended the mean time to reaching the tumor end point volume… Thus, treatment with an anti-PD-1 antibody has a direct in vivo inhibitory effect on tumor growth. ***See also*** **[585-611]** reporting the efficacy of individually administered anti-PD-1 and anti CTLA-4 antibodies as well as their combined administration against MC38 colorecal cancer cells and SA1/N fibrosarcoma cells. **[002]**…Immune suppression can be reversed by inhibiting the local interaction of PD-1 with PD-L1, and the effect is additive when the interaction of PD-1 with PD-L2 is blocked as well (Iwaietal. (2002) Proc. Natl. Acad. Sci. USA 99:12293-7: Brown et al (2003).J. Immunol, 170:1257-66). Korman ‘‘401; see also [0467] **Kohwi (Ex. 1007)** Two strains of *Bifidobacterium* [,B. infantis and B. adolescentis,] isolated from a human exhibited a remarkable antitumor effect to Meth-A sarcoma cells transplanted into syngeneic BALB/c mice. p**. 5, 1st col.** **Test of Antitumor Effect of Microoganisms…**A volume of 0.1 ml of a suspension containing a known number of Meth-A cells was inoculated intraperitoneally or subcutaneously into BALB/c mice, with or without bacteria. In the latter case, the mice were repeatedly injected with bacteria at the tumor inoculated site. Two KE of OK-432 or

‘302 Patent Claims	Prior Art
	10^9 *Bifidobacterium* cells were used for a single dose into the tumor. **p. 1, 1st col.** **Effect of Intraregional Injection of Bacteria on Subcutaneously Transplanted Meth-A Tumor …**results are shown in Fig. 1 and Table I…[N]o significant difference in tumor sizes in mice inoculated with 25 x 10^3 tumor cells, measured on the 8th day, was observed between control given PBS and the groups treated with bacteria. In later days, however, many of the established tumors underwent complete or partial regression in mice treated with B. infantis, killed B. infantis, B. adolescentis, or with OK-432, although in the control mice, tumors grew to kill the hosts. **¶ bridging p. 2-3.** **Effect of Bacteria on Mixed Implantation of Meth-A Tumor** A mixture of bacteria and Meth-A cells was inoculated subcutaneously into mice. As shown in Table II, tumor did not grow in a majority of the recipient mice inoculated with 25 x 10^3 tumor cells mixed with RP of B. infantis. Killed B. infantis and OK-432 were also effective to Meth-A tumor cells. **p. 3, 1st and 2nd cols.** **Effect of Intraperitoneal Injection of Bacteria on Intraperitoneally Transplanted Meth-A Tumor…** the antitumor effect of bacteria depended on the number of inoculated tumor cells. Injection of B. infantis, killed B. infantis, or OK-432 into mice inoculated with 50 x 10^3 Meth-A cells resulted in a marked suppression on tumor graft and many of the mice survived. By contrast, to mice which were inoculated with 500 x 10^3 tumor cells, injections of either bacterium were effective only to a

‘302 Patent Claims	Prior Art
	small extent. **¶ bridging pp. 3-4; see also Tables III and IV.** **Retransplantation of Meth-A Cells into Mice Cured from the Tumor** In the preceding experiments, 2 groups of mice cured from tumor inoculation were obtained; group 1 of mice cured from tumor transplanted mixed with bacteria and group 2 of mice cured by therapeutic treatment of subcutaneous tumor. All these mice, as well as the non-treated control mice, accepted subcutaneous rechallenge of 25 x 10^3 Meth-A cells. All 10 untreated control and 20 of group 1 mice died due to tumor growth, whereas 63 out of 67 of group 2 mice rejected the rechallenged Meth-A cells and survived subcutaneous rechallenge of 25 x 10^3 Meth-A cells. All 10 untreated control and 20 of group 1 mice died due to tumor growth, whereas 63 out of 67 of group 2 mice rejected the rechallenged Meth-A cells and survived. **¶ bridging p. 4-5** In the therapeutic model, where the treatment with bacteria was undertaken the day after tumor inoculation, tumor grew for 1 week and then regressed. This finding may suggest the involvement of a host-mediated immunological response to tumor, at least to some extent, together with the nonspecific local reaction. This assumption could be substantiated from the finding that the mice that survived this experiment rejected the rechallenged tumor cells, indicating the acquirement of transplantation immunity to Meth-A cells… Taken together, destruction of a part of tumor cells by the local reaction induced by the bacteria and the following immunological stimulation with the tumor may account for the

'302 Patent Claims	Prior Art
	antitumor mechanism of the bacteria. **p. 5, 1st and 2nd col.**

E. (Ground 6) Korman '401 in View of Kohwi and Further in View of Singh Render Obvious Claims 5-6 and 23-24

As previously explained, Singh reported that "oral administration of *Bifidobacterium longum* exerts strong antitumor activity…" Ex. 1004, p. 1, Abstract. Singh showed that daily oral administration of "[l]yophilized cultures of *B. longum* … equivalent to 4 x 10^{10} live cells/g diet" (*Id* at p. 2, 2nd col.) resulted in "significant suppression of colon tumor incidence, tumor multiplicity, and reduced tumor volume. *Id.*, Abstract, *see also* pp. 2, 4, and 5. Ex. 1002 at ¶ 189.

In light of Singh's teaching that oral administration of *Bifidobacterium longum* was a viable route of administration to achieve antitumor activity, it would have been obvious to a POSITA to administer the *Bifidobacterium infantis* and *Bifidobacterium adolescentis* of Kohwi orally. Accordingly, Korman '401 in view of Kohwi and further in view of Singh render obvious claims 5-6 and 23-24, which include oral administration of the bacterial formulation. Ex. 1002 at ¶ 190.

5. The method of claim 1, wherein the bacterial formulation is administered by oral administration or rectal administration.	**Singh (Ex. 1004)** Data suggest that oral administration of probiotic B.*longum* exerts strong antitumor activity, as indicated by modulation of the intermediate biomarkers of colon cancer, and consequently reduced tumor outcome. P. 1, **Abstract**

6. The method of claim 5, wherein the bacterial formulation is administered by oral administration.	*See* citations and prior art analysis for claim 5.

F. (Ground 7) Korman '401 in View of Kohwi and Further in View of Van der Waaij Render Obvious Claims 10, 11 and 26.

It would have been an obvious to one of ordinary skill in the art to administer an antibiotic prior to the administration of the bacterial formulation to reduce the microflora population in the subject and repopulate the microflora population with the Bifidobacterium in order to increase the amount of Bifidobacterium in the microflora population. Van der Waaij (Ex. 1010.) Ex. 1002 at ¶ 191.

Further, administering the antibiotic at least 1 day before the bacterial formulation is administered to the subject would have been considered routine optimization. Accordingly, Korman '401 in view of Kohwi and further in view of Van der Waaij render obvious claims 10, 11, and 26. Ex. 1002 at ¶ 192.

G. (Ground 8) Korman '401 in View of Kohwi and Further in View of Topalian Render Obvious Claims 18 and 29

Claims 18 and 29 list known immune checkpoint inhibitors, including anti-PD-1 antibodies named nivolumab and BMS-936558. Claims 18 and 29 also list an anti-PD-L1 antibody BMS936559. Ex. 1002 at ¶ 193.

Topalian describes immune checkpoint inhibitors to treat cancer in human patients, including anti-PD-1 antibodies named nivolumab and BMS-936558 and an

anti-PD-L1 antibody named BMS936559. As previously explained, Korman '401 teaches a method of treating cancer in humans by systemically administering immune checkpoint inhibitors such as anti PD-1 and anti CTLA-4 antibodies that bind to their respective immune checkpoint proteins, PD-1 and CTLA-4. It would have been obvious to a POSITA to substitute the anti PD-1 or PD-Ll-1 immune checkpoint inhibitor antibodies described in Topalian for the immune checkpoint inhibitor antibodies of Korman '401. Accordingly, Korman '401 in view of Kohwi and further in view of Topalian render obvious claims 18 and 29. Ex. 1002 at ¶ 194.

H. (Ground 9) Korman '401 in View of Mohania and Prakash '449 Render Obvious Claims 1-9, 12-17, and 19-25, and 27-28

Korman '401 teaches a method of treating cancer in humans by systemically administering immune checkpoint inhibitors such as anti PD-1 and anti CTLA-4 antibodies that bind to their respective immune checkpoint proteins, PD-1 and CTLA-4. Ex. 1001 at [401, 467]. Ex. 1002 at ¶ 196.

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. 1001 at [498, 501] and the Figures cited therein. Ex. 1002 at ¶ 197.

Mohania (Ex. 1008) tested the effect of a fermented milk product (Dahi) on PD-1 expression in the colorectum of rats having colorectal carcinogenesis induced by 1,2-dimethylhydrazine (DMH). PD-1 expression was shown to be reversed with

oral administration of the fermented milk product (Dahi) which contained Lactobacillus acidophilus (LaVK2) and *Bifidobacterium* bifidum (BbVK3). *Id.* at pp. 1-6. Ex. 1002 at ¶ 198.

Mohania concluded that the present study suggests that probiotic Dahi can be used as an effective chemopreventive agent in the management of colorectal cancer. Ex. 1008, p. 1, Abstract. Ex. 1002 at ¶ 199.

Prakash *et al.*, U.S. 2010/0028449 (Prakash '449; Ex. 1009) teaches 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 [0025, 0030, 0079]. Ex. 1002 at ¶ 200.

It would have been obvious to a POSITA at the time of the '302 patent's purported invention to combine Mohania's orally administered *Bifidobacterium Bifidium* with Korman's systemic injection of an immune checkpoint inhibitor such as anti PD-1 and/or anti CTLA-4 antibody to treat cancer in a human subject. Ex. 1002 at ¶ 201.

A POSITA would have been motivated to co-administer the *Bifidobacterium* bifidum of Mohania and immune checkpoint inhibitor of Korman '401 such as an anti PD-1 and/or anti CTLA-4 antibody to treat cancer in a human subject because anti PD-1 and anti CTLA-4 antibody immune checkpoint inhibitors had been shown to possess antitumor activity against a small number cancers, including colon cancer

(*see* ¶¶ 106-109, *supra*), and bifidobacterium bifidum was described by Mohania as "an effective chemopreventive agent in the management of colorectal cancer." Ex. 1008, p. 1. Furthermore, Prakash '449 stated that a few *Bifidobacterium* species, including *Bifidobacterium* bifidum, could be used to treat colon cancer. Ex. 1009 at [0025, 0030, and 0079]. Ex. 1002 at ¶ 202.

In addition, both the anti PD-1 antibody of Korman '401 and *Bifidobacterium* bifidum of Mohania act to minimize the function of the immune checkpoint protein, the PD-1 receptor. The anti-PD-1 antibody blocks the PD-1 receptor from being activated by its cognate ligand(s) PD-L1 and/or PD-L2. The *Bifidobacterium* bifidum downregulates the PD-1 receptor's expression, leaving less PD-1 receptor capable of activation. Thus, the anti-tumor activities of the *Bifidobacterium* bifidum and anti-PD1 antibody are additive. Indeed, Korman '401 acknowledges that decreasing the absolute activity of the PD-1 receptor results in lessening immune suppression. Ex. 1002 at ¶ 203.

> Immune suppression can be reversed by inhibiting the local interaction of PD-1 with PD-L1, and the effect is additive when the interaction of PD-1 with PD-L2 is blocked as well (Iwai *et al.* (2002) Proc. Natl. Acad. Sci. USA 99:12293-7: Brown *et al.* (2003). J. Immunol, 170:1257-66)

Ex. 1003 at [0003]. In short, the anti-tumor efficacies of the anti-PD-1 antibody and *Bifidobacterium* bifidum are additive. Ex. 1002 at ¶ 203.

The Examiner agreed with this analysis during the prosecution of child application 15/718,735. In response to applicant's assertion that the Mohania probiotic and anti PD-1 antibody of Korman '401 acted through "mutually counter productive mechanisms," the Examiner countered:

> However, it is the position of the Office, that the action of PD-1 is not counterproductive. Nothing in Korman *et al.*, Mohania *et al.*, and/or Prakash *et al.*, have the opposite of the desired effect wherein the desired effect is to treat cancer. Furthermore, **the administered composition of Korman *et al.*, Mohania *et al.*, and/or Prakash *et al.*, all work to decrease PD-1 or inhibit PD-1 function. Those purposes are not counter-productive**.

Ex. 1015 at 68 (emphasis added). Ex. 1002 at ¶ 204.

One of ordinary skill in the art would have possessed a reasonable expectation of success that the combined administration of the immune checkpoint inhibitor of Korman '401 and the Bifidobacterium bifidum of Mohania would be effective to treat, in humans, cancers known to be responsive to immune checkpoint inhibitors, including colon cancer, because immune checkpoint inhibitors had been shown to possess that activity, and the *Bifidobacterium* bifidum had also been shown to possess anti-tumor activity against colon tumors and to provide an additive anti-tumor effect to the anti PD-1 antibody of Korman '401. One of ordinary skill in the art would also have possessed a reasonable expectation of success that the immune checkpoint inhibitor of Korman '401 and Bifidobacterium bifidum would yield an

additive anti-cancer effect for treating such cancers for the reasons discussed above. Ex. 1002 at ¶ 205.

For the foregoing reasons and as explained in more detail in in the claim chart below, the combination of Korman '401 in view of Mohania and Prakash '449 render obvious claims 1-9, 12-17, 19-25, and 27-28 of the '302 patent. Ex. 1002 at ¶ 206, 211. Indeed, passages recited in the claim chart below describe Mohania orally administering multiple doses of 2-20 x 10^8 CFU/g of *B.bifidis* or Prakash teaching oral administration solely of 10^9 or 10^{12} of *B.Bifidis or B.longum*, thus rendering obvious claims 2-9 and 20-25. The passages also show Kormon '401 injecting immune checkpoint inhibitor anti PD-1 antibody which binds to immune checkpoint PD-1, thus rendering obvious claims 12-17, 19 and 27-28. *See* Ex. 1002 at ¶ 211.

'302 Patent Claims	**Prior Art**
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.*	**Korman '401 (Ex. 1003)** **[001]** The present invention relates generally to immunotherapy in the treatment of human disease …[T]he present invention relates to the use of anti-PD-1 antibodies and the use of combination immunotherapy, including the combination of anti-CTLA-4 and anti-PD-1 antibodies, to treat cancer… **[0467] …** The present invention relates to treatment of a subject in vivo using an anti-PD-1 antibody such that growth of cancerous tumors is inhibited. **[0498]** Mouse tumor models (MC38 colon cancer and SAl/N fibrosarcoma) were used to examine the in vivo effect of treating a tumor by

‘302 Patent Claims	Prior Art
	combining immunostimulatory therapeutic antibodies anti-CTLA-4 and anti-PD-1… [I]t was found that anti-CTLA-4 antibody treatment alone and anti-PD-1 antibody … treatment alone had a modest effect on reducing tumor growth in the MC38 tumor model (see, e.g., FIGS. 21, 24 and 27). The anti-CTLA-4 antibody alone was quite effective in the SAl/N tumor model (see FIG. 30D), which required a lower anti-CTLA-4 antibody dose for the combination studies in this model. [T]he combination treatment of anti-CTLA-4 antibody and anti-PD-1 antibody showed an unexpected, significantly greater effect on reducing tumor growth as compared to treatment with either antibody alone (see, e.g., FIGS. 21D, 24D, 30F and 33H-J). **0581]…** The mice were implanted subcutaneously in the right flank with $2x10^6$ SAl/N fibrosarcoma cells… The animals were dosed by intraperitoneal injection with approximately 200 µ1 of PBS containing antibody or vehicle… The results are shown in FIG. 20. The anti-PD-1 antibody extended the mean time to reaching the tumor end point volume… Thus, treatment with an anti-PD-1 antibody has a direct in vivo inhibitory effect on tumor growth. ***See also*** **[585-611]** reporting the efficacy of individually administered anti-PD-1 and anti CTLA-4 antibodies as well as their combined administration against MC38 colorecal cancer cells and SA1/N fibrosarcoma cells. **[0003]**…Immune suppression can be reversed by inhibiting the local interaction of PD-1 with PD-L1, and the effect is additive when the interaction of PD-1 with PD-L2 is blocked as well (Iwaietal. (2002) Proc. Natl. Acad. Sci. USA 99:12293-7: Brown et al (2003).J.

‘302 Patent Claims	Prior Art
	Immunol, 170:1257-66). Korman ‘‘401; see also [0467] **Mohania** Feeding rats with probiotic Dahi … decreased the expression of PD-1 in DMH-induced colorectal mucosa… The present study suggests that probiotic Dahi can be used as an effective chemopreventive agent in the management of colorectal cancer (www.actabiomedica.it)” **Abstract, p. 102** Probiotic LaBb-Dahi was prepared by culturing standardized buffalo milk with L. acidophilus LaVK2, B. bifidum BbVK3 and Dahi starter. The final product contained lactococci, 1-2x10^9 cfu/g, L. acidophilus, 2-20x10^8 cfu/g and B. bifidus, 2-20x10^8cfu/g. **p. 102, 2nd col.** …[W]e prepared the buffalo milk-based probiotic Dahi by co-culturing two combinations of selected strains of lactobacillus with Dahi: (A) Lactobacillus acidophilus (LaVK2) along with Lactobacillus plantarum (Lp9) and Dahi culture (B) Lactobacillus acidophilus (LaVK2) along with *Bifidobacterium* bifidum BbVK3 and Dahi culture. Consumption of the fermented product was then evaluated for its effects on the expression of programmed death-1 (PD-1) in DMH-induced colorectal carcinogenesis in rats. **p. 103, 1st col.** Treatment with … probiotic Dahi significantly decreased DMH-induced expression of PD-1 in epithelial cells of colorectum… [B]oth probiotic Dahi (LaLp and LaBb Dahi) were almost equally effective in reducing DMH-induced accumulation of PD-1 in epithelial cells of colorectum. **p. 105, 2nd col.**

‘302 Patent Claims	Prior Art
	Both probiotic Dahi (LaBb Dahi or LaLp Dahi) were equally effective in reducing PD-1 expression in the colorectum of DMH-treated rats. Furthermore, the combination of piroxicam and probiotic Dahi treatment decreased DMH-induced initiation and progression of neoplastic lesions more effectively, suggesting that this treatment combination is effective in preventing the initiation and progression of carcinogenesis. Hence, the role of probiotic Dahi (LaBb Dahi or LaLp Dahi) as an alternate biotherapeutic agent in the treatment of colorectal cancer may also be explored. **p. 106, 1st and 2nd cols.** **Prakash ‘449** **[0025]** …[T] here is provided the use of the oral formulation of the present invention for the preparation of a medicament for the treatment or prevention of a disease or disorder. **[0030]** The disease or disorder includes cancer, such as breast cancer, colorectal cancer, prostate cancer, lung cancer, colon cancer and inflammation-related colon cancer, including adenoma, carcinoma, leiomyosarcoma, carcinoid tumor, or squamous cell carcinoma. … *Bifidobacterium* infantis, *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium* bifidum. **[0079]** .. the bacteria to be encapsulated is… *Bifidobacterium*. Known such bacteria include … B. *longum* and B. *breve*…The preferred bacteria used in accordance with the present invention are…*Bifidobacterium* bifidus

‘302 Patent Claims	Prior Art
2. The method of claim 1, wherein at least 50% of the bacteria in the bacterial formulation are of the genus *Bifidobacterium.*	**Mohania** Probiotic LaBb-Dahi was prepared by culturing standardized buffalo milk with L. acidophilus LaVK2, B. bifidum BbVK3 and Dahi starter. The final product contained lactococci, 1-2x10^9 cfu/g, L. acidophilus, 2-20x10^8 cfu/g and B. bifidus, 2-20x10^8cfu/g. **p. 102, 2nd col.** **Prakash ‘449** **[0030]** The disease or disorder includes cancer, such as breast cancer, colorectal cancer, prostate cancer, lung cancer,colon cancer and inflammation-related colon cancer, including adenoma, carcinoma, leiomyosarcoma, carcinoid tumor, or squamous cell carcinoma. … *Bifidobacterium* infantis, *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium* bifidum. **[0032]** The bacteria may be present in a range from 10^9 to 10^{12} colony forming units (CFU) **[0079]** .. the bacteria to be encapsulated is … *Bifidobacterium*. Known such bacteria include … B. *longum* and B. *breve*…The preferred bacteria used in accordance with the present invention are *Bifidobacterium* bifidus It would have been obvious to administer a bacterial formulation in which at least 50% of the formulation is a member of the genus *Bifidobacterium.*
3. The method of claim 1, wherein at least 90% of the bacteria in the bacterial formulation are of the genus *Bifidobacterium.*	*See citations and prior art analysis for clam 2.* It would have been considered routine optimization to one of ordinary skill in the art choice to administer a bacterial formulation in

‘302 Patent Claims	Prior Art
	which at least 90% of the formulation is the genus *Bifidobacterium.*

7. The method of claim 1, wherein the bacterial formulation comprises at least 5×10^6 CFU of bacteria of the genus *Bifidobacterium*.	**Mohania** Probiotic LaBb-Dahi was prepared by culturing standardized buffalo milk with L. acidophilus LaVK2, B. bifidum BbVK3 and Dahi starter. The final product contained lactococci, 1-2x10^9 cfu/g, L. acidophilus, 2-20x10^8 cfu/g and B. bifidus, 2-20x10^8cfu/g. **p. 102, 2nd col.** Each rat was fed 20 g supplements of … probiotic Dahi, followed by basal diet ad libitum. Following 28 day feeding… **p. 104, 2nd col.** **Prakash ‘449** **[0030]** The disease or disorder includes cancer, such as breast cancer, colorectal cancer, prostate cancer, lung cancer, colon cancer and inflammation-related colon cancer, including adenoma, carcinoma, leiomyosarcoma, carcinoid tumor, or squamous cell carcinoma. … *Bifidobacterium* infantis, *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium* bifidum. **[0032]** The bacteria may be present in a range from 10^9 to 10^{12} colony forming units (CFU) **[0079]** .. the bacteria to be encapsulated is … *Bifidobacterium*. Known such bacteria include … B. *longum* and B. *breve*…The preferred bacteria used in accordance with the present invention are …*Bifidobacterium* bifidus

I. (Ground 10) Korman ‘401 in View of Mohania and Prakash ‘449 and Further in View of Van der Waiij Render Obvious Claims 10, 11 and 26.

It would have been obvious to one of ordinary skill in the art to administer an antibiotic prior to the administration of the bacterial formulation to reduce the microflora population in the subject and repopulate the microflora population with the *Bifidobacterium* in order to increase the amount of *Bifidobacterium* in the microflora population. Van der Waaij (Ex. 1010). Ex. 1002 at ¶ 207.

Further, administering the antibiotic at least 1 day before the bacterial formulation is administered to the subject would have been considered routine optimization. Accordingly, for the foregoing reasons, and as explained in more detail in in the claim chart appearing in ¶ 208, Korman ‘401 in view of Mohania and Prakash ‘449 and further in view of Van der Waiij render obvious claims 10, 11, and 26. Ex. 1002 at ¶ 208.

J. (Ground 11) Korman ‘401 in View of Mohania and Prakash and Further in View of Topalian Render Obvious Claims 18 and 29

Claims 18 and 29 list known immune checkpoint inhibitors, including anti PD-1 antibodies named nivolumab and BMS-936558. Claims 18 and 29 also list an anti PD-L1 antibody BMS936559. Ex. 1002 at ¶ 209.

Topalian describes immune checkpoint inhibitors to treat cancer in human patients, including anti PD-1 antibodies named nivolumab and BMS-936558 and an anti PD-L1 antibody named BMS936559. As previously explained, Korman ‘401

teaches a method of treating cancer in humans by systemically administering immune checkpoint inhibitors such as anti PD-1 and anti CTLA-4 antibodies that bind to their respective immune checkpoint proteins, PD-1 and CTLA-4. It would have been obvious to a POSITA to substitute the anti PD-1 and PD-L1-immune checkpoint inhibitor antibodies described in Topalian for the immune checkpoint inhibitor antibodies Korman '401. Accordingly, Korman '401 in view of Mohania and Prakash '449 and further in view of Topalian renders obvious claims 18 and 29. Ex. 1002 at ¶ 210.

IX. CONCLUSION

For the foregoing reasons, the Board should grant Genome & Company's Petition.

Dated: October 2, 2018

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. §42.24(d), Patent Owner hereby certifies, in reliance on the word count of the word-processing system (Microsoft Office Word 2010) used to prepare this petition, that the number of words in this paper is 17,309. This word count excludes the tables of contents, tables of authorities, mandatory notices under 37 C.F.R. § 42.8, certificate of word count, certificate of service, appendix of exhibits, and claim listing.

Dated: October 2, 2018

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CERTIFICATE OF SERVICE

I certify that a copy of the foregoing petition for Post Grant Review and all of its referenced exhibits were served on the Patent Owner at the correspondence address of record for the ’302 Patent by sending a copy by Priority Mail Express® to:

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