

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MICROBIOTICA, LIMITED,
Petitioner

v.

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

Case PGR2023-00026
U.S. Patent No. 11,395,838

DECLARATION OF WENDY S. GARRETT, M.D., PH.D.

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I, Wendy S. Garrett, M.D., Ph.D., hereby declare as follows.

I. INTRODUCTION

1. I am over the age of 18 and competent to make this declaration.

2. I have been retained as an expert witness on behalf of Patent Owner Board of Regents, The University of Texas System for the above-captioned post-grant review (PGR). I am being compensated for my time in connection with this PGR at my standard consulting rate, which is \$750 per hour.

3. I understand that this Declaration accompanies a Patent Owner's Preliminary Response for PGR2023-00026 involving U.S. Patent No. 11,395,838 ("the '838 Patent") (EX1001), which resulted from U.S. Patent Application No. 16/337,820 ("the '820 application"). I understand that the '820 application was originally filed as Application No. PCT/US2017/053717, filed on September 27, 2017. I understand that the '838 Patent claims the benefit of the following provisional applications:

- Provisional Appl. No. 62/400,372, filed September 27, 2016;
- Provisional Appl. No. 62/508,885, filed May 19, 2017; and
- Provisional Appl. No. 62/557,566, filed September 12, 2017.

4. In preparing this Declaration, I have reviewed the '838 Patent, its prosecution history, and each of the documents cited herein, in light of general knowledge in the art before September 27, 2016 and September 27, 2017.

5. In formulating my opinions, I have relied upon my experience, education, and knowledge in the relevant art. In formulating my opinions, I have also considered the viewpoint of a person of ordinary skill in the art (“POSA”), as defined below in § V), as of the timeframes discussed below, in light of general knowledge in the art.

II. SUMMARY OF OPINIONS

6. I have been asked to consider whether Dr. Robinson’s asserted prior art (Honda and Gajewski for Ground 4, and Honda, Gajewski, and Miquel for Ground 5) present a new basis for finding obviousness compared to the prosecution of the ’838 Patent. The prior art combinations do not present a new basis for finding obviousness because the teachings of Honda, Gajewski, and Miquel—as well as Dr. Robinson’s arguments based on these references—are entirely cumulative of (i.e., the same or substantially the same as) the references and arguments that were expressly discussed and overcome during prosecution of the ’838 Patent. I refer to my discussion in Sections XIII-XVI below.

7. I have also been asked to consider whether, before September 27, 2016, the prior art that Dr. Robinson asserts under Ground 4 or Ground 5 would have rendered the challenged claims of the ’838 Patent obvious. In view of the state of the art before September 27, 2016, a POSA would not have found the challenged claims obvious over the prior art for at least two separate reasons.

8. First, Dr. Robinson fails to explain why a POSA would have had a reason to combine Honda and Gajewski (Ground 4) or Honda, Gajewski, and Miquel (Ground 5) with a reasonable expectation of success. For example, a POSA would not have used Honda's "Th17-inducing bacterial compositions" to reduce or delay the growth of skin cancer because the prior art demonstrated Th17 cells *promote* tumor growth. EX1003, ¶167; EX2021, Abstract; EX2022, 10113; EX2003, 927. Second, a POSA would not have understood *Ruminococcus*¹ as beneficial for skin cancer tumors because Gajewski teaches "the presence or increased level of" bacteria, including *Ruminococcus*, actually "potentiates cancer/tumor growth." EX1012, 22:6-9. Furthermore, Gajewski teaches *Bifidobacterium*, and not *Ruminococcus*, are beneficial for anti-cancer effects, further highlighting the lack of motivation a POSA would have had to combine Gajewski and Honda. EX1012, 49:3-24. Dr. Robinson similarly fails to establish why a POSA would have had a reasonable expectation of success in administering Ruminococcaceae for skin cancer treatment when, prior to September 27, 2016, the field taught that bacterial taxa *other than* Ruminococcaceae were important for an anti-cancer response. EX2004, Abstract; EX2005, Abstract. I refer to Sections VII

¹ *Ruminococcus* is a genus of bacteria within the family Ruminococcaceae. EX1015, 1016.

and VIII below.

9. I have also been asked to consider whether a POSA would have found the '838 Patent's claimed methods to be adequately described in the patent (Ground 1), and if a POSA would have required undue experimentation to practice the claimed methods in light of the teachings in the '838 Patent specification (Ground 2). In view of the state of the art as of September 27, 2017, and in light of the teachings in the '838 Patent, a POSA would not have found the challenged claims to lack written description support or enablement. First, Dr. Robinson fails to explain why the clinical data from human patients and experimental data from mice in the '838 Patent specification are not predictive of treating human patients using the claimed methods. Second, regarding enablement, Dr. Robinson fails to establish why a POSA would have been unable to perform the claimed methods without engaging in undue experimentation given that formulating and administering bacterial compositions, such as FMT and bacterial-based compositions, was well known in the art as I discuss in Sections IX and X below.

10. Further, I have been asked to consider whether a POSA would have understood the metes and bounds of the claimed methods of the '838 Patent (Ground 3). The claims of the '838 Patent are not indefinite, and a POSA would have understood the scope of the claimed methods. Dr. Robinson failed to establish why a POSA would not have understood with reasonable certainty the phrase

“isolated or purified” in light of the clear definitions provided in the specification, as I discuss in Section XI below. Dr. Robinson also failed to establish that a POSA would not have understood with reasonable certainty the scope of “bacteria belonging to the family *Ruminococcaceae*” as of September 27, 2017, and only discussed the scope in 2006, 2009, and 2019.

11. Finally, I have also been asked to consider whether Dr. Robinson’s arguments under Grounds 1-3 provide a new basis for finding lack of written description support, enablement, or definiteness compared to what was already assessed during prosecution of the ’838 Patent. Dr. Robinson’s arguments do not present a new basis for finding lack of written description support, enablement, or definiteness, because his arguments are entirely cumulative of (i.e., the same or substantially the same as) the arguments that were expressly discussed and overcome during prosecution of the ’838 Patent. Dr. Robinson also does not compare the arguments considered by the Examiner during prosecution with his arguments. I refer to my discussion in Section XII below.

III. MY BACKGROUND AND QUALIFICATIONS

12. I am a board-certified medical oncologist, treating gastrointestinal malignancies in patients at Dana-Farber Cancer Institute and Brigham Women’s Hospital. In addition to holding an M.D., I also hold a Ph.D. in Cell Biology and I am the Irene Heinz Given Professor of Immunology and Infectious Diseases at

Harvard T.H. Chan School of Public Health, as well as a tenured Professor of Medicine at Harvard Medical School. In addition, I am a member of the Harvard Digestive Diseases Center at Boston Children's Hospital, Gastrointestinal Cancer Center at Dana-Farber/Harvard Cancer Center, and associate member of the Infectious Disease and Microbiome Program at the Broad Institute of MIT and Harvard.

13. I am the Co-Founder and Co-Director of the Harvard Chan Microbiome in Public Health Center, Director of the Gnotobiotic Center for Mechanistic Microbiome Studies at Harvard T.H. Chan School of Public Health, and the Associate Director of the Graduate Program of Immunology and Infectious Diseases at Harvard Medical School's Division of Medical Sciences. I am on the Principal Investigator Team of the Human Microbiome Bioactives Resource affiliated with the University of Maryland, Harvard T.H. Chan School of Public Health, and the Broad Institute. I am the Co-Leader of Team OPTIMISTICCC Bowel Cancer Microbiome Research Programme, funded by Cancer Research UK Grand Challenges, based in London, UK.

14. I am a member of the American Association of Immunologists, American Association for Cancer Research, American Society for Microbiology, American Society for Clinical Investigation, and Association of American Physicians.

15. I have extensive experience in the fields of Immunology, Oncology, and Microbiology, including experience in researching the microbiome, and have been conducting research in these fields since 1994. I have focused on the relationship between the gut microbiota and cancer since 2005, and have been treating cancer patients as an attending physician since 2008.

16. I have provided a copy of my *curriculum vitae* as EX2002.

17. I graduated from Yale University, New Haven, Connecticut, with a B.S. and M.S. in Molecular Biophysics and Biochemistry in 1994. While at Yale, I received the Richter Fellowship for Research in 1991 and Phi Beta Kappa for Academics in 1993. I received a M.Phil. and a Ph.D. in Cell Biology in 2000 and 2001, respectively, from Yale University. I also obtained a Medical Degree from Yale School of Medicine in 2002. At Yale, I was the recipient of the M.D. Ph.D. Thesis Prize, Student Research Day Thesis Prize, Farr Scholar Award, Janet M. Glasgow Memorial Achievement Citation, and Alpha Omega Alpha award in recognition of my research and academic excellence.

18. Upon completion of my Medical Degree, I was an Intern and then Resident in the Department of Internal Medicine at Brigham and Women's Hospital from 2002-2004, a Clinical Fellow in the Department of Internal Medicine at Harvard Medical School from 2002-2007, a Clinical Fellow in the Department of Hematology and Oncology at Dana-Farber Cancer Institute from

2004-2008, and a Postdoctoral Research Fellow in Immunology and Infectious Diseases at Harvard T.H. Chan School of Public Health from 2005-2009. I received the Dunne Award for Compassionate Clinical Care from Brigham and Women's Hospital in 2003, the Medical Student Housestaff Recognition Award for Clinical Teaching from Harvard Medical School in 2004, and the Career in Medical Sciences Research Award from Burroughs Wellcome Fund in 2008.

19. After completing my first fellowship, I joined Harvard Medical School as an Instructor in 2007, holding the position until 2011. I held the position of Assistant Professor from 2011-2017, Associate Professor from 2017-2020, and Professor since 2021. From 2014-2017, I led the Immunology Program at Harvard Medical School. Shortly after joining Harvard, I joined the Departments of Immunology and Infectious Diseases and Genetics and Complex Diseases at Harvard T.H. Chan School of Public Health as an Assistant Professor from 2010-2014, Associate Professor from 2014-2015, and Professor since 2016. In recognition of my research on the interactions between intestinal microbiota and the immune system, I received the Searle Scholars Award from the Kinship Foundation in 2011, the Merkin Family Foundation Fellow Award from the Merkin Family Foundation and Broad Institute of Harvard & MIT in 2017. I was elected and inducted as a Fellow in the American Academy of Microbiology and American Society for Clinical Investigation in 2020 and the Association of

American Physicians in 2023. I received the Marian W. Ropes, M.D. Award from American Society for Clinical Investigation in 2023.

20. From 2017-2021, I served as the Co-Director of the Biobank for Microbiome Research in Massachusetts (BIOMMass) Initiative, which was subsumed into the Harvard Chan Microbiome in Public Health Center that I co-founded and currently co-direct. I served on the National Scientific Advisory Committee for the Crohn's and Colitis Foundation of America (CCF) from 2015-2018 and currently co-lead the CCF Preclinical Working Group, Clinical Immunology Committee for the American Association of Immunologists from 2015-2018, Institute for Laboratory Animal Research (ILAR) Roundtable Microbiome Planning Committee for the National Academy of Sciences from 2016-2017, and was the Chair of the Abstract Review Committee for American Gastroenterological Association (AGA) Institute. In 2019, I served on the Humans and Microbiome Program Advisory Board for the Canadian Institute for Advanced Research in Toronto, Ontario. I was a member of the Society for Microbial Ecology and Disease from 2010-2017, and served as a Councilor from 2011-2015. In addition, I served as a Faculty Member of Immunology for *Faculty of 1000* from 2010-2018, Editorial Board Member of *Cell Reports* from 2011-2023, Editorial Board Member of the *Journal of Clinical Microbiology* from 2011-2020, Board of Reviewing Editors for *eLife* from 2015-2016, and Editorial Board Member of

Nature Reviews Gastroenterology & Hepatology from 2018-2020.

21. Since 2005, the primary area of my research has been on the relationships among the immune system, gut microbiome, and disease. In particular, my research has focused on identifying microbes and their metabolites that promote colorectal cancer and modulate antitumor immunity. My research also includes investigating the mechanism of interaction between the human gut microbiome, immune system, and response to anti-PD-1 therapy and identifying therapeutic bacterial strains for treating solid tumors.

22. My research has led to over 70 peer-reviewed research publications, over 40 of which relate to the relationship between the microbiome and disease, including inflammatory bowel diseases, colorectal cancer, and melanoma. I have also received almost 40 grants. I frequently peer review publications related to the gut microbiome and disease as a Senior Editor for *eLife* and an *ad hoc* reviewer for *Cell*, *Cell Host and Microbe*, *Frontiers in Cellular and Infection Microbiology*, *Immunity*, *Infection and Immunity*, *Journal of Biomedicine and Biotechnology*, *Journal of Experimental Medicine*, *Journal of Immunology*, *mBio*, *Nature*, *Nature Reviews Microbiology*, *Proceedings of the National Academy of Sciences*, *Science*, *Science Translational Medicine*, and *Trends in Immunology*.

23. In addition to my educational training and professional and research experiences, I have kept abreast of the fields of immunology, microbiology, and

oncology (e.g., in the treatment of colorectal cancer and skin cancer) by reading scientific literature, conferring with colleagues in the field, and attending and presenting lectures at scientific conferences. I review grants for the AACR and the G. Harold and Leila Y. Mathers Foundation related to anti-tumor immunity, including grants relating to skin cancer. I teach courses on anti-tumor immunity at Harvard that include studies on the microbiome and anti-tumor response in skin cancer. I have co-organized several symposia on these topics including Gut Microbiota and Immune Regulation for Cell Press and LabLinks Symposium, Microbiome, Host Resistance and Disease for Keystone Symposium, Major Symposium B for the Microbiota in Immunity and Inflammation Annual Meeting, and Microbiome and Cancer Symposium for the Early Detection of Cancer Conferences.

IV. LIST OF DOCUMENTS CONSIDERED

Exhibit No.	Description
1001	U.S. Patent No. 11,395,838 (“the ’838 Patent”)
1002	U.S. Patent No. 11,395,838 File History
1003	Declaration of Mat Robinson, Ph.D.
1004	<i>Curriculum vitae</i> of Mat Robinson, Ph.D.
1005	Patyar et al. “Bacteria in cancer therapy: a novel experimental Strategy”, Journal of Biomedical Science 17:21 http://www.jbiomedsci.com/content/17/1/21 (2010) (Patyar)

Exhibit No.	Description
1006	Wei et al., “Bacterial targeted tumour therapy-dawn of a new era”, Cancer Letters 259 16–27 (2008) (Wei)
1007	Pitt et al., “Resistance Mechanisms to Immune-Checkpoint Blockade in Cancer: Tumor-Intrinsic and -Extrinsic Factors”, Immunity 44:1255-1269 (June 21, 2016) (Pitt)
1008	Viaud et al., “Gut microbiome and anticancer immune response: really hot Sh*t!”, Cell Death and Differentiation 22:199–214 (2015) (Viaud)
1009	Lopez-Siles et al., “Changes in the Abundance of <i>Faecalibacterium prausnitzii</i> Phylogroups I and II in the Intestinal Mucosa of Inflammatory Bowel Disease and Patients with Colorectal Cancer”, Inflamm Bowel Dis 22(1): 28-41 (20 November 2015) (Lopez-Siles)
1010	Martin-Orozco et al., T Helper 17 Cells Promote Cytotoxic T Cell Activation in Tumor Immunity”, Immunity 31:787–798 (2009) (Martin-Orozco)
1011	Honda et al. / Riken et al., WO2015/156419, published October 15, 2015 (Honda)
1012	Gajewski et al. / The University of Chicago, WO2016196605A1, published December 8, 2016 from PCT/US2016/035228, filed June 1, 2016 (Gajewski)
1013	Gajewski et al. / The University of Chicago, PCT/US2016/035228, filed June 1, 2016 (from WIPO public database for Gajewski, showing that content of Gajewski is the same as the content of PCT/US2016/035228 as filed June 1, 2016)
1014	Miquel et al., “Faecalibacterium prausnitzii and human intestinal health”, Current Opinion in Microbiology, 16:255–261 (2013) (Miquel)
1015	Volume 3 of Bergey’s Manual of Systemic Bacteriology (2nd Ed. 2009)
1016	Tindall, Int J Syst Evol Microbiol 69:3927–3932 (2019)

Exhibit No.	Description
1017	Louis et al., “Diversity, metabolism and microbial ecology of butyrate-producing bacteria from the human large intestine” FEMS Microbiol Lett. 294:1–8 (2009)
1018	Barcenilla et al., “Phylogenetic relationships of butyrate-producing bacteria from the human gut”, Appl Environ Microbiol. 66:1654–1661 (2000)
1019	Duncan SH, Hold GL, Harmsen HJ, Stewart CS, Flint HJ, “Growth requirements and fermentation products of <i>Fusobacterium prausnitzii</i> , and a proposal to reclassify it as <i>Faecalibacterium prausnitzii</i> gen. nov., comb. nov.”, Int J Syst Evol Microbiol 2002, 52:2141-2146
1020	Walker AW, Duncan SH, Harmsen H, Holtrop G, Welling GW, Flint HJ, “The species composition of the human intestinal microbiota differs between particle-associated and liquid phase communities”, Environmental Microbiology (2008) 10(12), 3275–3283.
1021	Gopalakrishnan, P. et al., “Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients”, Science (2018) 359, 97-103.
1022	Definition of “bacterial isolate”, Collin English Language Dictionary: https://www.collinsdictionary.com/dictionary/english/bacterial-isolate
1023	Definition of “purify”, Collin English Language Dictionary: https://www.collinsdictionary.com/dictionary/english/purify
1024	Pardon, “The blockade of immune checkpoints in cancer immunotherapy”, Nat Rev Cancer 12(4): 252-264 (2012), Author Manuscript, published May 4, 2016
1025	Ma et al., “Current status and perspectives in translational biomarker research for PD-1/PD-L1 immune checkpoint blockade therapy”, Journal of Hematology & Oncology (2016) 9:47
2002	<i>Curriculum Vitae</i> of Wendy S. Garrett, M.D., Ph.D.

Exhibit No.	Description
2003	Nardinocchi <i>et al.</i> , “Interleukin-17 and interleukin-22 promote tumor expression in human nonmelanoma skin cancer,” <i>European Journal of Immunology</i> , 45:922-931 (March 2015)
2004	Vetizou <i>et al.</i> , “Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota,” <i>Science</i> , 350(6264):1079-1084 (November 2015)
2005	Sivan <i>et al.</i> , “Commensal <i>Bifidobacterium</i> promotes antitumor immunity and facilitates anti-PD-L1 efficacy,” <i>Science</i> , 350(6264):1084-1089 (November 2015)
2006	Ye <i>et al.</i> , “The Role and Regulation of Human Th17 Cells in Tumor Immunity,” <i>The American Journal of Pathology</i> , 182(1):10-20 (January 2013)
2007	He <i>et al.</i> , “IL-17 promotes tumor development through the induction of tumor promoting microenvironments at tumor sites and myeloid derived suppressor cells,” <i>Journal of Immunology</i> , 184(5):2281-2288 (March 2010)
2008	Brandt <i>et al.</i> , “An overview of fecal microbiota transplantation: techniques, indications, and outcomes,” <i>Gastrointestinal Endoscopy</i> , 78(2):240-249 (May 2013)
2009	Vindigni <i>et al.</i> , “Fecal Microbiota Transplantation,” <i>Gastroenterology Clinics of North America</i> , 46(1):171-185 (March 2017)
2010	Youngster <i>et al.</i> , “Oral, frozen fecal microbiota transplant (FMT) capsules for recurrent <i>Clostridium difficile</i> infection,” <i>BMC Medicine</i> , 14:134 (September 2016)
2011	Khan <i>et al.</i> , “Antioxidants Keep the Potentially Probiotic but Highly Oxygen-Sensitive Human Gut Bacterium <i>Faecalibacterium prausnitzii</i> Alive at Ambient Air,” <i>PLOS One</i> , 9(5):e96097 (May 2014)
2012	U.S. Patent Application Publication No. 2016/0193257 A1 to Honda <i>et al.</i> , published July 7, 2016

Exhibit No.	Description
2013	Kuzu <i>et al.</i> , “Current State of Animal (Mouse) Modeling in Melanoma Research,” <i>Cancer Growth and Metastasis</i> , 8(Suppl 1):81-94 (October 2015)
2014	Dankort <i>et al.</i> , “Braf ^{V600E} cooperates with <i>Pten</i> loss to induce metastatic melanoma,” <i>Nature Genetics</i> , 41(5):544-552 (May 2009)
2015	Segata <i>et al.</i> , “Metagenomic biomarker discovery and explanation,” <i>Genome Biology</i> , 12(6):R60 (June 2011)
2016	Hadrup <i>et al.</i> , “Effector CD4 and CD8 T Cells and Their Role in the Tumor Microenvironment,” <i>Cancer Microenvironment</i> , 6(2):123-133 (August 2013)
2017	Peske <i>et al.</i> , “Control of CD8 T-cell Infiltration into Tumors by Vasculature and Microenvironment,” <i>Advanced Cancer Research</i> , 128:263-307 (June 2015)
2018	Chaput <i>et al.</i> , “Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab,” <i>Annals of Oncology</i> , 28(6):1368-1379 (June 2017)
2019	Baruch <i>et al.</i> , “Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients,” <i>Science</i> , 371(6529):602-609 (February 2021)
2020	Davar <i>et al.</i> , “Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients,” <i>Science</i> , 371(6529):595-602 (February 2021)
2021	Wang <i>et al.</i> , “IL-17 can promote tumor growth through an IL-6-Stat3 signaling pathway,” <i>The Journal of Experimental Medicine</i> 206(7):1457-1464 (July 2009)
2022	Wang <i>et al.</i> , “IL-17 Enhances Tumor Development in Carcinogen-Induced Skin Cancer,” <i>Cancer Research</i> , 70(24):10112-10120 (December 2010)

Exhibit No.	Description
2023	Villarino <i>et al.</i> , “Composition of the gut microbiota modulates the severity of malaria,” <i>Proceedings of the National Academy of Sciences</i> , 113(8):2235-2240 (February 2016)
2024	Xin <i>et al.</i> , “Isolation, identification and characterization of human intestinal bacteria with the ability to utilize chloramphenicol as the sole source of carbon and energy,” <i>FEMS Microbiology Ecology</i> , 82(3):703-712 (December 2012)
2025	Milojević, S., “Nature, Science, and PNAS Disciplinary profiles and impact,” <i>Scientometrics</i> , 123:1301-1315 (May 2020)

V. PERSON OF ORDINARY SKILL IN THE ART

24. As an expert, I have offered opinions throughout this declaration from the perspective of a POSA. I understand that a POSA is a hypothetical person who is presumed to be aware of all pertinent art, who thinks along conventional wisdom in the art, and is a person of ordinary creativity.

25. I understand that Dr. Robinson opined that “a POSA in September 2016 would have had education and/or experience in the field of microbiology, and/or oncology, and knowledge of the scientific literature concerning the same [and the] experience and education levels may vary between persons of ordinary skill, with some persons holding a basic Bachelor’s degree with four to five years of relevant work experience, and others holding a Masters or Ph.D. but having fewer years of experience.” EX1003, ¶25. I disagree with Dr. Robinson’s

assessment of the level of skill of a POSA. Given that the '838 Patent is directed to methods of reducing or delaying the growth of skin cancer tumors, the level of skill of a POSA provided by Dr. Robinson is too low.

26. Instead, a POSA relevant to the '838 Patent would typically have an advanced degree such as an M.D. or a Ph.D., with experience and training in oncology and several years of experience with administering oncology treatments to subjects and evaluating results of such treatments, and have experience or knowledge in microbiome science and its modulation, inclusive of studies that involve stool microbiome profiling, as well as experience in, or knowledge of, related research and development of bacterial-based cancer treatments.

27. A POSA may also have worked as part of a multi-disciplinary team, drawing upon his or her own skills and taking advantage of certain specialized skills of others in the team, to solve a given problem. For example, such a team may include a clinician, immunologist, microbiologist, bioinformatician, molecular biologist, manufacturing specialist, and/or pharmaceutical formulator.

VI. LEGAL BASIS FOR MY ANALYSIS

28. In formulating my opinions set forth in this Declaration, I have applied the following legal principles.

A. Claim construction

29. I understand that in a PGR, patent claim terms are given their ordinary

and customary meaning as understood by a POSA at the time of the invention, in view of the patent's specification and its prosecution history – unless the patent explicitly defines the claim term. I also understand that when a patent explicitly defines a claim term in the specification, the patent's definition controls.

30. I understand that claim 1 is the sole independent claim in the '838 Patent and that claims 2-19 are dependent claims (depending directly or indirectly from claim 1). I understand that a dependent claim contains all limitations of the claim(s) from which it depends. Thus, I understand that claims 2-19 contain all limitations of claim 1, as well as any additional claims from which they depend.

B. Written description

31. I understand that the written description provided by a patent specification must convey clearly to POSAs, that the applicant was in possession² of the claimed invention as of the patent's filing date. And I understand that this involves an objective inquiry into the four corners of the specification from the perspective of a POSA.

32. I further understand that this written description requirement must be applied in the context of the particular invention and the state of the knowledge in

² I understand possession does not mean physical possession and does not require making or testing the invention.

the art. In addition, I understand that a patent specification is written for a POSA, and that such a hypothetical person presumably has all of the knowledge of the state of the art as of the patent's filing date, in addition to the knowledge provided by the patent specification itself.

33. I understand that there is sufficient written description support when a POSA can visualize or recognize the identity of the claimed subject matter, and that the claimed subject matter need not be provided verbatim in a specification because a skilled artisan comes to the patent with knowledge in the art and it is therefore unnecessary to spell out every detail of the invention in the specification for a skilled artisan to conclude that there is written description support.

34. I understand that assessing whether there is written description support for a genus³ claim in the biological arts involves consideration of a number of factors, including (i) nature and scope of the claims; (ii) existing knowledge in the particular field and extent and content of the prior art; (iii) maturity of the science of technology and scientific and technologic knowledge already in existence; and (iv) predictability of the aspect at issue.

³ I understand a genus claim to be a claim covering multiple embodiments, or "species."

C. Enablement

35. I understand that an enabling disclosure must allow a POSA to make and use the full scope of the claimed invention without undue experimentation as of the filing date. I understand that the following factors can be used to determine whether undue experimentation is needed (the so-called *Wands* factors): (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

36. I understand that the determination that “undue experimentation” would have been needed to make and use the claimed invention is a conclusion reached by weighing the above-noted factual considerations.

D. Indefiniteness

37. I understand that a patent claim is indefinite if, when read in light of the patent’s specification and the prosecution history, the claim fails to inform a POSA as to the scope of the invention with reasonable certainty. I understand that the level of ordinary skill in the art plays a role in an indefiniteness analysis, because the patent claims are assessed from the viewpoint of a POSA.

E. Obviousness

38. I understand that an obviousness analysis involves comparing a claim

to the prior art to determine whether the claimed subject matter would have been obvious to a POSA in view of the prior art and general knowledge in the prior art. I understand that obviousness must be assessed from the viewpoint of a POSA at the time of the invention. I further understand that to establish obviousness, a party must perform the following factual inquiries: (a) determining the scope and content of the prior art; (b) ascertaining the differences between the claimed invention and the prior art; and (c) resolving the level of skill in the art.

39. I understand that combining or modifying the teachings of the prior art to achieve the claimed invention is a way to establish obviousness. I understand that where there is a reason to modify or combine the prior art to achieve the claimed invention, there must also be a reasonable expectation of success in doing so. I understand that the reason to combine prior-art references can come from a variety of sources, not just the prior art itself or the specific problem the patentee was trying to solve. And I understand that the references themselves need not provide a specific hint or suggestion of the alteration needed to arrive at the claimed invention; the analysis may include recourse to logic, judgment, and common sense available to a person of ordinary skill that does not need to be explicit in any reference.

40. I understand that a “reasonable expectation of success” is assessed in view of the prior art and general knowledge in the art from the viewpoint of a

POSA, and it does not require an absolute certainty of success.

41. I also understand that, before reaching a conclusion that the claimed invention would have been obvious, one must consider any objective evidence of non-obviousness. The objective evidence of non-obviousness can include evidence of commercial success attributable to the claimed invention, evidence of industry praise for the claimed invention, evidence of a long-felt need that was solved by the claimed subject matter, evidence that others copied the claimed subject matter, or evidence that the claimed subject matter achieved an unexpected, superior result relative to the closest prior art. I understand that such evidence must have a nexus, or causal relationship, to the claimed subject matter beyond what was available in the prior art, and must be commensurate in scope with the patent claim(s) at issue.

VII. THE '838 PATENT CLAIMS WOULD NOT HAVE BEEN OBVIOUS IN VIEW OF HONDA AND GAJEWSKI

A. Dr. Robinson fails to show that a POSA would have had a reason to combine Honda and Gajewski for reducing or delaying growth of a skin cancer tumor.

1. Dr. Robinson fails to discuss the cancer-promoting role of Th17 cells demonstrated in the art.

42. Dr. Robinson opines that “both Honda and Gajewski pertain to bacteria of *Ruminococcus*⁴ for addressing cancer,” and that “a POSA would be motivated to apply Honda’s more generalized teachings related to ‘cancer’

⁴ *Ruminococcus* is a genus within the family Ruminococcaceae.

treatment to the specific cancers recited in Gajewski.” EX1003, ¶182. In particular, Dr. Robinson opines that a POSA would have chosen Honda because the reference “is directed to compositions of human-derived bacteria that induce proliferation of Th17 cells.” EX1003, ¶165. I disagree. Dr. Robinson fails to account for the fact that the prior art discloses that Th17 cells can *promote* tumor growth, including skin cancers. EX2021, Abstract; EX2022, 10113; EX2003, 927.

43. Dr. Robinson fails to mention the contrasting observations in the field prior to September 2016 regarding the role of Th17 cells⁵ in tumors. In fact, Wang 2010 (“Wang II”) disclosed that “the presence of Th17 cells in tumors has been associated with *both* favorable and unfavorable prognoses.” EX2022, 10112. Wang 2009 (“Wang I”) reported that “Th17 cells promote tumor growth” of melanoma in mice. EX2021, Abstract, FIG. 1, 1459. Detrimental Th17 responses were described in carcinogen-induced skin cancer as well, with Wang II concluding that “Th17 responses can enhance carcinogenesis” and that IL-17 “is an important tumor-promoting element in [] skin carcinogenesis.” EX2022, 10113. Likewise,

⁵ A POSA would have understood that T-helper 17 (“Th17”) cells are a subset of T helper cells that produce the cytokine IL-17 and generally function in a host’s defense against microbial infections but can also promote inflammatory and autoimmune diseases. EX2006, 10-11.

Nardinocchi 2015 disclosed that for nonmelanoma skin cancer (basal-cell carcinoma and squamous-cell carcinoma), “IL-17...promote[s] tumor-cell proliferation and migration in vitro, and tumor-cell growth in vivo.” EX2003, 927. Therefore, it was general knowledge in the art prior to September 2016 that Th17 cells can promote cancer, including skin cancers.

44. Dr. Robinson fails to provide an explanation of why, in light of this art, a POSA would then have had a reason to use Honda’s methods of inducing Th17 cell proliferation for reducing or delaying growth of skin cancer when the art taught that such a composition could *promote* cancer. As such, a POSA would not have started with Honda’s compositions to arrive at the claimed methods for reducing or delaying the growth of cancer in the ’838 patent.

2. Neither Honda nor Gajewski disclose Ruminococcaceae bacteria are beneficial for reducing or delaying growth of skin cancer.

45. Dr. Robinson further argues a POSA would have been motivated to combine the teachings of Honda and Gajewski because “both Honda and Gajewski pertain to bacteria of *Ruminococcus*...for addressing cancer in a subject” and Gajewski identifies that *Ruminococcus* bacteria “would be useful” for skin cancer tumors. EX1003, ¶¶181-182. Dr. Robinson is wrong. Gajewski does *not* teach that *Ruminococcus* is beneficial for reducing or delaying growth of a skin cancer tumor.

46. In fact, Gajewski states that “the presence or increased level of one or

more microbes,” including bacteria belonging to the genus *Ruminococcus*, “*potentiates cancer/tumor growth*, spread (e.g., malignancy), and/or evasion of treatment/immune response.” EX1012, 22:11-14 (emphasis added). Gajewski further suggests “modulating the levels of one or more commensal microbes,” which includes *Ruminococcus*, by “*decreasing levels*” of the microbe. EX1012, 2:14-19 (emphasis added). Dr. Robinson fails to explain why a POSA would have had a reason to administer *Ruminococcus* bacteria to reduce or delay tumor growth, in view of the disclosures in Gajewski.

47. Dr. Robinson also wrongly asserts that Gajewski teaches that bacteria belonging to the genera *Ruminococcus* were associated with anti-tumor activity. EX1003, ¶173. Specifically, Dr. Robinson incorrectly states that “[c]omparative analysis of specific bacterial taxa showed that 97 taxa were significantly more abundant in JAX mice relative to TAC mice, and 15 taxa were significantly increased in JAX-fed TAC mice relative to TAC-fed TAC mice, including bacteria belonging to the genera [sic] *Ruminococcus*.” EX1003, ¶173. Again, Dr. Robinson misreads Gajewski. Gajewski identified “51 taxa” that were significantly increased in JAX-fed TAC mice, not “15 taxa.” EX1012, 49:3-5. However, Dr. Robinson fails to explain how or why a POSA would have chosen *Ruminococcus* from this list of 51 taxa.

48. Importantly, after analyzing the data from the 51 taxa, Gajewski

concluded that out of the 51 potential anti-skin cancer taxa identified, the *only* taxon with a significant positive association with anti-tumor response was *Bifidobacterium*, and not Ruminococcaceae. EX1012, 49:3-24. Gajewski further stated as a conclusion to the experiments described that “[c]ollectively, these data point to *Bifidobacterium* as a positive regulator of anti-tumor immunity in vivo.” EX1012, 50:22-23. As such, a POSA reviewing Gajewski would have been motivated to administer *Bifidobacterium* instead of Ruminococcaceae to reduce or delay tumor growth.

49. Dr. Robinson provides no explanation of why a POSA would have disregarded Gajewski’s conclusions regarding *Bifidobacterium* and chosen *Ruminococcus* instead. Thus, a POSA would not have been motivated to combine Honda and Gajewski to arrive at the claimed methods because Honda’s methods promote cancer growth and Gajewski concludes that only *Bifidobacterium* are beneficial for skin cancer treatment.

B. Dr. Robinson also fails to explain why a POSA would have had a reasonable expectation of success in light of the prior art.

50. Dr. Robinson opines that a POSA would have had a reasonable expectation of success in arriving at the claimed methods because “it was state of the art to modify bacterial microbiomes for purposes of treating cancer, and both Honda and Gajewski pertain to bacteria of *Ruminococcus*...for addressing cancer in a subject.” EX1003, ¶182. I disagree because contrary to Dr. Robinson’s

opinions, a POSA would have understood that the two studies that looked at the connection between the gut microbiome and anti-skin cancer response prior to September 2016, Sivan and Vetizou, did not find Ruminococcaceae as useful for treating skin cancer, and specifically pointed to bacteria other than Ruminococcaceae as beneficial. EX2004, Abstract; EX2005, Abstract. Thus, a POSA would not have had a reasonable expectation of success in reducing or delaying growth of a skin cancer tumor with Ruminococcaceae because no study had identified these bacteria as associated with an anti-tumor response.

51. Vetizou analyzed the composition of the gut microbiome in patients with metastatic melanoma and reported that the *Bacteroides* genus (specifically *B. fragilis* and/or *B. thetaiotaomicron*) and the Burkholderiales order were positively associated with anti-cancer effects in melanoma patients and having a “tumoricidal effect” in mice. EX2004, Abstract, FIG. 3. Vetizou did not identify Ruminococcaceae as one of the bacteria with such anti-cancer effects. EX2004, Abstract, FIG. 3. A POSA would have understood that the human gut microbiome contains bacteria from the family Ruminococcaceae because Ruminococcaceae are commonly found in significant numbers in the human gut microbiota. EX2004, FIG. 4; EX1014, 3. Yet, Vetizou concludes that “the antitumor effects of [immunotherapy] depend on distinct *Bacteroides* species.” EX2003, Abstract. Thus, a POSA would have concluded from reviewing Vetizou that the *Bacteroides*

genus was associated with anti-cancer effects, rather than Ruminococcaceae.

52. In contrast, Sivan found that *only* the genus of *Bifidobacterium* (species *B. breve*, *B. longum*, and *B. adolescentis*) “showed a positive association with antitumor T cell responses” in a mouse melanoma model. EX2005, 1085, FIG. 3B. Sivan compared subcutaneous melanoma growth in genetically similar mice derived from two different mouse facilities, Jackson Laboratory (JAX) and Taconic Farms (TAC). EX2005, 1084. A POSA would have understood that the gut microbiome of JAX mice naturally contains both *Bacteroides* and Ruminococcaceae bacteria. EX2005, 1085; EX2023, FIG. S6C. However, Sivan did not observe a positive association between Ruminococcaceae or *Bacteroides* and antitumor T cell responses. Therefore, a POSA would have concluded that *Bifidobacterium* and not *Bacteroides* or Ruminococcaceae were associated with an anti-cancer response.

53. Furthermore, Dr. Robinson’s own cited reference, Pitt 2016 (EX1007), discusses the inconsistencies between the Vetizou and Sivan papers. Indeed, Pitt 2016 explains that the Vetizou and Sivan studies “differ with respect to the specific bacteria identified as causing [anticancer] effects” and further discloses that “there is a complexity here that must be addressed in future studies.” EX1007, 1262. However, Dr. Robinson fails to explain how a POSA viewing these references would have had a reasonable expectation of success in view of the

unpredictability and inconsistency in the findings of Vetizou and Sivan, when Dr. Robinson's Pitt 2016 references clearly identifies such inconsistencies. Nor has Dr. Robinson explained why a POSA would have reasonably expected success in reducing or delaying growth of skin cancer by administering bacteria from the family Ruminococcaceae in view of the art directing POSAs to other taxa of bacteria: *Bifidobacterium*, *Bacteroides*, or Burkholderiales and not Ruminococcaceae.

54. Dr. Robinson further opines that a POSA would have had a reasonable expectation of success because both Honda and Gajewski “demonstrated a delay in tumor growth through a similar mechanism of action” and “enhance[d] induction and infiltration of tumor-specific CD8⁺ T cells⁶.” EX1003, ¶183. I disagree because Honda did not disclose any experiments related to tumor growth, and Th17 cells were not “known in the art to enhance induction and infiltration of tumor-specific CD8⁺ T cells.” EX1003, ¶183. As I discuss above, Dr. Robinson failed to mention the cancer-*promoting* effects of Th17 cells. Dr. Robinson also ignored that IL-17 produced by Th17 cells had also been shown to *inhibit* CD8⁺ T cell infiltration into tumors. EX2007, Abstract; EX2021, Abstract; EX2022, 10113; EX2003, 927. A POSA would not have reasonably expected a Ruminococcaceae

⁶ CD8⁺ T lymphocytes kill cancer cells within the tumor. EX2016, 124.

composition would reduce or delay skin cancer tumor growth when Honda showed Ruminococcaceae bacteria increase infiltration of Th17 cells.

55. Thus, contrary to Dr. Robinson's allegations, a POSA would not have had a reasonable expectation of success in reducing or delaying growth of a skin cancer tumor by administering Ruminococcaceae.

VIII. THE '838 PATENT'S CLAIM 4 WOULD NOT HAVE BEEN OBVIOUS IN VIEW OF HONDA, GAJEWSKI, AND MIQUEL

56. Dr. Robinson opines that claim 4 would have been obvious in view of Honda, Gajewski, and Miquel because "Miquel teaches that '*Faecalibacterium prausnitzii* is the most abundant bacterium' in feces of healthy adults, and is one of the most prolific members of the Ruminococcaceae family." EX1003, ¶186. Dr. Robinson provides no further arguments than those put forth regarding Honda and Gajewski, other than to say "a POSA would have recognized that the fecal compositions administered in Honda and Gajewski would have contained beneficial Ruminococcaceae bacteria of the species *Faecalibacterium prausnitzii*." EX1003, ¶187. As I discussed in detail in Section VII.B, nothing in Honda or Gajewski would have led a POSA to choose Ruminococcaceae, let alone *F. prausnitzii*, and Dr. Robinson fails once again to explain how a POSA would have a reason to combine Honda, Gajewski, and Miquel to arrive at claim 4. Therefore, in my opinion, a POSA would not have had a reason to combine Honda, Gajewski, and Miquel and would not have had a reasonable expectation of success in arriving

at claim 4.

**IX. THE '838 PATENT CONTAINS ADEQUATE WRITTEN
DESCRIPTION SUPPORT FOR THE CLAIMED INVENTION**

57. Dr. Robinson opines that claims 1-19 lack adequate written description support because the '838 Patent specification allegedly “contains no disclosure whatsoever that can be said to reasonably convey to a POSA that the inventors had possession of a composition for reducing or delaying growth of all skin cancer tumors in all subjects as of September 27, 2016.” EX1003, ¶¶110-142. Dr. Robinson makes several arguments to support his opinion that the '838 Patent lacks adequate written description support. As I discuss in Section VI.B, I understand that the written description provided by a patent specification must convey to a POSA that the applicant was in possession of the claimed invention. In contrast to the implications made by Dr. Robinson, I understand possession does not mean physical possession and does not require making or testing the invention. I further understand there is sufficient written description support (and, thus, possession) when a POSA can visualize or recognize the identity of the claimed subject matter, and I understand that the claimed subject matter need not be provided verbatim. Additionally, I understand that a POSA comes to the patent with knowledge in the art. A POSA would come to the '838 Patent with a higher level of skill than claimed by Dr. Robinson, as I describe in Section V. Accordingly, a POSA would disagree with each of Dr. Robinson's arguments for

the reasons discussed below.

A. Dr. Robinson wrongly argues that the '838 Patent lacks actual clinical data

58. Dr. Robinson argues the '838 Patent allegedly has inadequate written description for practicing the claimed methods in humans because the only experiments allegedly conducted with human patients “involved the *characterization* of gut and buccal microbiome of metastatic melanoma patients,” to “identify potential differences in the respective bacterial composition of the microbiome” between responder and non-responder patients. EX1003, ¶114. Not so. The '838 Patent provides data from human melanoma patients undergoing anti-PD-1 therapy that demonstrates clinical response is associated with Ruminococcaceae bacteria. EX1001, FIGs. 1-24. Indeed, Example 1 of the '838 Patent disclosed that human melanoma patients with a high abundance of Ruminococcaceae had “significantly prolonged PFS [progression-free survival] versus those with low abundance,” which a POSA would have understood to mean there is an association between increased abundance of Ruminococcaceae and delaying growth of melanoma. EX1001, 154:18-20, 156:9-157:9, FIGs. 4A-D, 18-22. Moreover, Example 1 discloses that after comparing the tumor associated

immune infiltrates⁷ a “higher density of CD8+ T lymphocytes in baseline⁸ samples of [responders] versus [non-responders]” were observed. EX1001, 156:9-157:9, FIGs. 4A-D, 18-22. CD8+ T lymphocytes are “direct cancer cell killers” within the tumor, and the “density and distribution [of CD8+ T cells in tumor infiltrate] was shown to independently predict...survival in patients with melanoma.” EX2016, 124. Specifically, a major determinant of responsiveness to immunotherapy “is the presence of effector CD8 T-cells in tumors *prior to initiating therapy*,” as was described in the ’838 Patent. EX2017, 3. Therefore, a POSA would have understood that the high density of CD8+ T lymphocytes shown in tumors of responder patients, which are enriched for Ruminococcaceae, indicates anti-tumor activity. EX2017, 3. Although these clinical data are absent in Dr. Robinson’s discussion, the specification would inform a POSA that the inventors of the ’838 Patent had possession of a composition for reducing or delaying growth of skin cancer in humans.

⁷ Tumor infiltrates consist of immune cells that infiltrate tumor tissue.
EX2017, 1.

⁸ Baseline samples are samples taken prior to administering any anti-tumor therapy.

B. A POSA would have understood that the '838 Patent's experiments conducted using a mouse melanoma model system were predictive of other subjects and other cancer types

59. Dr. Robinson wrongly argues that the disclosed experiments using a mouse melanoma model system in the '838 Patent specification constitutes a “limited disclosure.” EX1003, ¶¶113-117. I understand an aspect of assessing written description support involves considering the predictability of the science, and a POSA would have been aware of—and read the specification in light of—references describing the extensive use of mouse models to predict clinical response in humans. Indeed, Kuzu 2015 disclosed that mice were “[t]he most widely used preclinical model” because they “accurately simulate true melanoma behavior” and “recapitulate natural tumor progression, from proliferation to invasion and metastasis.” EX2013, 81-82. Kuzu 2015 further disclosed that the same mouse melanoma model used in the '838 Patent experiments “allow[s] for the interaction of melanoma cells with competent T-cells and B-cells found naturally in the human melanoma microenvironment,” which a POSA would have understood to be clinically relevant in humans, because it recapitulates the immune system interactions that would have an effect on disease progression in humans. EX2013, 84. Further, Dankort 2009 describes that this mouse melanoma model “may afford a detailed analysis of mechanisms that promote melanoma cell migration, local invasion and metastasis in a manner that more closely

recapitulates the clinical course of melanoma recurrence in humans.” EX2014, 550. Thus, a POSA would have understood the ’838 Patent’s experiments in mice were not a “limited disclosure,” but rather experiments that are clinically relevant to the treatment of humans.

60. Dr. Robinson also argues “a POSA would not have understood PO to be in possession of a method of treating every type of ‘skin cancer tumor’ in every type of subject,” and states in relation to the experimental results in mice that “much of the data presented in the specification is unreliable” or lacked “statistical significance.” EX1003, ¶¶137-138. Dr. Robinson is wrong on all counts. First, Dr. Robinson fails to explain why melanoma would not be representative of other types of skin cancer tumors. Second, a POSA would not have understood the data presented in the ’838 Patent to be “unreliable” because, unlike Dr. Robinson, a POSA would have considered the entirety of what was disclosed. For instance, Example 4 of the ’838 Patent describes three fecal microbiome transplantation experiments (FMT1, FMT2, and FMT3) in which germ-free⁹ mice were transplanted with human stool from a responder (R-FMT) or from a non-responder (NR-FMT) to anti-PD-1 therapy and then injected with melanoma cells. EX1001, 182:11-25. These experiments demonstrated FMT from responder patients,

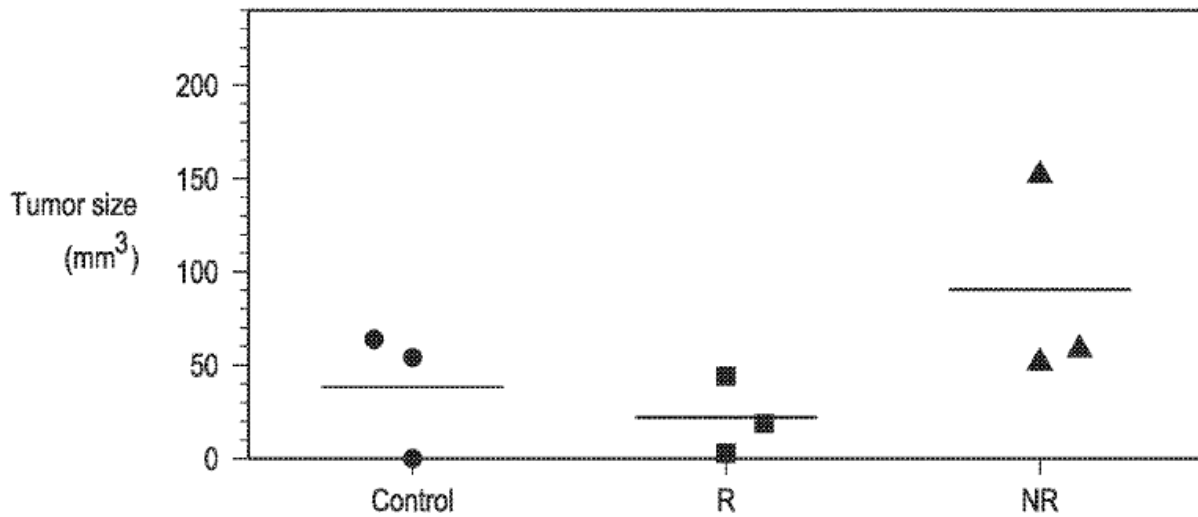
⁹ Germ-free mice lack an endogenous microbiome.

abundant in Ruminococcaceae, resulted in a statistically significant ($p=0.04$) delay in melanoma growth in mice (FMT1), which was “validate[d]” by “using stools from different [] patients” in FMT3, and resulted in an “enhanced response to PD-L1 therapy” in FMT2. EX1001, 182:62-65, 184:27-30, Example 4, FIGs. 28A-C, 32A-C.

61. FMT1 results “demonstrated *significantly delayed tumor growth* by day 14 in R-FMT group compared to mice in those transplanted with stool from NR to anti-PD-1,” which were statistically significant ($p=0.04$). EX1001, 182:7-50, Example 4, FIG. 25B¹⁰. Indeed, Figure 25B shown below depicts a comparatively smaller tumor size in mice transplanted with stool from responders (squares) compared to mice transplanted with stool from non-responders (triangles). EX1001, FIG. 25B.

¹⁰ There seems to be a typographical error on column 182, line 31 where the ’838 Patent indicates that the results from FMT1 are shown in Figure 1B instead of Figure 25B.

FIG. 25B

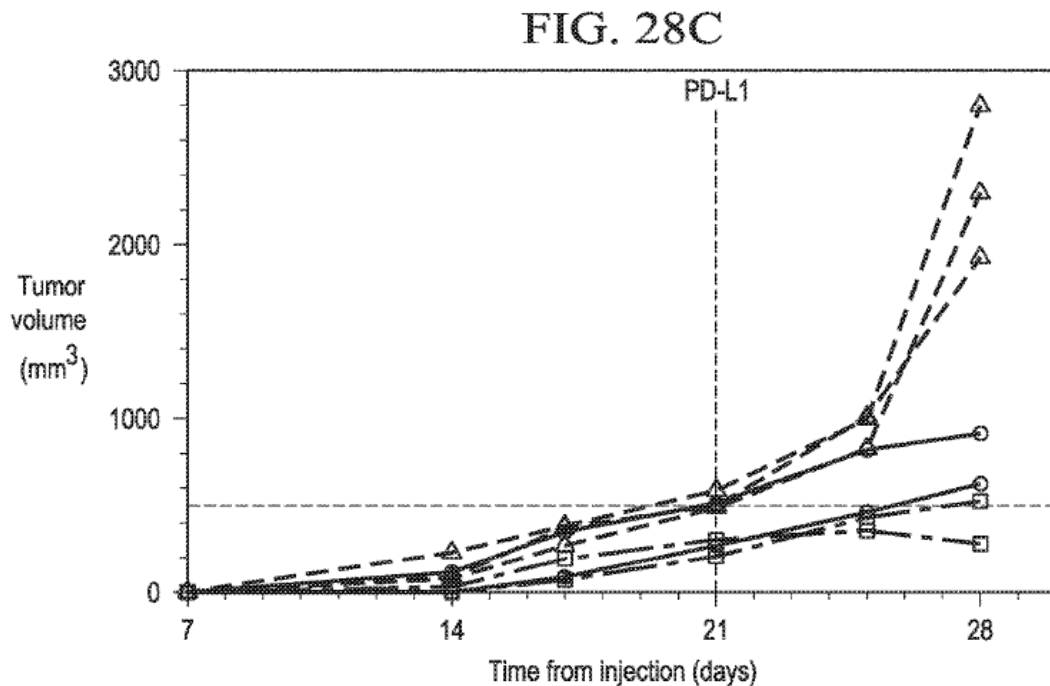


EX1001, FIG. 25B.

62. Experiment FMT2 repeats the procedure of FMT1 and further describes treating mice with anti-PD-L1¹¹ antibodies once tumor volume reached a certain size. EX1001, 183:7-9. R-FMT mice treated with anti-PD-L1 antibodies demonstrated an enhanced response to the therapy compared to NR-FMT mice, in addition to delayed tumor growth before anti-PD-L1 treatment. EX1001, 183:10-16, FIGs. 28B-C. Dr. Robinson opines that “while the tumor size in mice receiving FMT2 in Example 4 were significantly different at day 14 (before anti-PD1 treatment), no such statistical significance was observed at the end of the experiment,” and concludes the data “do not provide evidence of enhancing anti-PD(L)1.” EX1003, ¶138.

¹¹ PD-L1 is a ligand of the PD-1 receptor. EX1001, 26:36-38.

63. On the contrary, even without statistical significance a POSA would have understood from Figure 28C that mice receiving FMT from responder patients (R-FMT) clearly had improved responses to anti-PD-L1 therapy relative to mice receiving FMT from non-responder patients (NR-FMT). EX1001, FIG. 28C (reproduced below). The final tumor volume in R-FMT (squares) was less than half the size of NR-FMT (triangles) by day 28, and the result is visually apparent. EX1001, FIG. 28C.



EX1001, FIG. 28C.

64. Further, Dr. Robinson takes issue with the sample size in experiment FMT3, in which mouse tumor growth was measured for 28 days after receiving R-FMT or NR-FMT to “validate the finding that a ‘favorable’ gut microbiome

restrains tumor growth...similar to FMT1 using stools from different R and NR patients.” EX1001, 184:27-44. As described above, FMT1 demonstrated “significantly delayed tumor growth by day 14 in R-FMT group,” and FMT3 demonstrated the same pattern using different responder and non-responder patients. EX1001, 182:28-31, 184:27-30. Even if a POSA understood the sample size to be “simply too small to show ‘significance’” (EX1003, ¶138), a POSA would nonetheless have understood that the results recapitulate the same finding shown in the data from FMT1 because the same methods were performed with different donor patients and a similar result was demonstrated. EX1001, 184:40-44. Conveniently, Dr. Robinson cherry-picks FMT3 to discuss in support of his allegation that the data presented are “unreliable,” and fails entirely to mention FMT1 - the study it was designed to validate. Therefore, in contrast to Dr. Robinson’s opinion, a POSA would have found the experiments disclosed in the ’838 Patent to be relevant to the treatment of other subjects, including humans, and to support the claimed methods.

C. Dr. Robinson wrongly argues that the experimental results in the ’838 Patent could not be ascribed to bacteria from the family Ruminococcaceae

65. Dr. Robinson further states that none of the “results of the experimentation...[can] be ascribed to bacteria particularly from the family Ruminococcaceae,” and “bacteria from the family Ruminococcaceae were found in

both the ‘responder’ and ‘non-responder’ fecal samples.” EX1003, ¶115. However, a POSA would disagree with Dr. Robinson as the ’838 Patent demonstrated that Ruminococcaceae were the most distinguishing taxa of the responder gut microbiota. EX1001, 153:12-40; 154:5-10; 153:37-45; FIGs. 2C-F, 3D, Tables 4-5. The ’838 Patent disclosed using linear discriminant analysis of effect size (LEfSe), which “detect[s] bacterial organisms and functional characteristics differentially abundant between two or more microbial environments,” to identify the taxonomic differences in the gut microbiome between responders and non-responders. EX1001, 153:28-34; EX2015, 3. Ruminococcaceae were consistently the most differentially-abundant gut bacteria in responder patients, which was shown with a high degree of statistical significance ($p < 0.001$) and effect size in Figure 2E. EX1001, FIG. 2E. Within the family Ruminococcaceae, the genus *Faecalibacterium* and species *Faecalibacterium prausnitzii* were also significantly differentially-abundant in responder patients ($p < 0.05$). Thus, a POSA would have understood the ’838 Patent to disclose the gut microbiota of responder patients were clearly enriched for Ruminococcaceae on all taxonomic levels. EX1001, 153:12-40, 154:5-10, 153:37-45, FIGs. 2C-F, 3D, Tables 4-5.

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

a POSA would disagree with Dr. Robinson's statement that "a POSA would understand that at least several species of Ruminococcaceae would *not* result in the claimed 'reduction' or 'delay' in skin cancer tumor growth" because they were not shown to be significantly associated with non-response to anti-PD-1 therapy.

EX1003, ¶131. In addition, as of September 27, 2017, a POSA would have assessed the specification of the '838 Patent in light of Chaput, which confirmed a positive association between Ruminococcaceae bacteria and skin cancer treatment in human patients. EX2018, Abstract, 1370. Chaput disclosed metastatic melanoma patients "whose baseline microbiota was enriched with *Faecalibacterium* genus and other Firmicutes...had longer progression-free survival ($P=0.0039$) and overall survival ($P=0.051$)" compared to patients enriched with *Bacteroides*. EX2018, Abstract, 1370.

D. Dr. Robinson fails to consider the considerable knowledge a POSA would have had in formulating and administering bacterial-based compositions

67. Dr. Robinson argues that formulating a composition to perform the claimed method would require "a comprehensive pre-formulation strategy that includes a host of experimentation and testing." EX1003, ¶120. I disagree. Even a POSA meeting Dr. Robinson's lower defined skill level would have understood how to formulate and administer bacterial compositions, including FMT and bacterial-based compositions, in light of the specification and numerous references

addressing these subjects that Dr. Robinson failed to discuss. EX1015, 1016; EX2008, 240; EX2010, 2; EX2009, 172, Table 1, 180. A POSA formulating bacterial-based compositions would have had ample instruction from the prior art, and thus a POSA would not have needed the specification to spell out every detail of these methods to adequately describe the claimed method. For example, there was guidance in the prior art on formulating bacterial-based compositions with Ruminococcaceae bacteria such as *F. prausnitzii*. EX2011. Khan demonstrated that despite *F. prausnitzii* being anaerobic, formulation with “the antioxidants cysteine and riboflavin plus the cryoprotectant inulin” facilitated “survival of *F. prausnitzii* upon exposure to air” which “paves the way for the development of synbiotics containing faecalibacteria.” EX2011, Abstract, 4.

68. Similarly, for a POSA using FMT, references such as Brandt and Vindigni would have provided guidance for the following questions: “How is FMT performed?”; “How should donors and recipients be screened?”; “Which route of administration is best?”; “Which diluent should be used?”; “How much stool is needed?”; etc. EX2008; EX2009. References such as Youngster would have taught a POSA about techniques related to “oral” FMT. EX2010, 2. Further, a POSA would have been able to apply these methods to anaerobic bacteria such as Ruminococcaceae because these culture and formulation methods were also established. EX2011, Abstract.

69. Thus, Dr. Robinson mischaracterizes the data presented in the '838 Patent and the state of the art in 2017. Further, I understand that written description is assessed as of September 27, 2017; however, the subject matter of the '838 Patent claims is also adequately described in light of the state of the art as of September 27, 2016, because the existing knowledge in the field was mature as exemplified by references such as Brandt, Youngster, and Khan described above. EX2008; EX2010; EX2011.

X. THE '838 PATENT CLAIMS ARE ENABLED

A. Dr. Robinson failed to demonstrate that practicing the claimed methods would have required undue experimentation

70. Dr. Robinson argues that claims 1-19 of the '838 Patent lack enablement because the “specification fails to teach a POSA how to make and use the full scope of the claimed invention without considerable experimentation.” EX1003, ¶143. However, Dr. Robinson does not demonstrate the need for undue experimentation, which I understand is the legal standard for enablement. In fact, Dr. Robinson provides no other arguments and instead relies on the written description portion of his Declaration. EX1003, ¶143. For the same reasons discussed in Section IX, Dr. Robinson failed to discuss the instructive prior art that a POSA would have been aware of, and thus failed to articulate, let alone demonstrate, that any experimentation needed to practice the claimed methods would have been undue.

71. Dr. Robinson opines that “[c]ultivating and formulating bacteria into pharmaceutically acceptable compositions can also present myriad issues,” but he fails to explain how this statement demonstrates a requirement for undue experimentation. EX1003, ¶98. Further, a POSA would have understood that practicing the claimed methods would not require “cultivating” Ruminococcaceae. For example, the ’838 Patent describes obtaining a composition comprising Ruminococcaceae can be obtained from “human fecal suspension...using a 100µm strainer.” EX1001, 184:65-185:2. As I describe in Section IX.D above, preparing a fecal sample for FMT was routine practice for a POSA and would not have required undue experimentation. Dr. Robinson concedes that a POSA would have known that “the bacterial product can be purified and concentrated,” or obtained using “serial dilutions of fecal content samples cultured by plating under a [sic] strictly anaerobic conditions.” EX1003, ¶167. Dr. Robinson also states a POSA would have also known “how to formulate and administer the compositions.” EX1003, ¶168. Thus, Dr. Robinson failed to demonstrate undue experimentation would be required for a POSA to practice the claimed methods.

B. Dr. Robinson ignored post-filing date evidence demonstrating the claimed methods can be practiced in humans as described in the specification

72. I understand that post-filing evidence can be used to demonstrate that the disclosure in the specification would have been enabling. Two such studies

published in 2021, Baruch and Davar, validated the methodology disclosed in the '838 Patent. Baruch published a study titled "Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients." EX2019. Baruch "performed a phase 1 clinical trial to assess the safety and feasibility of fecal microbiota transplantation (FMT) and reinduction of anti-PD-1 immunotherapy in 10 patients with anti-PD-1-refractory metastatic melanoma." EX2019, Abstract. Similar to the mouse FMT examples in the '838 Patent, Baruch disclosed selecting fecal donors who "had previously been treated with anti-PD-1 monotherapy for metastatic melanoma and had achieved a [complete response (CR)] for at least 1 year." EX2019, 1. Baruch disclosed preparing the donor feces for colonoscopy and oral administrations of FMT according to "Good Manufacturing Processing conditions," and followed methods described by Youngster *et al.* in 2016. EX2019, Suppl. Materials, 3. FMT was "performed by means of both a colonoscopy (protocol day 0) and the administration of oral stool capsules followed by reinduction of anti-PD-1 therapy." EX2019, 1.

73. The patients receiving FMT from donor 1 did not have a different microbiome composition than the donor 2 group pre-treatment, but the two groups had "a clear post-treatment donor-based division," indicating that the FMT was effective in modulating the microbiome. EX2019, 2, FIG. 2A. Three patients demonstrated a complete or partial response to treatment, including "a complete

resolution of all lesions” (i.e., reduction of tumor size), and all three received FMT from donor 1. EX2019, 2, FIG. 1. While both donors were selected based on favorable microbiota profiles, some taxa were differentially abundant between donor 1 and donor 2, including two species of Ruminococcaceae being significantly more abundant in donor 1. EX2019, 2, 4, FIGs. 2B, S8. To achieve these results, Baruch described utilizing the FMT procedure described and claimed in the '838 Patent. EX1001, Example 5, Claim 1. Specifically, Baruch describes administering a purified composition consisting of “a fecal suspension...sieved to remove particulate matter” similar to the '838 Patent’s description of administering a “cleared supernatant from...[a] human fecal suspension [] obtained using a 100 µm strainer.” EX2019, Suppl. Materials; EX1001, 184:65-67. Further, as described above, the FMT composition included “bacteria belonging to the family Ruminococcaceae.” EX2019, 2, 4, FIG. 2B, S8. . As such, a POSA would not have understood Baruch to have undertaken undue experimentation to practice the claimed methods of the '838 Patent.

74. Similarly, Davar published a study titled “Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients” in 2021 that also validated the methodology disclosed in the '838 Patent without the need for undue experimentation. EX2020. Indeed, Davar disclosed a “single-arm clinical trial to evaluate the safety and efficacy of FMT obtained from individual long-term

responder (R) melanoma patients together with anti-PD-1 in PD-1-refractory metastatic melanoma patients.” EX2020, 1. Sixteen melanoma patients received FMT from “[s]even donors, including four with complete response (CR) and three with partial response (PR),” administered in a “single donor-derived FMT.”

EX2020, 1. The FMT was effective as “gut microbiota composition changed after a single FMT in Rs and nonresponders (NRs).” EX2020, 3. In total, six patients demonstrated a “clinical benefit” from treatment. EX2020, 1. Three patients had “objective responses,” including one with a complete response and two with a partial response. EX2020, 1. Further, an additional three patients demonstrated “durable [stable disease] lasting >12 months,” meaning progression did not occur for at least one year. EX2020, 1. Davar disclosed “[m]ost of the significantly enriched taxa in Rs belonged to the phyla Firmicutes (Lachnospiraceae and Ruminococcaceae families) and Actinobacteria (Bifidobacteriaceae and Coriobacteriaceae families).” EX2020, 3. Similar to Baruch, Davar described using the FMT technique in the ’838 Patent. Thus, Davar, too, disclosed being able to practice the claimed method, without reporting any undue experimentation.

75. Both Baruch and Davar were published in *Science*, which is one of the “most prestigious” scientific journals and “among the most influential journals.” EX2025, Abstract. Given their impact in the field, a POSA would have been aware of these articles, yet Dr. Robinson notably did not mention either study.

76. Thus, in view of the above, a POSA would not have required undue experimentation to practice the claimed methods of the '838 Patent. Further, I understand enablement is assessed as of September 27, 2017, however, in my opinion the claimed methods of the '838 Patent would have also been enabled in light of the state of the art as of September 27, 2016, because as I discuss in Section IX.D., the existing knowledge in the field was mature as exemplified by references such as Brandt, Youngster, and Khan. EX2008; EX2010; EX2011.

XI. THE '838 PATENT CLAIMS ARE NOT INDEFINITE

77. Dr. Robinson argues that claims 1-19 of the '838 Patent are indefinite because “the ‘isolated’ and ‘purified’ claim limitations...fail to reasonably inform a POSA about the scope of the claimed invention.” EX1003, ¶¶144-145. For example, Dr. Robinson argues the “plain and ordinary meaning of the terms ‘isolated’ and ‘purified’ does not comport with the patent record and, thus, cannot reasonably inform a POSA about the scope of the claimed invention.” EX1003, ¶147. A POSA would disagree with Dr. Robinson’s assertions regarding the interpretation of the claims. It is my understanding that when a patent specification provides an explicit definition for a claim term, the patent’s explicit definition is used to interpret the claims, in lieu of any “plain and ordinary” meaning that a claim term may have. A POSA reading the '838 Patent specification would have understood that the specification provides explicit definitions for the terms

“isolated” and “purified.” EX1001, 28:40-29:11. Further, Dr. Robinson provides no citations or other support for the claim that a POSA would not have “any understanding as to the metes and bounds of these two claim limitations.” EX1003, ¶159. Dr. Robinson also takes issue with the ’838 Patent describing “an ‘isolated’ bacterium is one that is ‘produced, prepared, purified, and/or manufactured *by the hand of man*’.” EX1003, ¶154. However, a POSA would have understood “by the hand of man” to distinguish from a composition that is naturally occurring.

78. Dr. Robinson further argues the claims of the ’838 Patent are indefinite because “‘bacteria belonging to the family *Ruminococcaceae*’ is a moving target,” and supports this argument with references from 2006, 2009, and 2019. EX1003, ¶¶161-163. A POSA would disagree with Dr. Robinson because as of September 27, 2017, the term “*Ruminococcaceae*” was not unclear, and Dr. Robinson failed to assess the term as of this date. Further, Dr. Robinson complains that a reference from 2006 proposed adding a 12th genus of *Ruminococcaceae*, yet this additional genus was still discussed in *the initial announcement* of the *Ruminococcaceae* family. EX1003, 162; EX1015, 1016. Therefore, a POSA would have learned of all 12 genera from the *same reference* in 2009 and would certainly have been aware of all 12 genera as of the filing date, as well as the earliest priority date, of the ’838 Patent. Dr. Robinson’s arguments hinge on incorrect assumptions; thus, a POSA would not agree that the claims of the ’838 Patent are indefinite.

XII. THE EXAMINER CONSIDERED THE SAME OR SUBSTANTIALLY THE SAME ARGUMENTS AS NOW PRESENTED BY DR. ROBINSON

79. Dr. Robinson argues that the claims are allegedly unpatentable for lack of adequate written description support, lack of enablement, and indefiniteness. However, Dr. Robinson does not explain whether or how his arguments differ from what the Examiner already considered during prosecution.

80. As outlined above, I have reviewed the prosecution history of the '838 Patent and I note that the Examiner rejected the then-pending claims for “failing to comply with the written description requirement.” The Examiner explained:

Because, the specification while [sic] provides support for reduc[ing] implanted melanoma tumor growth in germ-free mice by direct injection of a fecal microbiota sample (FMT) to said tumor... it does not necessarily provide[] support for “**administering to the subject a composition comprising one or more isolated or purified population of bacteria belonging to the family Ruminococcaceae**” for treating **cancer** or reducing or delaying **tumor growth** in a subject in need thereof, as required by amended claim 44.

EX1002, 89 (emphasis added).

81. Amended claim 44 as referred to by the Examiner when rejecting the claims for lack of written description corresponds to claim 1 of the '838 Patent after amendment. I provide a comparison of the two claims in the table below (**Table A**).

Amended claim 44 referred to by the Examiner	Claim 1 of the '838 Patent
“A method of treating cancer or reducing or delaying tumor growth in a subject in need thereof, comprising administering to the subject a composition comprising one or more isolated or purified population of bacteria belonging to the family Ruminococcaceae.” EX1002, 107.	“A method of reducing or delaying growth of a skin cancer tumor in a subject in need thereof, comprising administering to the subject a composition comprising an isolated or purified population of bacteria belonging to the family Ruminococcaceae.” EX1001, 189:2-6.

82. In response to the Examiner’s written description rejection, Patent Owner filed a response (EX1002, 43-49), explaining, for example, that the clinical data in Example 1 show “statistically significant enrichment of the family Ruminococcaceae in responder (‘R’) samples relative to non-responder (‘NR’) samples” and “**a strong positive correlation between the abundance of Ruminococcaceae/*Faecalibacterium* in the gut and cytotoxic T-cell infiltrate in the tumor.**” EX1002, 44-45. Patent Owner also explained that “in Example 4, stool samples from R or NR patients were administered orally to germ-free mice” and that administration of “an FMT sample derived from an R patient... **significantly delayed tumor growth relative to NR FMT administration.**” EX1002, 46. The Examiner reviewed Patent Owner’s response and required deleting “treating cancer” and changing “tumor growth” to “growth of a **skin cancer tumor**” to allow the claims, which I understand indicates that the Examiner withdrew the written description rejection. EX1002, 11-19.

83. Dr. Robinson's arguments under written description, enablement,¹² and indefiniteness rely on the same factual considerations discussed during prosecution. Each bolded feature considered by the Examiner in her written description rejection (reference is made to the citations above with added emphases) is the same as Dr. Robinson's focus on claim breadth. I provide an overview of Dr. Robinson's and the Examiner's arguments in the following table (**Table B**):

¹² I note that in the context of his enablement arguments Dr. Robinson merely refers to the arguments under written description, and he does not provide additional arguments regarding enablement. EX1003, ¶143.

Examiner's argument ¹³	Dr. Robinson's argument
“the specification... does not necessarily provide[] [sic] support for ‘administering to the subject a composition comprising one or more isolated or purified population of bacteria belonging to the family Ruminococcaceae’ for treating cancer or reducing or delaying tumor growth in a subject in need thereof, as required by amended claim 44.” EX1002, 89 (emphasis added).	<u>Written Description</u> “‘administering’, ‘subject’, ‘composition’, and ‘skin cancer tumor’ have such <i>limitless range</i> that the <i>scope</i> of the Challenged Claims are entirely untethered from any reasonable construction of PO’s purported ‘invention’ described in the specification.” EX1003, ¶110 (emphasis added). “The <i>over breadth</i> of Claim 1 is further compounded by PO’s use of the ‘comprising’ transition.” EX1003, ¶134 (emphasis added).
“the specification... does not necessarily provide[] [sic] support for ‘administering to the subject a composition comprising one or more isolated or purified population of bacteria belonging to the family Ruminococcaceae’ for treating cancer or reducing or delaying tumor growth in a subject in need thereof, as required by amended claim 44.” EX1002, 89 (emphasis added).	<u>Enablement</u> “As set forth in §VII.A of the Petition [i.e., the section regarding Written Description], a POSA would conclude that the specification, considered as a whole, fails to enable a POSA to formulate any composition of bacteria belonging to the Ruminococcaceae family, that can be administered through any means possible, at any concentration, in any type of subject, and is safe and effective at treating any type of skin cancer tumor... Thus, in view of the foregoing, a POSA would conclude that the ’838 Patent specification fails to teach a POSA how to make and use the <i>full scope</i> of the claimed invention....” EX1003, ¶143 (emphasis added).

¹³ In the context of the Examiner’s written description rejection.

Examiner's argument ¹³	Dr. Robinson's argument
“the specification... does not necessarily provide[] [sic] support for ‘administering to the subject a composition comprising one or more isolated or purified population of bacteria belonging to the family Ruminococcaceae’ for treating cancer or reducing or delaying tumor growth in a subject in need thereof, as required by amended claim 44.” EX1002, 89 (emphasis added).	<u>Indefiniteness</u> [T]he ‘isolated’ and ‘purified’ claim limitations... fail to reasonably inform a POSA <i>about the scope</i> of the claimed invention.” EX1003, ¶144 (emphasis added). “This fits the definition of indefiniteness, and, in addition, gives rise to lack of enablement <i>across the breadth of the claims</i>.” EX1003, ¶145. EX1003, ¶154, referring to “unbridled breadth” of the term isolated. EX1003, ¶163, referring to “<i>scope</i> of the <i>Ruminococcaceae</i> taxonomic family” (emphasis added).

84. Dr. Robinson also argues that the claims are not supported because “the only experiments conducted with human patients involved the *characterization* of gut and buccal microbiome of metastatic melanoma patients.” EX1003, ¶114. Further, Dr. Robinson alleges that the patent’s experimental results cannot be “ascribed to bacteria particularly from the family Ruminococcaceae.” EX1003, ¶115. I disagree with these arguments for the reasons that I discuss above in ¶¶58, 65, and 66. Further, the Examiner also considered the sufficiency of clinical data during prosecution. In the response to the Examiner’s Written Description rejection, Patent Owner discussed Example 1 and its results. EX1002,

44-45 (“Example 1... demonstrates [] statistically significant enrichment of the family Ruminococcaceae in responder (‘R’) samples relative to non-responder (‘NR’) samples”; “[the analysis] demonstrate[ed] **a strong positive correlation between the abundance of Ruminococcaceae/*Faecalibacterium* in the gut and cytotoxic T-cell infiltrate in the tumor**, and a strong negative correlation with Bacteroidales”; **“patients with high abundance of Ruminococcaceae had higher levels of effector CD4+ and CD8+ T cells in the systemic circulation with a preserved cytokine response to PD-1 blockade**, whereas patients with a higher abundance of Bacteroidales in the gut microbiome had higher levels of regulatory T cells (Treg) and myeloid derived suppressor cells (MDSC)”).

85. Moreover, Dr. Robinson argues that the disclosed experiments on a mouse melanoma model system in the ’838 Patent specification constitute a “limited disclosure” and that “much of the data presented in the specification is unreliable.” EX1003 at ¶¶117, 138. As I discuss above in ¶¶59-64, Dr. Robinson’s arguments are incorrect. And I note that the Examiner was also aware of the Patent Owner’s mouse experiments and considered the same during prosecution. For example, the Examiner explained in the written description rejection recited above that “the specification [] provides support for reduc[ing] implanted melanoma tumor growth in germ-free mice by direct injection of a fecal microbiota sample (FMT) to said tumor.” EX1002, 89. And the Examiner also considered Patent

Owner's submission discussing the experimental data in mice. EX1002, 46-47 ("in Example 4, stool samples from R or NR patients were administered orally to germ-free mice"; "FMT1 was an FMT sample derived from an R patient. Administration of FMT1 **significantly delayed tumor growth relative to NR FMT** administration"; "Relative to NR stool administration, FMT1 resulted in stable transplantation... and 'a higher percentage of innate effector cells (expressing CD45⁺CD11b⁺Ly6G⁺) and lower frequency of suppressive myeloid cells (expressing CD11b⁺CD11c⁺) in the spleen compared to mice in the NR-FMT group"; "To validate the experiment and control for FMT source, the tumor growth experiment was repeated with a different donor source (FMT3), and the result was the same"). Thus, Patent Owner clearly presented those experimental results to the Examiner.

86. Further, the Examiner discusses the claim terms "isolated" and "purified" during prosecution. As outlined above, the features "isolated" and "purified" were part of claim 44 rejected by the Examiner for lack of written description (EX1002, 89, and **Table A** above). Further, when applying Miquel (EX1014) during prosecution, the Examiner explained that it "disclose[s] a method of preventing cancer in a subject at risk of developing cancer comprising administering to the subject at risk of developing a cancer composition comprising at least one **isolated or purified** population of bacteria *Faecalibacterium*

prausnitzii (administering *Faecalibacterium prausnitzii* to mice...)." EX1002, 116 (emphasis in bold added) (citing Abstract, which discusses administering *F. prausnitzii* strain A2-165 and its culture supernatant).

87. Dr. Robinson also argues that the claims are allegedly indefinite as "[t]he Bacteria in the 'Family Ruminococcaceae' is a Moving Target." EX1003, § IX.C.2. In this context, I note that the Examiner, likewise, was aware of the *reclassification* of *Faecalibacterium prausnitzii* in 2002, as she pointed to "p. 255 left-hand column last paragraph" of Miquel, which discusses such reclassification. EX1002, 116.

88. Taken together, the Examiner expressly considered during examination the same or substantially the same factual issues now alleged by Dr. Robinson. I also note that Dr. Robinson did *not at all* address how the arguments presented now under written description, enablement, and indefiniteness are in any way different than what the Examiner already considered during prosecution.

XIII. HONDA IS CUMULATIVE TO TOKYO CITED AND DISCUSSED DURING PROSECUTION

89. Dr. Robinson relies on Honda (EX1011) and Gajewski (EX1012) for Ground 4 to contend that claims 1-3 and 5-19 would have been obvious over Honda in view of Gajewski, and on Honda, Gajewski, and Miquel (EX1014) for Ground 5, to allege that claim 4 would have been obvious over Honda in view of Gajewski and Miquel. EX1003, ¶108. Dr. Robinson asserts that "Honda is directed

to a method for treating, reducing the severity of, or preventing at least one disease or condition, such as infectious diseases or cancer, by orally administering to an individual in need thereof of [sic], a composition comprising bacteria within the family Ruminococcaceae.” EX1003, ¶165. The teachings Dr. Robinson relied on in Honda are entirely cumulative (i.e., the same or substantially the same as) of the teachings of Tokyo (US 2016/0193257; EX2012), which was cited during prosecution.

90. I reviewed the prosecution history of the '838 Patent (EX1002) and note that Tokyo, which I understand is a U.S. patent application published July 7, 2016, was submitted to the Examiner in an Information Disclosure Statement (IDS) as reference description (Ref. Des.) A1 (EX1002, 169). I understand that the Examiner's initials on Form 1449 indicate that she has considered Tokyo (EX1002, 125).

91. In the following table (**Table C**), I provide a comparison between the information Dr. Robinson extracts from Honda with the disclosure in Tokyo. Dr. Robinson does not provide such a comparison or a comparison of Honda to any other reference cited during prosecution. Dr. Robinson relies on disclosure in Honda that is substantially the same as the disclosure in Tokyo.

Dr. Robinson’s reliance on Honda	Tokyo’s same or substantially the same disclosure
<i>Role of commensal microorganisms</i>	
EX1003, ¶166, with reference to ¶2 of Honda: “Honda discloses that ‘[h]undreds of species of commensal microorganisms are harbored in the gastrointestinal tracts of mammals, where they interact with the host immune system.’ EX-1011 ¶2. The presence of these intestinal bacteria ‘enhances protective functions of the mucous membranes, enabling the host to mount robust immune responses against pathogenic microbes invading the body.’ <i>Id.</i>”	¶3 of Tokyo: “Hundreds of species of commensal microorganisms are harbored in the gastrointestinal tracts of mammals, where they interact with the host immune system. ...the presence of intestinal bacteria enhances protective functions of the mucous membranes, enabling the host to mount robust immune responses against pathogenic microbes invading the body.”
<i>Bacterial compositions; administration to humans</i>	
EX1003, ¶166, with reference to ¶¶6, 10, 12 of Honda: “Honda teaches that compositions, comprising one or more intestinal commensal bacteria cultured from human feces, can be administered to humans, including bacteria within the purported family Ruminococcaceae. EX-1011 ¶¶6, 10, 12¹⁴ (identifying	¶39 of Tokyo: “The method comprises administering to the individual a bacterial composition described herein or a pharmaceutical composition comprising a bacterial composition described herein. [The composition comprises] at least one organism... selected from the group consisting of:

¹⁴ I note that contrary to Dr. Robinson’s argument (EX1003, ¶166), none of the paragraphs Dr. Robinson cites (EX1011, ¶¶6, 10, 12) actually disclose that the bacteria “can be administered to humans.” Each of ¶¶6, 10, and 12 merely refers to

Dr. Robinson's reliance on Honda	Tokyo's same or substantially the same disclosure
'<i>Ruminococcus</i> sp. M-1, <i>Ruminococcus gnavus</i>... <i>Ruminococcus</i> sp. 16442... <i>Anaerotruncus colihominis</i>... or a culture supernatant of such bacteria')."	...<i>Anaerotruncus colihominis</i>, <i>Anaerotruncus colihominis</i> DSM 17241, <i>Ruminococcus</i> sp. ID8...;¹⁵ [or] a culture supernatant of one or more of the bacteria." (I also refer to ¶¶28, 32, 35, 37, 81, 87, 88, 89, 121 of Tokyo referring to compositions comprising bacteria from the family Ruminococcaceae.) ¶81 of Tokyo: "Bacteria described herein were isolated from human fecal samples using the methods outlined in Examples 19 to 28." ¶107 of Tokyo: "The composition of the present invention can be used for animals, including humans."
<i>Isolation of bacteria</i>	
EX1003, ¶167, with reference to ¶23 of Honda: "Honda teaches a method for obtaining Th17-inducing bacterial compositions	¶¶183, 184 of Tokyo: "<Isolation of Bacterial Strains> Bacterial strains were isolated from the cecal contents of [subjects] by plating

compositions comprising certain bacteria or their culture supernatant.

Nevertheless, Tokyo also discloses that bacteria "can be administered to humans."

¹⁵ Bacteria that all belong to the family of Ruminococcaceae.

Dr. Robinson’s reliance on Honda	Tokyo’s same or substantially the same disclosure
comprising, <i>inter alia</i>, ‘obtaining (at least one) sample, such as fecal sample ... culturing the sample ... and isolating pure bacterial strains from the resulting colonies.’ EX-1011 ¶23.... Beneficial commensal bacteria can also be isolated using ‘serial dilutions of [f]ecal¹⁶ content samples cultured by plating under a strictly anaerobic conditions.’ EX-1011 ¶23...”¹⁷	serial dilutions of the cecal samples under... strictly anaerobic conditions” ¶81 of Tokyo: “Bacteria described herein were isolated from human fecal samples using the methods outlined in Examples 19 to 28.” ¶138 of Tokyo:

¹⁶ Honda in ¶23 actually refers to cecal samples and not fecal samples.

While fecal samples refer to samples from excreted stool (such as from humans or mice), cecal samples refer to samples from isolated cecum (such as cecum isolated from mice). For example, ¶¶76, 78 of Honda refer to “[h]uman stool” and “UC patient feces,” whereas ¶¶80, 82 of Honda refer to “cecal contents from mice.” I also refer to ¶¶149 and 151 of Tokyo.

¹⁷ I note that Dr. Robinson also refers to “Honda disclos[ing] the use of antibiotics to screen and isolate useful bacteria from fecal samples.” EX1003, ¶167. The use of antibiotics to select for bacteria is one of several well-known techniques to isolate bacteria. I refer, for example, to Exhibit 2024 at 704 (showing isolation of human intestinal bacteria by dissolving fecal material in media containing the antibiotic chloramphenicol). Tokyo exemplifies other techniques for

Dr. Robinson’s reliance on Honda	Tokyo’s same or substantially the same disclosure
	“obtaining a fecal sample from the non-human mammal, diluting the fecal sample (for example diluting it by volume by a factor of 10, 100, 1,000, or 10,000), thereby producing a diluted fecal sample... plating serial dilutions, under... strictly anaerobic conditions..., and [] picking a single colony from the culture plate.”
EX1003, ¶167, with reference to ¶42 of Honda: “EX-1011... ¶42 (“human-derived bacteria” means bacterial species... isolated from a fecal sample... obtained from a human individual or whose ancestors were isolated’).”	¶85 of Tokyo: ““human-derived bacteria’ means bacterial species that have been isolated from a fecal sample... obtained from a human individual or whose ancestors were isolated...”
<i>Purification</i>	
EX1003, ¶167, with reference to ¶63 of Honda: “Honda teaches that the bacterial product can be purified and concentrated; for instance from fermentation broth. EX-1011 ¶63.”	¶113 of Tokyo: “The bacterial product can be purified and concentrated from the fermentation broth...”

isolation of bacteria using chemicals (“‘Chloroform treatment’ of a fecal sample... is a method that isolates the bacteria in the fecal sample”) (¶92 of Tokyo).

Dr. Robinson's reliance on Honda	Tokyo's same or substantially the same disclosure
<i>Formulation and administration</i>	
EX1003, ¶168, with reference to <u>¶¶21, 55</u> of Honda: “Honda teaches how to formulate and administer the compositions. Honda teaches that the commensal bacterial compositions can be administered by a variety of routes, including orally, and can be formulated into several different oral forms (e.g., powders, lyophilizates, liquids formulation, etc.). EX-1011 ¶¶21, 55.”	<u>¶46</u> of Tokyo: “The composition described herein can be administered by a variety of routes and in one embodiment, is administered orally to an individual in need thereof, such as a patient in need thereof. The composition may be administered in a number of oral forms, such as in spore-form (in a dry powder or dissolved in a liquid formulation), in enteric capsules, in sachets, or in a food matrix, such as yogurt, or a drink.” <u>¶99</u> of Tokyo: “Pharmaceutical preparations can be formulated from the bacterial compositions described by drug formulation methods known to those of skill in the art. For example, the composition can be used orally or parenterally in the form of capsules, tablets, pills, sachets, liquids, powders...”
EX1003, ¶168, with reference to <u>¶¶57-60</u> of Honda: “Honda teaches a variety of excipients, carriers, and other additives useful for formulating a pharmaceutically acceptable preparation for oral ingestion. EX-1011 ¶¶57-60.”	<u>¶¶100-103</u> of Tokyo: “For formulating these preparations, the bacterial compositions can be used in appropriate combination with carriers... including one or more of the following: ... a stabilizer... an excipient, a vehicle, a preservative, a

Dr. Robinson's reliance on Honda	Tokyo's same or substantially the same disclosure
	binder, a diluent... a buffer agent...and other additives." "A pharmaceutical preparation or formulation and particularly a pharmaceutical preparation for oral administration, comprises an additional component that enables efficient delivery of the bacterial composition of the present invention to the colon..."
<i>Dosing</i>	
EX1003, ¶168, with reference to ¶64 of Honda: "Honda discloses that the bacterial concentration 'is generally 0.01 mg/kg body weight to 100 mg/kg body weight, and in specific embodiments, 1 mg/kg body weight to 10 mg/kg body weight.' EX-1011 ¶64."	¶117 of Tokyo: "the amount per administration or ingestion is generally 0.01 mg/kg body weight to 100 mg/kg body weight, and, in specific embodiments, 1 mg/kg body weight to 10 mg/kg body weight."
<i>Evaluation of cell proliferation</i>	

Dr. Robinson's reliance on Honda	Tokyo's same or substantially the same disclosure
EX1003, ¶169, with reference to <u>¶71</u> of Honda: “Honda teaches a method to determine whether the desired Th17 cell proliferation effect has been induced (<i>i.e.</i>, through a measurement index comparing the number, ratio, function, or expression of Th17 cells), including specific means by which to measure that effect (<i>e.g.</i>, northern blotting, RT-PCR, radioimmunoassays, etc.). EX-1011 ¶71.”	<u>¶128</u> of Tokyo: “Whether administration of the bacterial composition induces the proliferation and/or accumulation of regulatory T cells can be determined by using, as an index, increase or reinforcement of at least one of the following: the number of regulatory T cells, the ratio of regulatory T cells in the T cell group of the colon, a function of regulatory T cells, or expression of a marker of regulatory T cells.” <u>¶129</u> of Tokyo: “Methods for detecting such expression include northern blotting, RT-PCR, and dot blotting for detection of gene expression at the transcription level; ELISA, radioimmunoassays...”
<i>Cancer; oral administration</i>	
EX1003, ¶165, with reference to <u>¶1</u> and claim 12 of Honda: “Honda is directed to a method for treating, reducing the severity of, or preventing at least one disease or condition, such as infectious diseases or cancer, by orally administering to an individual in need thereof of, a composition comprising bacteria within the family Ruminococcaceae, alone or in combination with an antigen. EX-	<u>¶146</u> of Tokyo: “The composition described herein can be administered by a variety of routes and in one embodiment, is administered orally to an individual in need thereof, such as a patient in need thereof.” <u>¶97</u> of Tokyo: “target diseases for which the composition is useful for treatment

Dr. Robinson's reliance on Honda	Tokyo's same or substantially the same disclosure
1011 ¶1; Claim 12.”	include colon cancer...” ¶132 of Tokyo: “a disease or condition for which the bacterial composition is a potential treatment [includes] cancer” ¶95 of Tokyo: “The bacterial composition of the present invention can be used, for example, as a pharmaceutical composition for preventing or treating (reducing, partially or completely, the adverse effects of)...” ¶96 of Tokyo: “target diseases for which the composition is useful for treatment (reducing adverse effects or prevention)...”
<i>Th17 cell accumulation</i>	
EX1003, ¶165, with reference to ¶1 of Honda: “Honda is directed to compositions of human-derived bacteria that induce proliferation of Th17 cells. EX-1011 ¶1.” EX1003, ¶194, with reference to ¶¶5, 33 and Table 1 of Honda:	¶3 of Tokyo: “commensal microorganisms influence... accumulation of unique lymphocytes in mucosal tissues, including... IL-17-producing CD4-positive T cells (Th17)...” ¶251 of Tokyo (Example 19): “Human stool... was suspended with 20 ml phosphate-buffered saline (PBS),

Dr. Robinson's reliance on Honda	Tokyo's same or substantially the same disclosure
“Table 1 of Honda identifies three <i>Ruminococcus</i> bacterial strains ‘isolated from the [f]ecal contents¹⁸ of mice colonized with human patient stool and treated with ampicillin’ and found to ‘strongly induce the... proliferation and accumulation of Th17 cells’ that are responsible for fighting infections and cancer. EX-1011 Table 1, ¶¶5, 33.”	mixed with or without chloroform... The suspensions of untreated human feces (designated as ‘huUT’) and chloroform-treated human feces (designated as ‘huChloro’) were orally inoculated into Germ-free (GF) mice [referred to as exGF mice]... The suspension of huUT was inoculated into 4 GF mice, which were numbered from #A1 to #A4 [exGF+hUT mice]... Notably... a significant accumulation of IL-17-expressing CD4+ cells (namely, Th17 cells) was observed in exGF+huUT mice... (FIG. 1E, F).” I also refer to FIGs. 1E and 1F, and ¶¶55, 56 of Tokyo.

92. In the context of Tokyo's results in Example 19 with regards to Th17 cells (discussed in the last line in **Table C** above), I also note that Table 1B of Tokyo shows bacterial species identified by “16srRNA coding gene amplification and PCR metasequencing of bacterial DNA extracted from the cecal contents of mouse #A1...”. EX2012, ¶77. Among the identified bacteria for mouse #A1 (for which Th17 cell accumulation was observed) was *Anaerotruncus colihominis*, a bacterium belonging to the family of Ruminococcaceae (Table 1B of Tokyo). Tokyo refers to *Anaerotruncus colihominis* throughout its specification (I refer, for

¹⁸ Honda in ¶33 refers to cecal contents.

example, to Tokyo at ¶¶35, 39, and additional referenced paragraphs in **Table C** above). I note that also Dr. Robinson refers to *Anaerotruncus colihominis* (belonging to the family Ruminococcaceae) in the context of Honda. EX1003, ¶166 (“Honda teaches that compositions, comprising... bacteria cultured from human feces, can be administered to humans, including bacteria within the purported family Ruminococcaceae. EX-1011 ¶¶6, 10, 12 (identifying ‘...*Anaerotruncus colihominis*...’); emphasis added).

93. Taken together, as shown above (**Table C**), Honda’s disclosure relied on by Dr. Robinson is the same or substantially the same disclosure as in Tokyo, which was cited during prosecution. The extensive disclosure overlap between Honda and Tokyo is not surprising, because *all* inventors listed on the face of Honda are also listed on the face of Tokyo. First page of EX1011 and EX2012, respectively (“(72) Inventors”).

XIV. TOKYO WAS APPLIED DURING PROSECUTION IN THE SAME MANNER AS DR. ROBINSON APPLIES HONDA

94. As outlined above, I understand that the ’838 Patent resulted from the ’820 Application, which was originally filed as international Application No. PCT/US2017/053717. I understand that an International Searching Authority (ISA) usually conducts a search to discover prior art that may be relevant to the invention claimed in the international patent application, and that the results of the search are provided in an International Search Report (ISR). I also understand that each ISA

shall, at the same time as it establishes the ISR, also issue a Written Opinion as to whether the claimed subject matter appears, for example, to be novel and non-obvious.

95. When reviewing the prosecution history, I noted that Tokyo was not only provided to the United States Patent and Trademark Office (USPTO) in an Information Disclosure Statement (IDS) during prosecution, but the Office itself, acting as ISA,¹⁹ also cited Tokyo in the ISR as a “document of particular relevance,” for example, to claim 44 in PCT/US2017/053717. EX1002, 177, 667. I understand that then-pending claim 44 was examined during prosecution (EX1002, 132, 265) and corresponds to claim 1 of the ’838 Patent after amendment.²⁰

¹⁹ I understand that the ISR and Written Opinion indicate in the section “Name and mailing address of the ISA” that the ISA is the USPTO (“ISA/US”). EX1002, 177, 182, 638, 667.

²⁰ The amendments changed “treating or preventing cancer” (then-pending claim 44) to “reducing or delaying growth of a skin cancer tumor” (claim 1 as granted with the ’838 Patent) and bacteria belonging to “the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus *Faecalibacterium*” (then-pending claim 44) to bacteria belonging to “the family Ruminococcaceae” (claim 1 as granted with the ’838 Patent). EX1002, 620;

96. In the Written Opinion, the Office also discussed Tokyo and asserted that, for example, then-pending claim 44 is not novel over Tokyo. EX1002, 191, 193, 647, 649. Dr. Robinson makes substantially the same arguments with reference to Honda as the ISA made with reference to Tokyo in the Written Opinion. For example, neither Tokyo nor Honda refer to skin cancer as acknowledged by the ISA in the Written Opinion (in the context of Tokyo) and Dr. Robinson (in the context of Honda). EX1002, 193, 649; EX1003, ¶182. I provide a comparison of the arguments in the table below (**Table D**):

Dr. Robinson's Honda argument	ISA Examiner's Tokyo argument in the Written Opinion
"Honda is directed to a method for treating, reducing the severity of, or preventing... cancer , by orally administering to an individual in need thereof of, a composition comprising bacteria within the family Ruminococcaceae.... " EX1003, ¶165.	"Tokyo discloses a method of treating or preventing cancer... in a subject comprising administering to the subject a composition (a pharmaceutical preparation for oral administration...) comprising... bacteria... belonging to... family Ruminococcaceae[e] "... "Tokyo discloses the administration of the gut bacteria to treat or ameliorate cancer. " EX1002, 191, 193, 647, 649.
"Honda teaches specific methods for ' isolating or purifying ' the desired	Tokyo discloses "methods of identifying and culturing intestinal

EX1001, 189:2-6.

Dr. Robinson's Honda argument	ISA Examiner's Tokyo argument in the Written Opinion
intestinal commensal bacteria.” EX1003, ¶193.	commensal bacteria, isolated from humans.” EX1002, 191, 647.
“Honda teaches a variety of excipients, carriers, and other additives useful for formulating a pharmaceutically acceptable preparation for oral ingestion.” EX1003, ¶168.	Tokyo discloses “a pharmaceutical preparation for oral administration compris[ing] an additional component that enables efficient delivery of the bacterial composition... to the colon.” EX1002, 191, 647.
“While Honda teaches the use of <i>Ruminococcus</i> for treatment of diseases and cancer, it does not specifically identify a subset of cancers for which it is useful [including skin cancer].” EX1003, ¶182.	“Tokyo discloses the method of claim 44 [referring to cancer in general], but Tokyo does not disclose wherein the cancer is a skin cancer.” EX1002, 193, 649.

97. As shown above (**Table D**), Dr. Robinson relies on substantially the same arguments with respect to Honda (which is cumulative to Tokyo) as the ISA did with respect to Tokyo in the Written Opinion. Further, as discussed above, then-pending claim 44 of PCT/US2017/053717 (which was assessed in the Written Opinion) was examined during prosecution and corresponds to claim 1 of the '838 Patent (which is now assessed by Dr. Robinson) after amendment. I understand that both the ISR and the Written Opinion were provided with the IDS during prosecution. EX1002, 171 (Ref. Des. C8). I understand that the Examiner's initials on Form 1449 indicate that she has considered both the ISR and the Written

Opinion (EX1002, 127). Dr. Robinson did not address the ISA's discussion of Tokyo; nor did he provide any comparison of Honda with Tokyo. But, for the reasons discussed above, a POSA would have understood that Honda and Tokyo are substantially the same, and Dr. Robinson and the ISA made substantially the same arguments with respect to these references. Additionally, Dr. Robinson did not identify any errors the ISA or the Examiner made in their assessment of Tokyo.

XV. GAJEWSKI WAS CITED AS A DOCUMENT OF PARTICULAR RELEVANCE DURING PROSECUTION

98. The Examiner also considered the Gajewski reference during prosecution. Gajewski was not only cited in an IDS (Ref. Des. B33, EX1002, 170)²¹, but it was also cited by the ISA in the ISR (EX1002, 178, 668). The ISA cited Gajewski as relevant to multiple claims, including then-pending claim 44. As outlined above at ¶95, claim 44 of PCT/US2017/053717 was examined during prosecution and corresponds to claim 1 of the '838 Patent after amendment. Gajewski is categorized in the ISR as an "X" document, which is defined in the ISR as a "document of particular relevance." EX1002, 177, 178, 667, 668. The ISA also indicated that "relevant passages" can be found throughout the "**entire document**" of Gajewski. EX1002, 178, 668 (emphasis added). Dr. Robinson does

²¹ I understand that the Examiner's initials on Form 1449 indicate that she has considered Gajewski (EX1002, 126).

not comment on the ISA's characterization of Gajewski, let alone distinguish his arguments regarding Gajewski from the ISA's characterization of Gajewski.

Similarly, Dr. Robinson does not identify any errors in the ISA's or the Examiner's assessment of Gajewski.

XVI. MIQUEL WAS APPLIED DURING PROSECUTION IN THE SAME MANNER AS DR. ROBINSON APPLIES MIQUEL

99. The Examiner of the '838 Patent also considered the Miquel reference Dr. Robinson cites. A side-by-side comparison of Dr. Robinson's Miquel argument with the Examiner's Miquel argument during prosecution (**Table E** below) shows that the Examiner in fact considered the *same* argument during prosecution.

Dr. Robinson's Miquel argument	Examiner's Miquel argument
"Miquel reports that <i>F. prausnitzii</i>... is the most abundant bacterium in feces of healthy adults." EX1003, ¶178, "Miquel teaches that '<i>Faecalibacterium prausnitzii</i> is the most abundant bacterium' in feces of healthy adults." EX1003, ¶186.	"<i>Faecalibacterium prausnitzii</i> is the most abundant bacteria in the intestinal microbiota." EX1002, 116.
"A POSA would have... recognized the major role these butyrate producing bacteria play in the physiology of the human gut, including the 'numerous beneficial effects for health through... reduction of cancer progression' as taught by Miquel." EX1003, ¶187.	Miquel "further teach[es] beneficial effects of butyrate-producing <i>Faecalibacterium prausnitzii</i> for health and reduction of cancer progression." EX1002, 116.

100. As shown above (**Table E**), the Examiner's argument during prosecution regarding Miquel is the same as Dr. Robinson's argument regarding Miquel. Thus, Dr. Robinson's argument based on Miquel was already considered and applied by the Examiner.

101. Taking the discussion under Sections XII to XVI together, both art and arguments put forward by Dr. Robinson are the same or substantially the same as the art and arguments already considered by the Examiner during prosecution of the '838 Patent.

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

Executed on this 22 day of August, 2023.



Wendy S. Garrett, M.D., Ph.D.