

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

DANA-FARBER CANCER INSTITUTE, INC.,
Petitioner

v.

E.R. SQUIBB & SONS, L.L.C. & ONO PHARMACEUTICALS CO., LTD.,
Patent Owner

Case IPR2023-00501

U.S. Patent No. 8,008,449 B2
Filed: January 29, 2009
Issued: August 30, 2011
Inventors: Alan J. Korman et al.

Title: Human Monoclonal Antibodies to Programmed Death 1 (PD-1) and Methods
for Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination with
Other Immunotherapeutics

EXPERT DECLARATION OF GERARD ZURAWSKI, PH.D.

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I, Gerard Zurawski, declare as follows:

I. INTRODUCTION

1. I have been retained by counsel for Dana-Farber Cancer Institute, Inc. (“Dana-Farber” or “Petitioner”) as a technical expert in connection with the above-captioned proceeding. I have been asked to provide my opinions and views on the materials that I have reviewed in relation to U.S. Patent No. 8,008,449 B2 (EX1001, “the ’449 patent”), which I understand is assigned to E.R. Squibb & Sons, L.L.C. & Ono Pharmaceuticals Co., Ltd. (collectively, “Patent Owner”).

2. I understand that Dana-Farber intends to petition for *inter partes* review of the ’449 patent (“the Petition”) and will request that the United States Patent and Trademark Office cancel claims 1, 7-9, 12-16, and 21-23 (the “Challenged Claims”) of the ’449 patent as unpatentable.

3. My opinions in this expert declaration support Dana-Farber’s request for *inter partes* review of the ’449 patent and the cancellation of the Challenged Claims.

4. I am being paid at an hourly rate for my work on this matter. I have no personal or financial stake in the outcome of the present proceeding.

II. QUALIFICATIONS AND EXPERTISE

5. I received a Bachelor of Science Degree in Microbiology from the University of Sydney in 1972 and a Ph.D. in Genetics from the University of

Sydney in 1976. I also studied as a Postdoctoral Fellow at Stanford University in the laboratory of Dr. Charles Yanofsky from 1976 to 1979 and as a Fellow at the Commonwealth Scientific and Industrial Research Organization in Canberra, Australia from 1979 to 1982.

6. I have more than 30 years of industry experience as a researcher and teacher in molecular biology and protein engineering. I began my career with the DNAX Research Institute in Palo Alto, CA in 1982 and held various research and management positions at DNAX for the next 21 years, in areas such as cytokine and cytokine receptor discovery and characterization.

7. When I started at DNAX in 1982, I was a research scientist performing research related to the human immune system. During this time at DNAX, I studied the human interleukin-4 (“IL-4”) and interleukin-13 (“IL-13”) receptors and identified and characterized cytokines and their receptor interactions, including IL-13 and interleukin-25. This work involved monoclonal antibodies directed to immune cell surface receptors, e.g., some anti-human IL-4 receptor antibodies were found to be antagonists of IL-4 and IL-13 binding to cells that respond to these cytokines. This study showed that a set of anti-human IL-4 α receptor monoclonal antibodies varied in their reactivity to hIL-4R α as judged by

blotting, precipitation, inhibition of ¹²⁵I-hIL-4 binding, and cross-competition revealing some of the mAbs see distinct epitopes. EX1045.

8. In 1990, I was promoted to an Associate Directorship position at DNAX. As Associate Director, I led a team of several scientists in research related to the interaction of interleukin-2 with its receptor, IL-4 interaction with IL-4 receptor (“IL-4R”), and the interaction of IL-13 with IL-13 receptor (“IL-13R”). The success of this research justified greater resources and in 1995, I was promoted to a Senior Directorship position at DNAX, during which time I led a team of over 20 researchers and scientists. During this time, our group continued to focus on cytokine and cytokine discovery effort through genomic applications. We were immensely successful in mining expressed sequence tag data for cytokine and cytokine receptor discovery and subsequent biological characterizations.

9. Importantly, during this time, my team and I discovered IL-13R and determined that the primary binding subunit of human IL-4R is also a component of IL-13R. This work involved the use of IL-4 muteins and monoclonal antibodies directed to human IL-4R that we used in our research to discover the compositions of, and the mechanisms by which, IL-4 and IL-13 receptors operate in humans.

10. In 2004, I went to work at the Baylor Institute for Immunology Research in Dallas, Texas, where I am still employed today. At Baylor, I have led a vaccine-development program based on targeting antigens directly to human dendritic cells using antibody-antigen conjugates. This work is based on monoclonal antibodies directed to human dendritic cell surface receptors, and our laboratory has derived and characterized many antibodies against several different receptors as part of this effort. The laboratory also developed and characterized monoclonal antibodies against many other immune related cytokines and receptors, several of which have been licensed for use in research and one is being developed for clinical application. Currently, with this dendritic cell targeting platform technology our Baylor team and outside collaborators have successfully tested in human *in vitro* systems, as well as in mouse and monkey *in vivo* studies, novel vaccines against influenza, cancers, HIV, HCV, and HPV. Vaccines based on these studies are now in clinical development for HIV-1 therapeutic and prophylactic applications and for treatment of HPV-based cancers of the mucosa. I was appointed as the Director for the Center for Biotechnology at Baylor Institute for Immunology Research in 2012 and Co-Director of Baylor Institute for Immunology Research in 2014.

11. My current work continues to involve the characterization and study of immune-related monoclonal antibodies, focused largely on their clinical utility.

12. In addition, I am an inventor on thirty issued U.S. Patents related to anti-viral vaccines, IL-17-related cytokines, IL-13, T cell activation markers, antibodies, and fusion proteins. I have authored or co-authored more than 100 peer-reviewed journal articles, including articles dealing with HIV vaccines, cancer vaccines, IL-13 receptor, IL-4 receptor, TNF- α , and antibodies. I have taught graduate courses in immunology, including subjects such as therapeutic antibodies. In addition, I have also supervised numerous postdoctoral fellows and graduate students in similar areas of research.

13. I am an inventor on many issued patents that relate to the development, generation, structure and function of antibodies, including U.S. Patent No. 10,087,256 (“Method of making an anti-CD40 antibody”); U.S. Patent No. 9,562,104 (“Anti-CD40 Antibodies”); U.S. Patent No. 9,102,734 (“Fusion Proteins Comprising Antibody And HPV E6 And E7 Antigens”); U.S. Patent No. 7,999,078 (“Antibodies That Bind DNAX Leukocyte Associated Immunoglobulin-like Receptor”); U.S. Patent No. 7,786,267 (“Multivariable Antigens Complexed With Targeting Humanized Monoclonal Antibody”).

14. Having the above knowledge and experience, I am well qualified to offer the opinions I express in this declaration. A summary of my experience, education, publications, and other qualifications is provided in my CV, a copy of which is submitted separately as EX1003.

III. SUMMARY OF OPINIONS

15. My opinions and views set forth in this declaration are based on my education, training, and research regarding the development and use of antibodies, my research experience with immunology and molecular biology, as well as the materials I reviewed in preparing this declaration and the state of scientific knowledge in the art pertaining to the subject matter of the '449 patent at the time of the earliest priority application, May 9, 2005.

16. In forming my opinions, I have reviewed the following materials: (a) the '449 patent and prosecution history of the '449 patent; (b) all priority applications leading to the issuance of the '449 patent; and (c) all other documents and exhibits cited herein and as listed in EX1004.

17. First, it is my opinion that claims 1, 7-8, 12-14, and 21-23 are anticipated by WO '875.

18. Second, it is my opinion that claims 14-16 are rendered obvious by WO '875.

19. Third, it is my opinion that claim 9 is rendered obvious by WO '875 in view of WO '557.

20. Finally, it is my opinion that the Challenged Claims are rendered obvious by WO '875 in view of WO '557.

IV. RELEVANT LEGAL STANDARDS

21. I am not an attorney, and therefore my understanding of patent law and the legal standards set forth in this report is based on explanations provided to me by counsel.

A. Person of Ordinary Skill in the Art

22. I have been asked to review the '449 patent from the perspective of the person of ordinary skill in the art ("POSA") as of the earliest claimed priority date for the patent, May 9, 2005. I have been informed that the POSA is a hypothetical person who is presumed to have known the relevant art at the priority date of the patent. I have also been informed that the POSA can possess the skills and experience of multiple individuals working together as a team.

23. It is my opinion that as of the effective filing date of May 9, 2005, the POSA relevant to the '449 patent would have at least a Ph.D. or an M.D., with experience in the development and use of antibodies and research experience in immunology, biochemistry, cell biology, molecular biology, or a related field or at least 2-3 years of professional experience in one or more of those fields.

Furthermore, the POSA would have had working knowledge regarding the generation of isolated human antibodies. Under this definition, I am qualified to offer opinions regarding the claims of the '449 patent.

B. Invalidity

24. I understand that Dana-Farber bears the burden of proving that the Challenged Claims of the '449 patent are unpatentable and it must prove this by a preponderance of the evidence, which means that unpatentability must be shown to be more likely than not.

1. Anticipation

25. I have been asked to consider the question of whether the claims of the '449 patent are anticipated. I understand that the concept of anticipation requires that each and every element of a challenged claim is present in or otherwise taught by a single reference.

26. I also understand that an anticipatory reference does not need to explicitly describe each element because anticipation can occur when a claimed limitation is necessarily inherent or otherwise implicit in the relevant reference. I have been informed that inherent anticipation requires more than mere probabilities or possibilities. I also understand that an inherent property need not be known by the POSA before the priority date, and that an inherent property of a reference can be shown by post-priority date evidence and experimentation.

2. Obviousness

27. I have been asked to consider the question of whether the claims of the '449 patent would have been obvious as of the effective filing date. I understand that this analysis must be conducted from the perspective of the POSA, and whether the skilled artisan would consider any differences between the prior art and what is claimed to have been obvious.

28. To make this assessment, I have been informed that the concept of patent obviousness involves four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations of non-obviousness.

29. I have been instructed that one must not engage in hindsight. Rather, I understand that one should instead consider what the POSA would have reason to pursue further, and steps that were routinely done, such as in response to known problems, steps, or obstacles.

30. It is my understanding that the following is a non-exhaustive list of rationales that may support the obviousness of an invention: combining prior art elements according to known methods to yield predictable results; simple substitution of one known element for another to obtain predictable results; use of a known technique to improve a similar device (method, or product) in the same

way; applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; and some teaching, suggestion, or motivation in the prior art that would have led the POSA to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention with a reasonable expectation of success.

31. It is my understanding that the motivation to combine prior art references may be implicit and may be found in the knowledge of the POSA, or in the nature of the problem to be solved. Specifically, it is my understanding that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but also when the “improvement” is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is more effective, safer, cheaper, or cleaner. In assessing implicit motivation, the question is whether the POSA possesses knowledge and skills rendering them capable of combining the prior art references. It is my further understanding that the motivation to combine references may be found in the nature of the problem to be solved where prior art references are directed to precisely the same problem.

32. I also understand that prior art may be relied on for its express disclosure and teachings. I also understand that the prior art may be relied upon for a teaching of features that are necessarily present in the prior art reference even if that specific feature is not expressly or explicitly disclosed. I have been informed by counsel that when the prior art does not expressly disclose a claim limitation, inherency may supply a missing claim limitation in an obviousness analysis. I understand that inherency is established in the context of obviousness when the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art.

33. I also understand that the reasonable expectation of success does not require certainty, absolute predictability of success, or conclusive proof of efficacy. All that is required is a reasonable expectation of success by the POSA in light of the prior art as of the effective filing date.

34. I understand that before reaching any final conclusion on obviousness, the obviousness analysis requires consideration of objective indicia of nonobviousness, if any such indicia are offered.

35. These must be considered to ensure that, for example, there were not some unanticipated problems, obstacles or hurdles that may seem easy to overcome in hindsight, but which were not readily overcome by the prior art to the

claims at issue. I understand that these objective indicia are also known as “secondary considerations of nonobviousness,” and may include long-felt but unmet need, unexpected results, commercial success, among others.

36. I also understand, however, that any offered evidence of secondary considerations of non-obviousness must be comparable with the scope of the challenged claims. This means that for any offered evidence of secondary considerations of non-obviousness to be given substantial weight, I understand the proponent of that evidence must establish a “nexus” or a sufficient connection or tie between that evidence and the merits of the claimed invention. I understand that there is a presumption that there is a nexus between the merits of the claimed invention only when the patentee shows that the offered evidence of secondary considerations is tied to a specific product and that product is the invention disclosed and claimed in the patent. If the secondary consideration evidence offered results from something other than the merits of the claim, such as features known in the prior art, then I understand that there is no nexus or tie to the claimed invention. I also understand it is the Patent Owner who has the burden of proving that a nexus exists, and I understand that secondary considerations will not overcome a strong showing of obviousness.

V. TECHNICAL BACKGROUND & STATE OF THE ART

A. PD-1

37. Programmed cell death protein 1 (PD-1) is a receptor that is found on the surface of T cells and B cells. EX1006, 57; EX1007, 12293. It is a member of the immunoglobulin gene super family.

38. T cell activity is inhibited when PD-L1 or PD-L2 ligands bind to the PD-1 receptor. EX1007, 12293; EX1009, 515. When PD-L1 or PD-L2 on a normal cell bind to this receptor, this interaction transmits inhibitory signals that prevent T cells from launching an immune response against that cell. Tumor cells can overexpress PD-L1 and this overexpression can have negative outcomes on T cells' response to those tumor cells—suppressing the proliferation, cytokine production, and cytotoxic activity of T cells. EX1007, 12293-95. This effectively inhibits the body's immune response to malignant tumor cells.

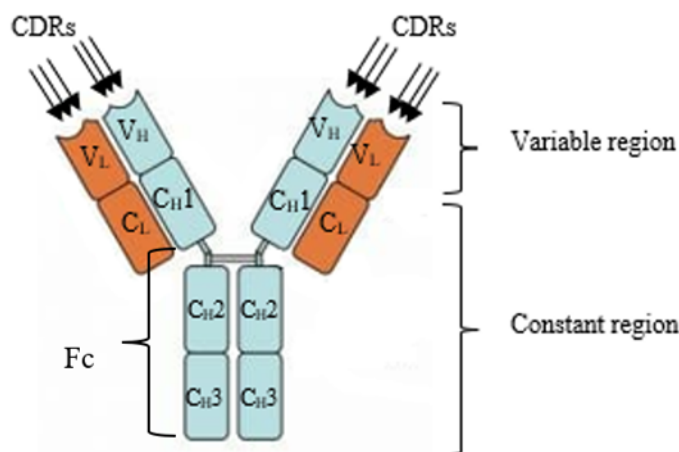
39. Anti-PD-1 monoclonal antibodies have been shown to impair the growth of tumors in mice by inhibiting the binding of PD-1 to PD-L1. EX1010, 1089, 1093. Such antibodies do so by inhibiting the binding of PD-1 to PD-L1, thereby ensuring that T cells are not inhibited from launching an immune response against the tumor cell. *Id.* It was known in the art that developing an anti-PD-1 antibody to obstruct the interaction of PD-1 with its ligands would be important in the field of cancer therapy as of May 9, 2005.

40. Patent Owner was not the first to discover the relationship between PD-1, PD-L1, and cancer. Dana-Farber and others, as described in U.S. Patent No. 7,595,048 (“Honjo-Freeman ’048”), made the groundbreaking discovery that such anti-PD-1 antibodies can be used to treat tumors. Honjo-Freeman ’048 discloses methods of treating cancers in humans using anti-PD-1 antibodies and describes at least one example of an anti-PD-1 antibody. EX1005, 10:37-38 (noting that inventors “invented” an “anti-PD-1 antibody”), 11:1-12. It explains that its described anti-PD-1 antibodies will “inhibit[] . . . PD-1 function” and suppress cancer growth. EX1005, 10:34-59.

B. Monoclonal Antibodies

41. Antibodies are Y shaped protein molecules that consist of two heavy chains and two light chains. EX1013, 13. Each chain of the antibody has a constant region and a unique variable region that includes the antigen binding site of the antibody. *Id.* The variable regions of an antibody include a variable heavy chain region (V_H) and a variable light chain region (V_L), both of which contain three complementarity determining regions (CDRs) that have highly variable amino acid sequences and determine the antigen specificity of an antibody. *Id.* The CDRs are located between framework regions, which are also part of the variable region of the antibody but have more constant amino acid sequences. *Id.* The Fc region of an antibody, which is not involved in antigen binding specificity,

is formed by parts of the constant regions of the two heavy chains and determines the isotype of the antibody (e.g., IgA, IgD, IgE, IgG, or IgM). *Id.*



42. As of May 9, 2005, the POSA understood that monoclonal antibodies were a promising therapeutic approach for treating diseases in humans. At this time, at least 12 therapeutic monoclonal antibodies were approved for human use by the U.S. Food and Drug Administration. EX1014. It was known in the art by POSAs that a promising and well-established therapeutic approach was to develop a monoclonal antibody against an antigen known to be involved in a human disease.

C. Isolating Antibodies

43. The POSA had numerous ways of discovering and isolating antibodies as of May 9, 2005, including by phage display and transgenic mice. EX1015, 536-38. All of these methods were well known in the art for initial

antibody screens. *See* EX1016. When using either phage display or transgenic mice techniques, antibodies can be made from human sequences so the entirety of such antibodies, including the antibody framework and CDR regions, are derived from human sequences. After the initial antibody screen, additional testing and engineering may be needed to further optimize and refine an antibody for therapeutic use.

44. A POSA would expect to screen numerous candidate antibodies having different sequences and structures to identify and characterize monoclonal antibodies with desired properties. The POSA also would expect to optimize the antibody for use in human patients, by making the antibody sequence as human as possible without losing the binding characteristics of the antibody. EX1015, 535-36; EX1013, 13-14.

45. As of the critical date of the '449 patent, the techniques for screening candidate antibodies and making human or humanized antibodies were routine and well-known. EX1001, 35:53-57 (“To create a humanized antibody, the murine CDR regions can be inserted into a human framework using methods known in the art (see e.g., U.S. Pat. No. 5,225,539 to Winter, and U.S. Pat. Nos. 5,530,101: 5,585,089; 5,693,762 and 6,180,370 to Queen et al.).”); *see also* EX1001, 38:22-26, 73:61-63.

D. Antibody Competition Assays

46. There were numerous techniques used to test the binding characteristics of antibodies to a specific antigen as of the priority date, May 9, 2005. One such technique is the competition assay, which assesses the relative ability of two antibodies to bind to the same or overlapping epitopes on an antigen. For example, Zurawski 1995 shows a method for “*Biotinylation and Cross-competition between mAbs for Binding to Cell Lines*”. EX1045, 13871.

47. As of May 9, 2005, there were various competition assays known to the POSA. Indeed, the ’449 patent refers to competition assays as “standard,” stating that “cross-competing antibodies can be identified based on their ability to cross-compete . . . in *standard* PD-1 binding assays.” EX1001, 26:31-34 (emphasis added). Examples of these standard assays include, for example, “BIAcore analysis, ELISA assays or flow cytometry,” which “may be used to demonstrate cross-competition with the antibodies of the current invention.” *Id.*, 26:34-36. The POSA would have been knowledgeable about each of these methods as of May 9, 2005, and could have readily used them to test an antibody against various reference antibodies for cross-competition.

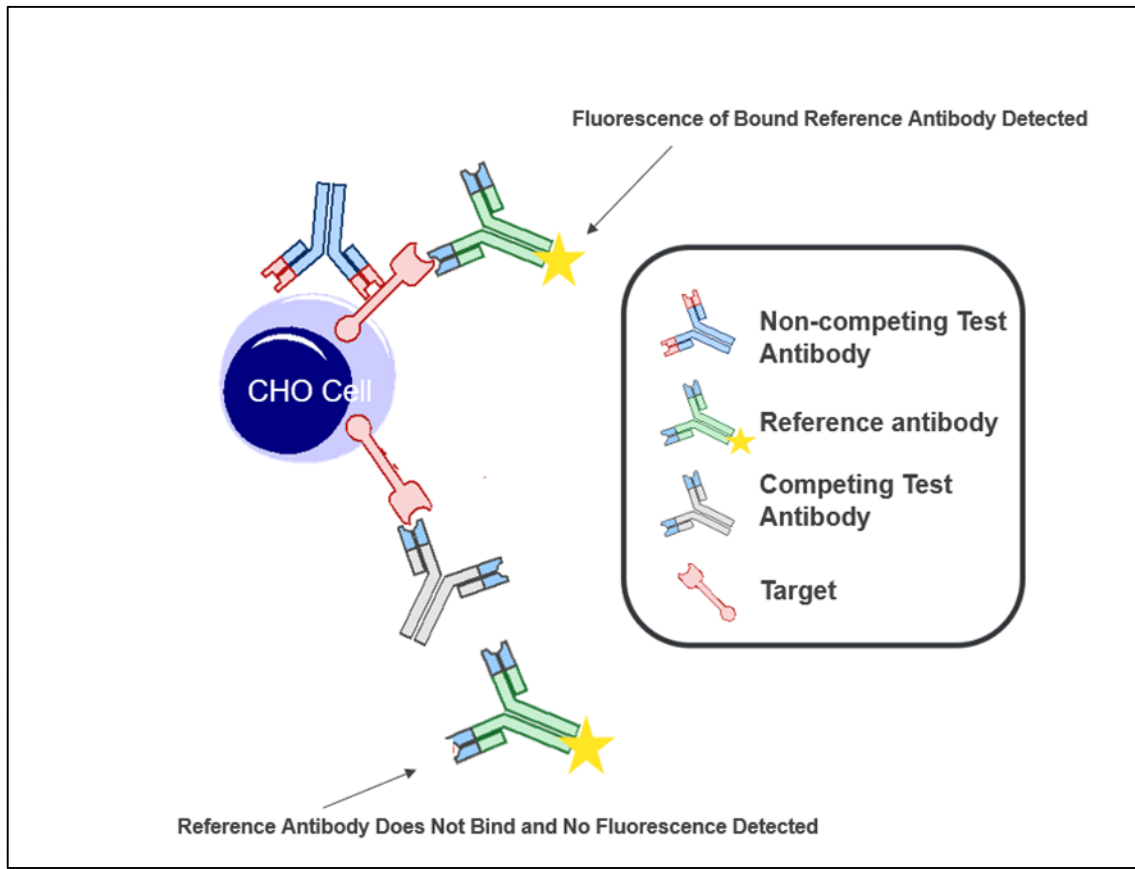
48. In a flow cytometry assay the antigen, here PD-1, is expressed on the surface of a cell. Then, a test competition antibody that binds to the antigen (e.g., PD1-17 or PD1-28, as discussed below) is applied to the cells concomitantly with

the labeled anti-PD-1 antibody. After a period allowing binding, all non-bound labeled and unlabeled antibody is washed away from the cell mixture and the cells are resuspended in a fixative to preserve the light-scattering characteristics and fluorescence intensities of the cells that have been stained for subsequent flow cytometry analysis.

49. In the final step, the cells are applied to a flow cytometer that detects the cells and the fluorescent marker. At a high level, flow cytometry is a standard tool used in immunology to measure optical and fluorescence characteristics of single cells within a population of cells as they pass through sensors. EX1046, 781-84. Physical properties of cells, like cell size, can be measured and used to identify certain cell populations. Additionally, fluorescent molecules can be used to label specific proteins on cell membranes or antibodies that bind to cells and the fluorescent light that is emitted by such molecules when bound to cells can be measured. *Id.* at 781. Inside a flow cytometer, cells in suspension are drawn into a stream and passed individually through a sensing point. At the sensing point, light from at least one laser is focused on the cells. *Id.* Light scatter and fluorescence signals are detected from each cell as it passes the sensing region and recorded for evaluation on an attached computer. These signals can be used to identify cells of interest and quantify the relative amount of labeled protein or antibody based on

the detected fluorescence intensity. *Id.* In flow cytometry, subpopulations of cells can be identified and “gated” based on parameters to identify and analyze cells of interest. Histograms and numerical evaluations can then be performed on the gated data which is typical practice in the field. *Id.*, 791-792. Similarly, fluorescence signals can be simply calculated as an average value per cell within the whole single cell population of each test condition.

50. The flow-based competition assay is illustrated in the cartoon below. A reference antibody is labeled with a fluorescent marker. A non-labeled antibody is added to assess competition with the reference antibody. In the case of anti-PD-1 antibodies, if there were binding to PD-1 by a fluorescently labeled anti-PD-1 antibody, the fluorescently labeled cells would be detected. If the unlabeled antibody competes with the fluorescently-labeled antibody for binding to PD-1 on the cell surface, there will be less fluorescent signal.



VI. THE '449 PATENT

51. The '449 patent issued on August 30, 2011. *See* EX1001. It is entitled “Human Monoclonal Antibodies to Programmed Death (PD-1) and Methods for Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination with Other Immunotherapeutics.” *Id.*

52. I understand that the '449 patent claims priority to a number of patent applications. I have been informed that the '449 patent issued from Application No. 11/913,217, filed on Jan. 29, 2009, which claims priority to a PCT application and three provisional applications: PCT No. PCT/JP2006/309606, filed on May 2,

2006 (EX1018); No. 60/679,466, filed on May 9, 2005 (EX1019); No. 60/738,434, filed on Nov. 21, 2005 (EX1020); No. 60/748,919, filed on Dec. 8, 2005 (EX1021).

53. The '449 patent claims I discuss in this declaration are cross-competition claims. For example, one such cross-competition claim is independent claim 1 of the '449 patent which states the following:

The invention claimed is:

1. An isolated human monoclonal antibody, or an antigen-binding portion thereof, wherein the antibody or antigen-binding portion thereof cross-competes for binding to PD-1 with a reference antibody or reference antigen-binding portion thereof comprising:

- a) a human heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 1 and a human light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 8;
- b) a human heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 2 and a human light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 9;
- c) a human heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 3 and a human light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 10;
- d) a human heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 4 and a human light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 11;
- e) a human heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 5 and a human light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 12;
- f) a human heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 6 and a human light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 13; or
- g) a human heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 7 and a human light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 14.

EX1001, cl. 1. This claim is directed to any “isolated human monoclonal antibody, or an antigen-binding portion thereof,” wherein the antibody or antigen-binding portion thereof “cross-competes for binding to PD-1” with any one of seven reference antibodies or reference antigen-binding portions thereof. *Id.*

54. Claim 1 contains amino acid sequences for the human heavy chain variable region and human light chain variable regions for these seven antibodies. *Id.* The seven reference antibodies in claim 1 with these sequences are described as antibodies 17D8 (SEQ ID Nos. 1 and 8), 2D3 (SEQ ID Nos. 2 and 9), 4H1 (SEQ ID No. 3 and 10), 5C4 (SEQ ID Nos. 4 and 11), 4A11 (SEQ ID No. 5 and 12), 7D3 (SEQ ID No. 6 and 13), and 5F4 (SEQ ID No. 7 and 14). EX1001, 9:14-10:32, Figs. 1A-7B. One of those reference antibodies, 5C4, is also known as nivolumab or commercially as Opdivo®. *See, e.g.,* EX1034, [0076] (“In one embodiment, the anti-PD-1 antibody is nivolumab. Nivolumab (also known as ‘OPDIVO®’; formerly designated 5C4, BMS-936558, MDX-1106, or ONO- 4538) is a fully human IgG4 (S228P) PD-1 immune checkpoint inhibitor antibody that selectively prevents interaction with PD-1 ligands (PD-L1 and PD-L2), thereby blocking the down-regulation of antitumor T-cell functions (EX1001; EX1070).

55. The ’449 patent itself does not define the phrase “cross-competes” in the claim. However, the specification of the ’449 patent does provide examples of

competition assays which can be used to assess cross-competition. The '449 patent states that “standard PD-1 binding assays” can be used to identify “cross-competing antibodies.” EX1001, 26:31-34. It provides examples of such “standard PD-1 binding assays,” such as “BIAcore analysis, ELISA assays or flow cytometry,” which can be used “to demonstrate cross-competition with the antibodies of the current invention.” *Id.*, 26:34-36. The POSA would understand the specification of the '449 patent to teach that any of these standard PD-1 binding assays, including BIAcore analysis, ELISA assays, or flow cytometry, can be used to show cross-competition. As explained further below, *see infra* Section IX, I have applied a flow cytometry assay using PD-1 expressing Chinese Hamster Ovary (“CHO”) cells to demonstrate the invalidity of the Challenged Claims—techniques which the '449 patent admits can be used to show cross-competition.

56. The only Example of the '449 patent which addresses cross-competition confirms that these standard PD-1 binding assays can be used to do so. Example 3 of the '449 patent, titled “Characterization of Binding Specificity and Binding Kinetics of Anti-PD-1 Human Monoclonal Antibodies,” explains that binding specificity and “cross-competition were examined by flow cytometry.” EX1001, 68:45-54. The Example describes the use of Chinese hamster ovary

(CHO) cells to determine the specificity of PD-1 binding by the monoclonal antibodies with flow cytometry:

Binding Specificity by Flow Cytometry

Chinese hamster ovary (CHO) cell lines that express recombinant human PD-1 at the cell surface were developed and used to determine the specificity of PD-1 human monoclonal antibodies by flow cytometry. CHO cells were transfected with expression plasmids containing full length cDNA encoding transmembrane forms of PD-1. Binding of the 5C4 and 4H1 anti-PD-1 human monoclonal antibodies was assessed by incubating the transfected cells with the anti-PD-1 human monoclonal antibodies at a concentration of 20 µg/ml. The cells were washed and binding was detected with a FITC-labeled anti-human IgG Ab. Flow cytometric analyses were performed using a FACScan flow cytometry (Becton Dickinson, San Jose, Calif.). The results are depicted in FIGS. 13A (5C4) and 13B (4H1). The anti-PD-1 human monoclonal antibodies bound to the CHO cells transfected with PD-1 but not to CHO cells that were not transfected with human PD-1. These data demonstrate the specificity of anti-PD-1 human monoclonal antibodies for PD-1.

EX1001, 69:20-38.

57. Example 3 describes that the tested anti-PD-1 monoclonal antibodies, 5C4 and 4H1 bound to the CHO cells transfected with PD-1, but not to CHO cells that were not transfected with the human PD-1 receptor. Thus, to the extent that the inventors evaluated cross-competition of the antibodies disclosed in the specification, it was indirectly measured by identifying antibodies that specifically bound to PD-1 and assuming that each individual antibody's ability to bind to

PD-1 demonstrates that the antibodies will cross-compete with each other for binding.

58. Example 3 also discusses that ELISA testing showed that antibodies 17D8, 2D3, 4H1, 5C4, and 4A11 each bound to human PD-1 with “high specificity,” but not to other CD28 family members:

Binding Specificity by ELISA Against Other CD28 Family Members 40

A comparison of the binding of anti-PD-1 antibodies to CD28 family members was performed by standard ELISA using four different CD28 family members to examine the specificity of binding for PD-1.

Fusion proteins of CD28 family members, ICOS, CTLA-4 45 and CD28 (R&D Biosystems) were tested for binding against the anti-PD-1 human monoclonal antibodies 17D8, 2D3, 4H1, 5C4, and 4A11. Standard ELISA procedures were performed. The anti-PD-1 human monoclonal antibodies were added at a concentration of 20 µg/ml. Goat-anti-human IgG 50 (kappa chain-specific) polyclonal antibody conjugated with horseradish peroxidase (HRP) was used as secondary antibody. The results are shown in FIG. 14. Each of the anti-PD-1 human monoclonal antibodies 17D8, 2D3, 4H1, 5C4, 4A11, 7D3 and 5F4 bound with high specificity to PD-1, but not to 55 the other CD28 family members.

EX1001, 69:39-56.

VII. CLAIM CONSTRUCTION

59. It is my further understanding that the numbered paragraphs at the end of the disclosure of a U.S. Patent are the patent “claims” that define the scope of

the alleged invention. I understand that the validity of these claims of the '449 patent is being challenged in the present IPR proceeding.

60. I have been informed that, in this proceeding, the Board must determine the scope of the claims by giving the claims their ordinary and customary meaning in light of the specification, as the claims would be interpreted by one of ordinary skill in the art. I also understand that the Board interprets claims at the time of the “effective filing date,” or “priority date,” which is (1) the actual filing date of the patent or the application containing a claim to the invention; or (2) the filing date of the earliest priority application that describes the subject matter of the claim.

61. I understand that patent claims generally include a “transitional” term or phrase, such as “consisting” or “comprising,” which may connect the preamble of the claim to the body of the claim. I have been informed that if a claim uses the term “consisting” as a transition term, that means that the claim is a “closed” claim, which means that the claim is limited to the claim features that follow the transition term and nothing else. On the other hand, I understand that the transition term “comprising” denotes an “open” claim, which means that the claim is not limited to only the features recited in the claim and could encompass the listed elements as well as other unrecited elements.

A. Expressly Defined Terms

62. Each of the claims I address below claim a “human monoclonal antibody, or an antigen-binding portion thereof.” EX1001, cl. 1. The POSA would understand this term to encompass “antibodies displaying a single binding specificity which have variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences.” EX1001, 16:33-36. That is how the specification of the ’449 patent explicitly defines this term and the POSA would understand this to be the meaning of “human monoclonal antibody” as used in the claims of the ’449 patent. Moreover, this express definition is also consistent with the ordinary meaning of the term “human monoclonal antibody” to POSAs.

63. Each of the claims I address here also cover an “*isolated* human monoclonal antibody.” EX1001, cl. 1 (emphasis added). Like the term “human monoclonal antibody,” the specification of the ’449 patent also defines the term “isolated.” The specification states that an “isolated” antibody is one that “is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that specifically binds PD-1 is substantially free of antibodies that specifically binds antigens other than PD-1).” EX1001, 16:3-7. The POSA would understand the term “isolated” to mean the same in light of this express definition. The ’449 patent’s definition of an “isolated” human monoclonal

antibody is also furthermore consistent with the plain and ordinary meaning of the term “isolated” in the context of human monoclonal antibodies.

64. Claim 7 of the '449 patent separately covers a “pharmaceutically acceptable carrier.” EX1001, cl. 7. The POSA, in reviewing the specification of the '449 patent, would understand that the specification expressly defines this term to include “any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible.” EX1001, 45:37-41. The POSA would understand the term “pharmaceutically acceptable carrier” in claim 7 to thus mean the same.

B. “cross-competes for binding to PD-1 with a reference antibody”

65. I understand that claim terms, in the absence of an express definition, as those discussed above, are given their ordinary and customary meaning, as would have been understood by a POSA at the time of the alleged invention.

66. In considering the meaning of the claims, I understand that one must consider the language of the claims in light of “the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” 37 C.F.R. § 42.100(b).

67. It is my opinion that the POSA would understand “cross-competes for binding to PD-1 with a reference antibody” to mean “inhibits the binding of a

reference antibody to human PD-1, as demonstrated by, for example, Biacore analysis, ELISA analysis, or flow cytometry.”

68. The ’449 patent does not expressly define “cross-competes for binding to PD-1 with a reference antibody,” but states:

Such cross-competing antibodies can be identified based on their ability to cross-compete with 17D8, 2D3, 4H1, 5C4, 4A11, 7D3 or 5F4 in standard PD-1 binding assays. *For example, BIACore analysis, ELISA assays or flow cytometry may be used to demonstrate cross-competition with the antibodies of the current invention.* The ability of a test antibody to *inhibit the binding* of, for example, 17D8, 2D3, 4H1, 5C4, 4A11, 7D3 or 5F4, to human PD-1 demonstrates that the test antibody can compete with 17D8, 2D3, 4H1, 5C4, 4A11, 7D3 or 5F4 for binding to human PD-1 and thus binds to the same epitope on human PD-1 as 17D8, 2D3, 4H1, 5C4, or 4A11.

EX1001, 26:31-42 (emphases added).

69. Thus, the ’449 patent describes how to measure the inhibition of an antibody to bind its target by a test antibody using BiAcCore, ELISA, or flow cytometry. Beyond inhibition of binding as measured by these “standard PD-1 binding assays,” the ’449 patent does not require any specific level of inhibition.

70. I understand that Patent Owner has taken a consistent position with respect to the claim construction of the limitation “cross-competes for binding to human PD-L1 with a reference antibody,” which also appears in U.S. Patent Nos.

9,580,505 and 9,580,507. EX1032, 6; EX1011, 3. While I understand that the specifications of U.S. Patent Nos. 9,580,505 and 9,580,507 are not identical to the '449 patent, both patents include a similar passage as that copied above with respect to cross-competition for binding to PD-L1. EX1058, 27:55-28:1; EX1059, 27:46-59. I understand that Patent Owner has proposed that the limitation in U.S. Patent Nos. 9,580,505 and 9,580,507 be construed as “[i]nhibits the binding of a reference antibody to human PD-L1 by, for example, Biacore analysis, ELISA analysis, or flow cytometry.” EX1032, 6; EX1011, 3. This is consistent with my opinion.

VIII. SCOPE AND CONTENT OF THE PRIOR ART REFERENCES

A. WO '875

71. International PCT Publication No. WO 2004/056875 A1 (“WO '875”) is a publicly available application filed by Wyeth and Cambridge Antibody Technology that is entitled “Antibodies Against PD-1 and Uses Therefor.” EX1033, 1. It published on July 8, 2004. *Id.* I understand from counsel that WO '875 is prior art to the '449 patent.

72. WO '875 discloses the use of anti-PD-1 antibodies to treat cancer. It describes the role of PD-1 as a “type I transmembrane receptor that was originally identified in a T cell line undergoing activation-induced apoptosis. PD-1 is expressed on T cells, B cells, and macrophages.” EX1033, [006]. It also describes

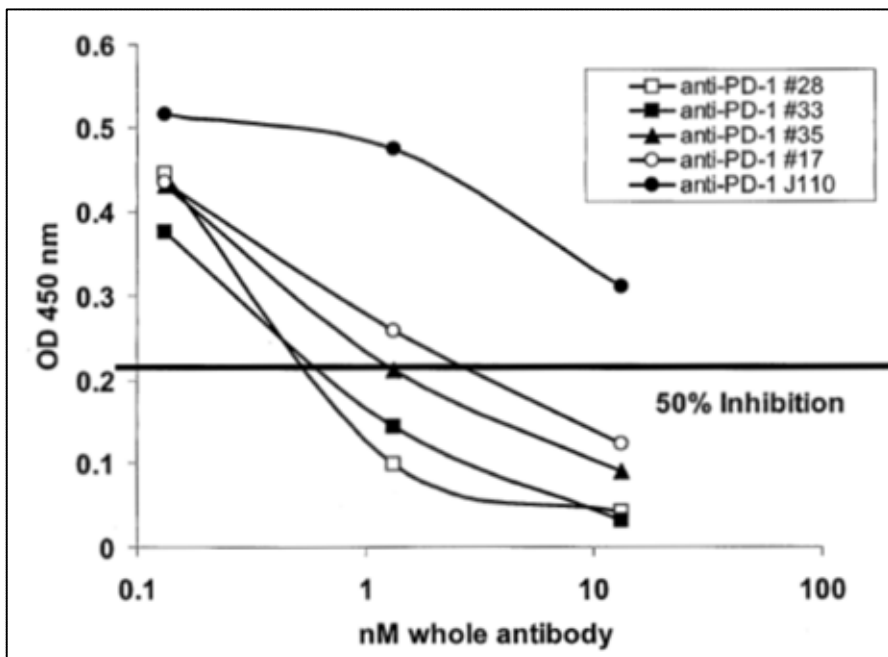
that there is a “need” to “provide safe and effective therapeutic methods for immune disorders such as cancer.” *Id.*, [009].

73. WO '875 specifically describes antibodies that act as antagonists of PD-1, thereby modulating immune responses regulated by PD-1, including “anti-PD-1 antibodies that comprise novel antigen-binding fragments.” *Id.*, [010]. It teaches that these antibodies are capable of “specifically binding to PD-1, including human PD-1,” “blocking PD-1 interactions with its natural ligand(s),” or both. *Id.*

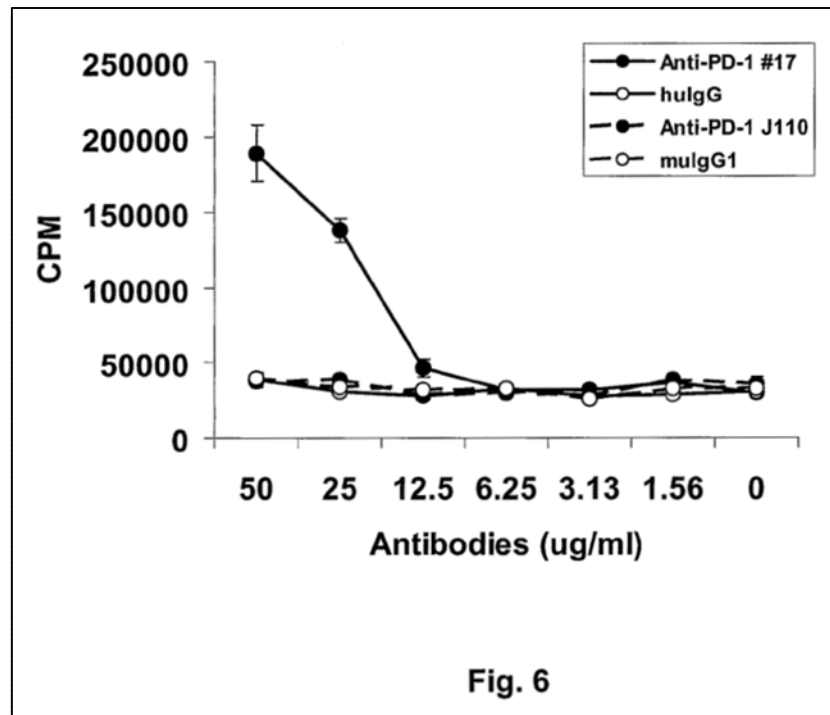
74. The inventors of WO '875 generated numerous examples of such anti-PD-1 human monoclonal antibodies. Specifically, they describe five different disclosed antibodies: PD1-17, PD1-28, PD1-33, PD1-35, and PD1-F2. *Id.*, [011]. WO '875 discloses the sequences of the V_H and V_L domains and CDRs of each of these anti-PD-1 antibodies. *Id.*, Table 1, Sequence Listing. As disclosed by WO '875, each of these anti-PD-1 antibodies “bind to the PD-L-binding domain of PD-1.” *Id.*, [046].

75. Example 6 of WO '875 discusses the performance of inhibition assays to assess the ability of the anti-PD-1 antibodies to block binding of PD-L1 to PD-1. The results of that experiment showed that anti-PD-1 antibodies PD1-17, PD1-28,

PD1-33, and PD1-35 “block PD-1/PD-L1 interaction.” EX1033, [0120]. These results are shown in Figure 3:



76. Example 9 of WO '875 discusses experiments which demonstrated that anti-PD-1 antibodies PD1-17 and PD1-35 “enhanced proliferation of primary T cells,” by “inhibit[ing] the interaction of PD-1 with its natural ligands and thereby block delivery of a negative signal.” EX1033, [0128]. The results for PD1-17 are shown in Figure 6:



77. As explained further below, I conducted cross-competition experiments utilizing two of the disclosed antibodies in WO '875—PD1-17 and PD1-28. *See infra* Section IX.

B. WO '557

78. International PCT Publication No. WO 01/14557 A1 (“WO '557”) is a publicly available application filed by Dana-Farber Cancer Institute Inc. and

Genetics Institute, Inc. that is entitled “PD-1, a Receptor for B7-4, and Uses Therefor.” EX1012. It published on March 1, 2001. *Id.* I understand from counsel that WO ’557 is prior art to the ’449 patent.

79. WO ’557 teaches the production of human monoclonal antibodies to PD-1 using conventional techniques well-known in the art as of May 9, 2005. *See* EX1012, 50:23-53:26 (immunization with all or part of PD-1); *id.*, 53:27-54:17 (phage display); *id.*, 54:18-23 (humanization); *id.*, 22:13-15 (antibodies may be “polyclonal or monoclonal”); *id.*, 50:23-56:3 (monoclonal techniques).

80. WO ’557 also teaches POSAs how to detect anti-PD-1 antibodies using conventional assays and it explains how those anti-PD-1 antibodies can prevent PD-1 mediated inhibitory signaling. *See* EX1012, 15:19-23; 16:7-13; 77:1-12; 88:18-23; 89:19-90:7; 90:8-16. Specifically, WO ’557 describes how the administration of an anti-PD-1 antibody can be used to treat human patients by blocking the interaction between the PD-1 receptor and PD-L1. *Id.*, 4:28-32; 82:18-24; 82:11-12; 135:24-27. By blocking this interaction, the anti-PD-1 antibody prevents “an inhibitory signal (*e.g.*, by using a non-activating antibody against PD-1) in immune cells [which] leads to upmodulation of immune cell responses (and resulting upmodulation of an immune response).” EX1012,

9:27-10:2. WO '557 also discloses that its inventors prepared fully human anti-PD-1 antibodies. EX1012, Example 9.

IX. MONOCLONAL ANTIBODY PRODUCTION AND TESTING

81. To establish whether PD1-17 and PD1-28 cross-compete with the reference antibody 5C4 (nivolumab), I undertook flow cytometry antibody competition assays.

82. As explained above, there are multiple, standard, techniques used to evaluate the relative ability of two antibodies to bind to the same or overlapping epitopes on an antigen. The '449 patent refers to competition assays as “standard,” stating that “cross-competing antibodies can be identified based on their ability to cross-compete . . . in *standard* PD-1 binding assays.” EX1001, 26:31-34 (emphasis added). Examples of these standard assays include, for example, “BIAcore analysis, ELISA assays or flow cytometry,” which “may be used to demonstrate cross-competition with the antibodies of the current invention.” *Id.*, 26:34-36.

83. The flow cytometry assay herein is standard and the POSA would have been knowledgeable about this method as of May 9, 2005, and the POSA could have readily used a flow-cytometry based assay to test an antibody against various reference antibodies for cross-competition. *See, e.g.*, EX1001, 26:31-34; EX1047, 664-67; EX1048, 142; EX1049, 7346.

84. For the work described here, I applied flow cytometry using PD-1 expressing Chinese Hamster Ovary (“CHO”) cells. As I explain, the results demonstrate that the prior art antibodies PD1-17 and PD1-28 cross-compete with the reference antibody, 5C4, as recited by the Challenged Claims.

85. The methods used to carry out the cross-competition assay were performed as described in detail in the following sections. The antibody testing discussed below was completed on January 13, 2022.

86. Per my standard practice, the experiments were carried out at my direction by Sandy Zurawski. I designed and oversaw the experiments and carried out the data analysis.

A. mAbs and PD-1 cDNA

1. Prior art antibodies PD1-17 and PD1-28

87. PD1-17 was obtained from Creative Biolabs, a commercial antibody supplier (CAT#: TAB-0961CL). *See* EX1050.

88. PD1-28 was obtained from Absolute Antibody, a commercial antibody supplier (Product #: Ab02652-10.0, Anti-PD-1 [PD1-28], Human IgG1, Lambda.). *See* EX1051.

89. In order to confirm that the PD1-17 antibody and PD1-28 antibody have the same amino acid sequences as the PD1-17 and PD1-28 antibodies

described WO '875, the PD1-17 and PD1-28 antibodies were amino acid sequenced.

90. Briefly, about 5 micrograms of the PD1-17 and PD1-28 antibodies were subjected to SDS-PAGE analysis under reducing conditions, followed by staining with Coomassie Brilliant Blue. The separated heavy and light chains were excised as gel slices and provided to the Proteomics Core Facility at UT Southwestern Medical Center for mass spectrometric analysis following elution and digestion by site specific proteases. The analysis established concordance between the expected (as published in WO '875) antibody sequences and the derived peptide fragments. The analysis of PD1-17 achieved coverages of 71.18% (heavy chain) and 82.41% (light chain). The analysis of PD1-28 achieved coverages of 70.86% (heavy chain) and 69.01% (light chain).

91. As can be seen in Appendix A, the amino acid sequence obtained for PD1-17 from Creative Biolabs is the same as that disclosed in Table 1 of WO '875.

Table 1: DNA and Amino Acid (AA) Sequences of V_H and V_L Domains and CDRs

Sequence	PD1-17	PD1-28	PD1-33	PD1-35	PD1-F2
V _H DNA	SEQ ID NO:1	SEQ ID NO:5	SEQ ID NO:9	SEQ ID NO:13	SEQ ID NO:46
V _H AA	SEQ ID NO:2	SEQ ID NO:6	SEQ ID NO:10	SEQ ID NO:14	SEQ ID NO:47
V _L DNA	SEQ ID NO:3	SEQ ID NO:7	SEQ ID NO:11	SEQ ID NO:15	SEQ ID NO:48
V _L AA	SEQ ID NO:4	SEQ ID NO:8	SEQ ID NO:12	SEQ ID NO:16	SEQ ID NO:49
H1 AA	SEQ ID NO:17	SEQ ID NO:23	SEQ ID NO:29	SEQ ID NO:35	SEQ ID NO:50
H2 AA	SEQ ID NO:18	SEQ ID NO:24	SEQ ID NO:30	SEQ ID NO:36	SEQ ID NO:51
H3 AA	SEQ ID NO:19	SEQ ID NO:25	SEQ ID NO:31	SEQ ID NO:37	SEQ ID NO:52
L1 AA	SEQ ID NO:20	SEQ ID NO:26	SEQ ID NO:32	SEQ ID NO:38	SEQ ID NO:53
L2 AA	SEQ ID NO:21	SEQ ID NO:27	SEQ ID NO:33	SEQ ID NO:39	SEQ ID NO:54
L3 AA	SEQ ID NO:22	SEQ ID NO:28	SEQ ID NO:34	SEQ ID NO:40	SEQ ID NO:55

92. As can be seen in Appendix B, the amino acid sequence obtained for PD1-28 from Absolute Antibody is the same as that disclosed in Table 1 of WO '875.

93. Thus, the PD1-17 and PD1-28 antibodies obtained from the respective suppliers correspond to the PD1-17 antibody and PD1-28 antibody described in WO '875.

2. Reference antibody 5C4

94. Reference antibody 5C4, as described by the '449 patent, is also known as nivolumab, which comprises a heavy chain variable region (VH) comprising SEQ ID NO:4 and a light chain variable region (VL) comprising SEQ ID NO:11.

95. Nivolumab was obtained from two sources – one stock from Creative Biolabs (source 1) and the other from the Baylor University Medical Center (BUMC) pharmacy (source 2). The nivolumab from Creative Biolabs was sequenced as described above. *See ¶90.*

96. By comparing the obtained sequences of nivolumab and the sequence of 5C4, I confirm that the nivolumab obtained from Creative Biolabs corresponds to the 5C4 antibody described in the '449 patent, specifically comprising a heavy chain variable region comprising SEQ ID NO:4 and a light chain variable region comprising SEQ ID NO:11 required by the claims. *See Appendix C.*

3. PD-1

97. Human PD-1 cDNA, encoding the full-length PD-1 protein was obtained from a commercially available cDNA clone. *See EX1057.*

98. The PD-1 cDNA was cloned into a mammalian expression vector, as described in EX1052, 2-6, see Section IX.B.1 *infra*. Following the cloning into the described expression vector, we confirmed by DNA sequencing that the construct would express the amino acid sequence of PD-1:

MQIPQAPWPVVWAVLQLGWRPGWFLDSPDRPWNPPTFSPALLVVT
EGDNATFTCSFSNTSESFVLNWYRMSPSNTDKLAAFPEDRSQPGQDC
RFRVTQLPNGRDFHMSVVRARRNDSTYLCGAISLAPKAQIKESLRA
ELRVTERRAEVPTAHPSPPRPAGQFQTLVVG VVGGLLGSLLVLLVW
VLAVICSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREK

TPEPPVPCVPEQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPED
GHCSWPL.

EX1053.

B. PD-1-expressing CHO Cell Antibody Competition Assays and Results

99. As a standard competition assay, I employed a flow cytometry-based assay. As described in more detail herein, we expressed PD-1 on the cell surface of CHO cells using an expression vector. We then used the PD-1-expressing CHO cells to measure the competition between the prior art antibodies PD1-17 and PD1-28 with the reference antibody 5C4.

1. Generation of PD-1-expressing CHO cells

100. CHO-S cells were transfected with a modified pIRES2 dsRed vector (EX1068, *see* EX1052, 2-3) carrying a human PD-1 cDNA insert encoding the full-length PD-1 protein derived from the commercially available cDNA clone MGC:103817 IMAGE:30915198.

101. Following construction of the PD-1 cDNA construct, we performed nucleic acid sequencing of the PD-1 cDNA insert to ensure that the construct was expressing the correct full-length PD-1 protein. The cloned PD-1 cDNA was confirmed to have the correct sequence correlating to the amino acid sequence specified in paragraph 98.

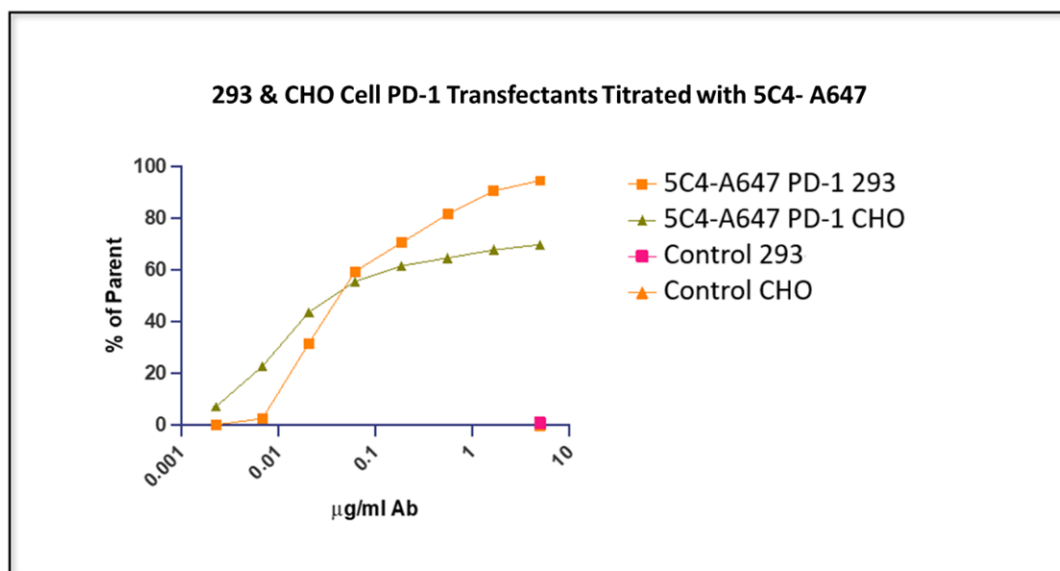
102. We next transfected the PD-1 cDNA construct into both CHO cells and 293 cells using the manufacturer's instructions for the CHOgro® High Yield Expression System (Mirus). *See* EX1054.

2. Alexa-647 dye labeling and titration of staining antibody

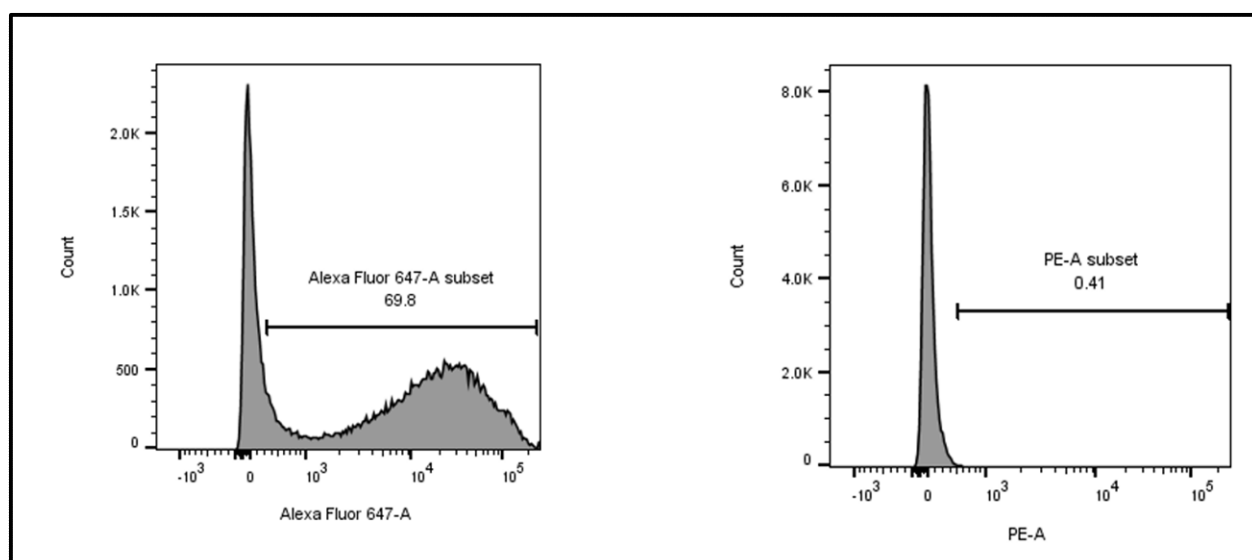
103. One milligram of Anti-PD-1 antibody (nivolumab source 2) was labeled with the Alexa Fluor™ 647 Protein Labeling Kit (A20173, <https://www.thermofisher.com/order/catalog/product/A20173>) as per the manufacturer's recommendations. *See* EX1055. The derivatized protein was dialyzed versus 5 changes of DPBS to remove unbound labeling reagent.

104. In a preliminary experiment the Alexa Fluor™ 647 labeled 5C4/nivolumab labeled protein was tested for specific binding to PD-1-transfected CHO or 293-F cells in a dose ranging study to demonstrate specific binding and determine a non-saturating antibody concentration suitable for use in a competition assay (in this case 0.1 µg/ml was selected). There was no staining detected on non-PD-1-transfected control CHO or 293 cells.

105. As shown in the figure below, the Alexa Fluor™ 647 labeled 5C4/nivolumab specifically binds to PD-1 expressed on both CHO and 293 cells, and the ~50% PD-1 saturation Alexa Fluor™ 647 labeled 5C4/nivolumab is ~0.1 µg/ml.



106. The FACS plot panels below show the actual staining data for the transfected CHO cells, stained with Alexa Fluor (left) or unstained (right).



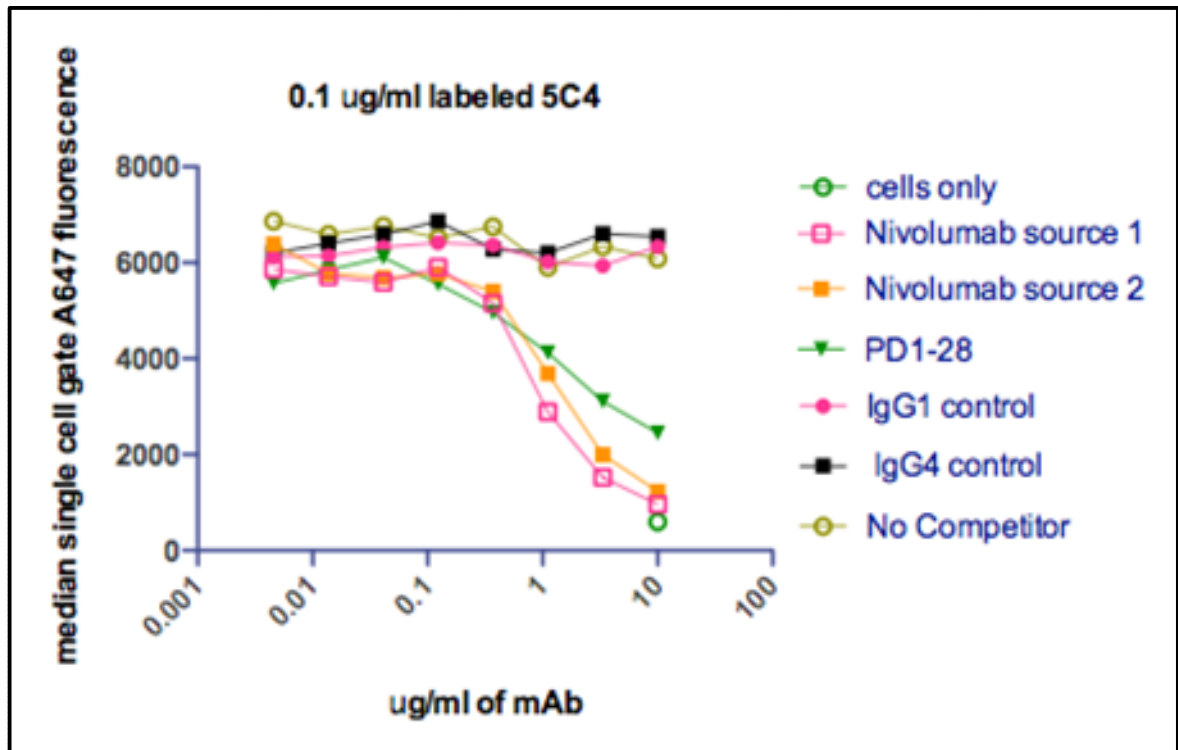
3. Cross-competition of prior art antibody PD1-28 with 5C4

107. In the competition assay, 5×10^5 cells per assay point were incubated in assay buffer (PBS, 2% BSA, 2 mM EDTA with 0.1 µg /ml 5C4-A647) with non-

labeled competitor antibody starting at 10 µg/ml with 3-fold serial dilutions over 8 wells. The cells, labeled 5C4-A647, and the titrated non-labeled competitor antibody were co-incubated on ice for 1 hour, then washed twice with assay buffer (PBS, 2% BSA, 2 mM EDTA), followed by resuspension in BD Cytotfix™ fixation buffer (554656), and analysis by flow cytometry with a FACS Canto II (BD Biosciences) instrument. Cytometry data was analyzed with FlowJo Software calculating the median fluorescence of cells within the singlets gate. Unstained cells and cells competed with 10 µg/ml unlabeled 5C4 antibody exemplified the baseline auto-fluorescent signal. Values above this signal indicated binding by labeled 5C4-A647. Note that the PD-1 -transfected CHO cells contain a population of cells which do not express PD-1.

108. The competition experiment included controls such as unlabeled nivolumab, and known non-PD-1 binding IgG1 and IgG4 antibodies that were available in the laboratory.

109. The following flow cytometry data was obtained:



110. Based on the data shown in the figure above, it can be seen that PD1-28 when present at the 10 $\mu\text{g/ml}$ and 3.3 $\mu\text{g/ml}$ concentrations, inhibited the binding of reference antibody 5C4 by greater than 50%. In contrast, the negative control, a human IgG1 mAb, did not show any significant amount of inhibition of binding to PD-1, while at concentrations $> 0.1 \mu\text{g/ml}$ unlabeled nivolumab (from two different sources) also inhibited the binding to PD-1.

111. Using this flow cytometry data, the percent inhibition was calculated as described in Perez 1999 (EX1047, 664) using the following equation:

$$PI = 1 - \frac{\text{Experimental} - \text{background}}{\text{Biotinylated mAb alone} - \text{background}} \times 100\%$$

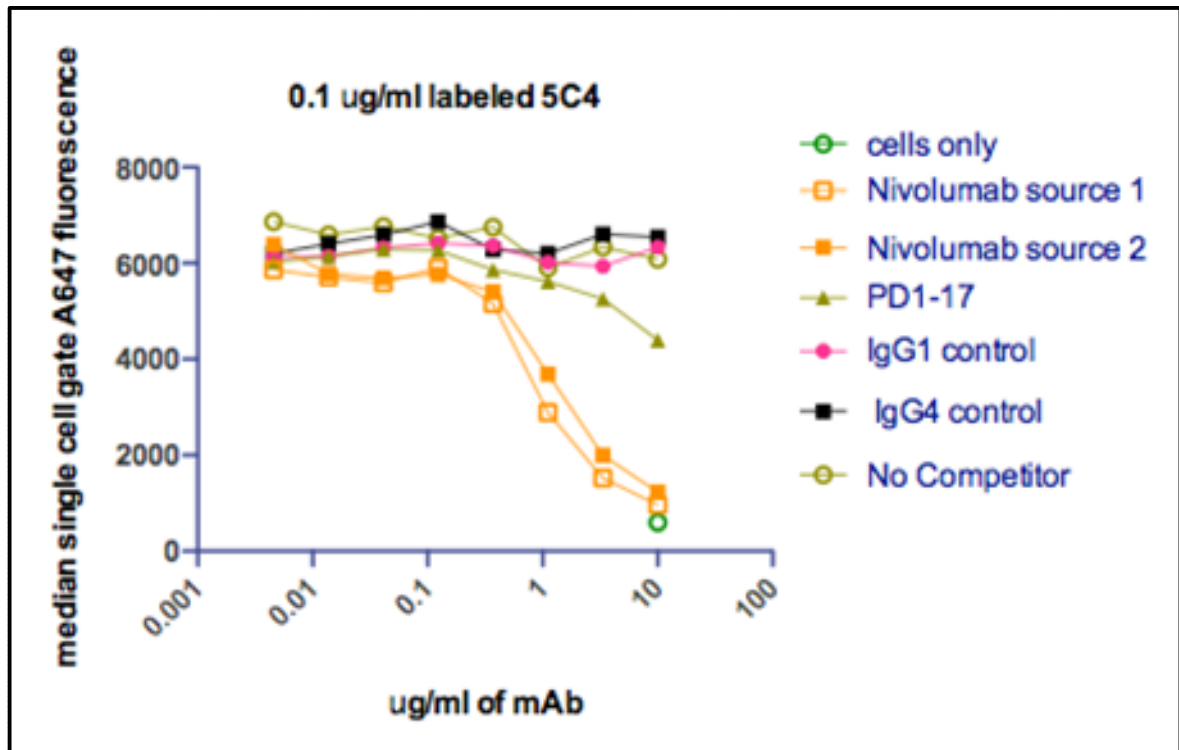
112. PD1-28 inhibited 68% percent of 5C4 binding to PD-1 when present at 10 µg/ml and inhibited 56% of 5C4 binding when present at 3.3 µg/ml. By comparison, a non-competing human IgG1 antibody (negative control) inhibits <4% percent of 5C4 binding to PD-1.

113. I note that Perez 1999 states that “[i]nhibition was considered significant when the [percent inhibition] was 50% or higher” (EX1047, 667, where Perez 1999 uses 50% as a “cut-off” for placing “mAbs into four groups of mutually competitive antibodies”). The 68% and 56% inhibition values I determined for cross-competition between PD1-28 and 5C4 for binding to PD-1 substantially exceed the 50% threshold set forth in Perez 1999. The full dose response analysis for inhibition of 5C4 binding by PD1-28 antibody permits calculation of the half-maximal inhibitory concentration (IC₅₀) as 1.243 µg/ml compared to 0.9117 µg/ml for competition by unlabeled 5C4 (see Appendix).

114. Consequently, it is my opinion that prior art PD1-28 antibody cross-competes with 5C4 for binding to PD-1 as recited by the Challenged Claims.

4. Cross-competition of prior art antibody PD1-17 with 5C4

115. The following flow cytometry data was obtained using the same assay for PD1-17:



116. Based on the data shown in the figure above, it can be seen that PD1-17 when present at 10 $\mu\text{g/ml}$ and 3.3 $\mu\text{g/ml}$ concentrations, inhibits the binding of reference antibody 5C4 to PD-1. Calculating the percent inhibition as described in Perez 1999 (EX1047), PD1-17 inhibited 45% and 37% of 5C4 binding to PD-1 at 10 $\mu\text{g/ml}$ and 3.3 $\mu\text{g/ml}$ respectively. While these percentages do not exceed the 50% threshold set forth in Perez 1999, PD1-17 clearly inhibited binding of 5C4 to PD-1. The full dose response analysis for inhibition of 5C4 binding by PD1-17 antibody permits calculation of the half-maximal inhibitory concentration (IC_{50}) as 11.48 $\mu\text{g/ml}$ compared to 0.9117 $\mu\text{g/ml}$ for competition by unlabeled 5C4 (see Appendix), indicating that if concentrations of PD1-17 $>12 \mu\text{g/ml}$ were used in this

competition experiment, the >50% inhibition criteria defined by Perez would have been met.

117. As I explained above, the POSA would understand that no specific level of inhibition is required for PD1-17 to “cross-compete[] for binding to PD-1 with a reference antibody,” as recited by the Challenged Claims. *See* Section VII.B.

118. Consequently, it is my opinion that the prior art PD1-17 antibody cross-competes with 5C4 for binding to PD-1 as recited by the Challenged Claims.

X. UNPATENTABILITY OF THE '449 PATENT

A. Claims 1, 7-8, 12-14 and 21-23 Are Unpatentable as Anticipated by WO '875

119. It is my opinion that claims 1, 7-8, 12-14, and 21-23 are anticipated by WO '875. At a high-level, as explained above, *see supra* Section VI, these claims encompass any isolated human monoclonal antibody which cross-competes for binding to PD-1 with any one of seven reference antibodies. One such reference antibody is 5C4, also known as nivolumab. EX1034, [0076] (“In one embodiment, the anti-PD-1 antibody is nivolumab. Nivolumab (also known as ‘OPDIVO®’; formerly designated 5C4, BMS-936558, MDX-1106, or ONO- 4538) is a fully human IgG4 (S228P) PD-1 immune checkpoint inhibitor antibody that selectively prevents interaction with PD-1 ligands (PD-L1 and PD-L2), thereby blocking the

down-regulation of antitumor T-cell functions (U.S. Patent No. 8,008,449; Wang *et al.* *In vitro* characterization of the anti-PD-1 antibody nivolumab, BMS-936558, and *in vivo* toxicology in non-human primates, *Cancer Imm Res*, 2(9):846-56 (2014))”).

120. As also discussed above, *see supra* Sections IX.B.3-4, I have conducted flow cytometry experiments showing that two human monoclonal antibodies disclosed by WO '875—PD1-17 and PD1-28—both cross-compete for binding to PD-1 with antibody 5C4. It is thus my opinion that WO '875's disclosure anticipates these claims.

1. Claim 1

121. Claim 1 of the '449 patent claims an “isolated human monoclonal antibody, or an antigen-binding portion thereof” that “cross-competes for binding to PD-1” with various antibodies, including an antibody with the recited human heavy chain variable region and human light chain variable region of disclosed antibody 5C4. *See* EX1001, cl. 1, Fig. 4A & 4B, 19:20-54. WO '875 anticipates this claim.

122. WO '875 discloses an “isolated human monoclonal antibody, or an antigen-binding portion thereof.” EX1001, cl. 1. WO '875 discloses various anti-PD-1 antibodies, including “PD1-17, PD1-28, PD1-33, PD1-35, and PD1-F2.” EX1033, [011]. It further states that its invention “provides anti-PD-1 antibodies

that comprise novel antigen-binding fragments.” *Id.*, [010]. Example 7 of WO ’875 states that “[i]nhibition assays were performed to map sites recognize[d] by the various human anti-human PD-1 antibodies,” including antibodies PD1-17 and PD1-28. *Id.*, [0121]-[0122]. In addition, claim 7 of WO ’875 claims “human” antibodies which comprise the disclosed amino acid sequences of PD1-17, PD1-28, PD1-33, PD1-35, or PD1-F2. *Id.*, cl. 7, [042]. Thus, the specification confirms that these antibodies are human anti-PD-1 antibodies.

123. This is also consistent with the definition provided by the ’449 patent. The ’449 patent defines the term “human monoclonal antibody” to encompass “antibodies displaying a single binding specificity which have variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences.” EX1001, 16:33-36. WO ’875 states that its “disclosure provides novel CDRs derived from human immunoglobulin gene libraries,” as the sequences of the disclosed antibodies are DNA and amino acid sequences for humans. EX1033, [041], Sequence Listing. WO ’875 thus discloses human monoclonal antibodies within the meaning of claim 1 of the ’449 patent.

124. With respect to the term “isolated,” WO ’875 states that after the nucleic acids “express[] the encoded product,” i.e., the anti-PD-1 antibodies, they “may be isolated and/or purified using any suitable technique, then used as

appropriate.” EX1033, [071]. It further describes that its “[a]ntigen-binding fragments . . . may be isolated and/or purified from their natural environment, in substantially pure or homogenous form.” EX1033, [072].

125. Furthermore, the definition of “isolated” in WO ’875 is consistent with the definition of “isolated” in the ’449 patent. WO ’875 defines “isolated” as a molecule that “is substantially free of its natural environment.” EX1033, [033]. The ’449 patent defines an “isolated antibody” as one “that is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that specifically binds PD-1 is substantially free of antibodies that specifically binds [sic] antigens other than PD-1).” EX1001, 16:3-7. The specification of the ’449 patent goes on to state that an “isolated antibody may be substantially free of other cellular material and/or chemicals.” *Id.*, 16:10-12. The POSA would understand the definition to be consistent with the definition in WO ’875 as a molecule that is substantially free of its natural environment would also be substantially free of other antibodies having different antigenic specificities and would be free of other cellular materials and/or chemicals.

126. WO ’875 also discloses the claim element “wherein the antibody or antigen-binding portion thereof cross-competes for binding to PD-1 with a reference antibody or reference antigen-binding portion thereof comprising . . . a

human heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 4 and a human light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 11.” EX1001, cl. 1.

127. As discussed above, WO '875 discloses various human monoclonal antibodies, including the PD1-17 and PD1-28 antibodies. *See supra* Section VIII.A. While WO '875 does not expressly state that these antibodies will cross-compete for binding to PD-1 with any of the reference antibodies of claim 1, it is an inherent characteristic of these antibodies that they do in fact cross-compete for binding to PD-1 with antibody 5C4.

128. As explained above, I conducted flow cytometry experiments, consistent with the disclosure of the '449 patent, to evaluate cross-competition of the PD1-17 and PD1-28 antibodies with reference antibody 5C4 for binding to PD-1. *See supra* Section IX. I also conducted mass spectrometry experiments to confirm that the antibodies I tested were the PD1-17 and PD1-28 antibodies disclosed by WO '875. *Supra* Section IX.A.1. Those tests demonstrate that both antibodies do in fact necessarily cross-compete with antibody 5C4 for binding to the human PD-1 receptor. *Supra* Sections IX.B.3-4. The binding of PD1-17 and PD1-28 to PD-1 is conferred by the amino acid sequences of the CDRs of PD1-17 and PD1-28, which recognize a precise PD-1 epitope. Antibodies having the

amino acid sequences of PD1-17 or PD-28, as described by WO '875, will bind precise amino acid residues of PD-1. EX1069 (“The amino-terminal variable or V domains of the heavy and light chains (V_H and V_L , respectively) together make up the V region of the antibody and confer on it the ability to bind specific antigen...”). The amino acid sequences influence the secondary and tertiary structures of the antibodies and ultimately the binding specificity of the CDRs. EX1069. The CDRs of 5C4, likewise, will bind precise amino acid residues of PD-1. As the experimental data above shows, the binding of PD1-17 and PD1-28 competes with 5C4 for binding to PD-1, which is an inherent characteristic conferred by antibody amino acid sequence.

129. For the reasons discussed above, because the disclosed isolated human monoclonal antibodies of WO '875, PD1-17 and PD1-28, both cross-compete with reference antibody 5C4, it is my opinion that WO '875's disclosure anticipates claim 1 of the '449 patent.

2. Claim 7

130. Claim 7 of the '449 patent claims a “composition comprising the antibody, or antigen-binding portion thereof, of any one of claim 1, 2, 3, and 4-6, and a pharmaceutically acceptable carrier.” EX1001, cl. 7. It is my opinion that WO '875 anticipates this claim.

131. As explained above, *see supra* Section X.A.1, WO '875 anticipates claim 1 by disclosing isolated human monoclonal antibodies, PD1-17 and PD1-28, that cross-compete with reference antibody 5C4 for binding to PD-1. The only additional limitation of claim 1 is that the claimed isolated human monoclonal antibody be in a composition with a “pharmaceutically acceptable carrier.”

132. The '449 patent states that a “pharmaceutically acceptable carrier” includes “any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible.” EX1001, 45:37-41. Under this definition, WO '875 also discloses the use of a “pharmaceutically acceptable carrier.” WO '875 states that “[p]harmaceutical compositions suitable for injection include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL (BASF, Parsippany, NJ) or phosphate buffered saline (PBS).” EX1033, [098]. It also states that preferred embodiments “include isotonic agents” and that the “carrier can be a solvent or dispersion medium,” both of which fall under the definition stated by the '449 patent. *Id.* It is thus my opinion that WO '875 also discloses the use of a “pharmaceutically acceptable carrier” and anticipates this claim.

3. Claim 8

133. Claim 8 of the '449 patent claims an “immunoconjugate comprising the antibody, or antigen-binding portion thereof, of any one of claim 1, 2, 3, and 4-6, linked to a therapeutic agent.” EX1001, cl. 8. It is my opinion that WO '875 anticipates this claim.

134. As explained above, *see supra* Section X.A.1, WO '875 anticipates claim 1 by disclosing isolated human monoclonal antibodies, PD1-17 and PD1-28, that cross-compete with reference antibody 5C4 for binding to PD-1. The only additional claim element of claim 8 is that it requires an “immunoconjugate” that links the antibody of claim 1 to “a therapeutic agent.” The '449 patent defines an “immunoconjugate” as “an anti-PD-1 antibody, or fragment thereof, conjugated to a therapeutic moiety, such as a cytotoxin, a drug . . . or a radiotoxin.” EX1001, 41:2-4.

135. WO '875 discloses an immunoconjugate comprising an antibody of claim 1 linked to a therapeutic agent. WO '875 states that the “[a]nti-PD1 antibodies described herein can be linked to another functional molecule, e.g., another peptide or protein (albumin, another antibody, etc.), toxin, radioisotope, cytotoxic or cytostatic agents.” EX1033, [063]. This disclosure is consistent with the definition of an immunoconjugate in the '449 patent.

4. Claim 12

136. Claim 12 of the '449 patent claims an “antibody or antigen-binding portion thereof of any of claims 1, 2, and 3, wherein the antibody or antigen-binding portion thereof inhibits the suppression of CD4+CD25-T cells by regulatory T cells.” EX1001, cl. 12. It is my opinion that WO '875 anticipates this claim.

137. As explained above, *see supra* Section X.A.1, WO '875 anticipates claim 1 by disclosing isolated human monoclonal antibodies, PD1-17 and PD1-28, that cross-compete with reference antibody 5C4 for binding to PD-1. The only additional element of claim 12 is that the claimed antibody of claims 1, 2, or 3 “inhibits the suppression of CD4+CD25-T cells by regulatory T cells.” *Id.*

138. It was well-understood by the POSA, as of May 9, 2005, that regulatory T cells, i.e., CD4+CD25+T cells act to suppress CD4+CD25-T cells and the body's immune response. As described by Holm 2004, a publicly available publication, “regulatory CD4+CD25+T cells (T_{reg} cells) play an important role in the maintenance of immunological self-tolerance, and that this cell subset exerts its function by suppressing the proliferation or function of autoreactive T cells.” EX0135, 629. Thus, regulatory T cells act to suppress normal autoreactive CD4+CD25-T cells.

139. WO '875 discloses that its anti-PD-1 antibodies, including PD1-17 and PD1-28 block PD-L1 ligand binding to PD-1 and stimulate cytokine secretion, including IL-2. EX1033, [0128] (“The blockade of the negative signal also results in enhanced proliferation and IL-2 production.”). This enhanced production of IL-2 necessarily inhibits the natural suppression of CD4+CD25-T cells by regulatory T cells. As explained by Thornton and Shevach 1998, “CD4+CD25+ cells [Treg cells] inhibit the induction of IL-2 production in the responder CD4+CD25– population, and suppression can be overcome by the addition of exogenous IL-2 or enhancement of endogenous IL-2 production.” EX1036, 288. Thus, the addition of IL-2 by the anti-PD-1 antibodies of WO '875 would inhibit the natural suppression of CD4+CD25-T cells by regulatory T cells.

140. Moreover, it was also well-known by the POSA, as of May 9, 2005, that one additional mechanism by which regulatory T cells suppress CD4+CD25-T cells is through the expression of PD-1. EX1037, 38 (Figure 6 illustrating several “TCR signaling pathways,” including from the “increased expression of the phosphatase-associated cell surface molecules CTLA-4, PD-1, and CD5”). As Holm 2004 also teaches, “PD-1 molecules expressed by T_{reg} cells are critical for the regulation of peripheral tolerance and autoimmunity.” EX1035, 634. Thus, the

expression of PD-1 itself on regulatory T cells is one mechanism by which they suppress CD4+CD25-T cells.

141. As explained above, and as shown by my experiments, the antibodies of WO '875, including PD1-17 and PD1-28, necessarily block PD-L1 binding to PD-1. They will thus also bind to PD-1 expressed on regulatory T cells, mediating those regulatory T cells suppressive effects. In other words, by blocking the PD-1 pathway for regulatory T cells, both PD1-17 and PD1-28 would thus also necessarily also inhibit the natural suppression of CD4+CD25-T cells by regulatory T cells by binding to PD-1 expressed by those regulatory T cells.

5. Claim 13

142. Claim 13 of the '449 patent claims an “antibody or antigen-binding portion thereof of any one of claims 1, 2, and 3, wherein the antibody or antigen-binding portion thereof enhances the antigen specific-memory response to a tumor or a pathogen.” EX1001, cl. 13. It is my opinion that WO '875 anticipates this claim.

143. As explained above, *see supra* Section X.A.1, WO '875 anticipates claim 1 by disclosing isolated human monoclonal antibodies, PD1-17 and PD1-28, that cross-compete with reference antibody 5C4 for binding to PD-1. The only additional element of claim 13 is that the claimed antibody of claims 1, 2, or 3

must “enhance[] the antigen specific-memory response to a tumor or a pathogen.”

Id.

144. The ’449 patent does not define the phrase “antigen specific-memory response.” It uses the term in various locations, but not in a way that defines the terms or elucidates what its meaning is to the POSA. EX1001, 14:19-20, 18:65-67, 24:1-2, 25:29-30. The POSA would understand this phrase to refer to the ability of the immune system, including memory T cells, to respond effectively to a pathogen or tumor cells that the same immune system previously encountered.

145. WO ’875 discloses this additional element as it describes how its antibodies can be used to “enhance a patient’s immune response in order to treat an immune disorder or cancer. The disorders being treated or prevented by the disclosed methods include but are not limited to infections with microbes (e.g., bacteria), viruses (e.g., systemic viral infections such as influenza, viral skin diseases such as herpes or shingles), or parasites; and cancer (e.g., melanoma and prostate cancers).” EX1033, [083]. The POSA would understand this “enhance[ment]” to a patient’s immune response to also encompass the enhancement of antigen specific-memory response to a tumor or pathogen.

146. It was well-known by POSA that PD-1:PD-L1 acts a negative regulator of memory cells, including secondary responses to specific antigens. *See*

e.g., EX1038, 97 (“our data demonstrated that the PD-1 ligand/PD-1 pathway functioned as a negative regulatory pathway for naïve T cell activation during a primary response to MBP or TT, and more importantly, on previously activated T cells or memory T cells during the secondary response.”). Thus, the antibodies of WO ’875, by blocking this negative regulatory pathway, would enhance the antigen specific-memory response to a tumor or pathogen.

6. Claim 14

147. Claim 14 of the ’449 patent claims an “antibody or antigen-binding portion thereof of any one of claims 1, 2, and 3, wherein the antibody or antigen-binding portion thereof confers a persistent immunity to tumor relapse.” EX1001, cl. 14. It is my opinion that WO ’875 anticipates claim 14.

148. As I explained above, *see supra* Section X.A.1, it is my opinion that WO ’875 inherently anticipates claim 1 by disclosing isolated human antibodies that cross-compete with nivolumab, i.e., antibody 5C4, for binding to PD-1.

149. The specification of the ’449 patent does not define or refer to “persistent immunity” to a tumor relapse. Example 19 of the ’449 patent refers to experiments in mice following single anti-PD-1 antibody therapy in combination with anti-CTLA-4 antibody with MC38 colorectal cancer cells. EX1001, 83:10-52.

150. The 11 treated mice, i.e., mice that were tumor-free after initial treatment, were then re-implanted with further MC38 colorectal cancer cells. All 11 mice did not develop tumors up to 18 days post-implantation. *Id.* The '449 patent states that this experiment shows that this “antibody therapy resulting in PD-1 and CTLA-4 blockade produces a persistent immunity to tumor relapse.” *Id.*, 83:49-51. This is the only support for the phrase “persistent immunity” in the specification.

151. Given that the experiment examined only whether mice developed further tumors 18 days after re-implantation with MC38 colorectal cancer cells, the phrase “persistent immunity” must be understood to encompass immunity to tumor relapse for this period of time after antibody treatment ceases.

152. It is my opinion that the anti-PD-1 antibodies of WO '875, including PD1-17 and PD1-28, would also confer “persistent immunity” to tumor relapse. These anti-PD-1 antibodies cross-compete for binding to PD-1 with the reference antibodies of claim 1, as shown by my flow cytometry experiments, which are also the same antibodies directly claimed by claims 2 and 3.

153. Even though Example 19 used a different anti-PD-1 mouse antibody than those of claims 1-3, Patent Owner relied on those results to disclose that anti-PD-1 antibodies, by producing a PD-1 blockade, can confer “persistent immunity”

to tumor relapse. The antibodies of WO '875, including PD1-17 and PD1-28 also bind to PD-1, including to the same epitope as the other antibodies referenced in claims 1-3. By binding to the same protein, as well as the same epitope, these anti-PD-1 antibodies would necessarily also produce the same PD-1 blockade and would confer “persistent immunity” to tumor relapse within the meaning of claim 14.

7. Claim 21

154. Claim 21 of the '449 patent claims an “antibody, or antigen-binding portion thereof of claim 1, wherein the reference antibody or reference antigen-binding portion thereof comprises: (a) a human heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 3; and (b) a human light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 10.” EX1001, cl. 21. The reference antibody of this claim, with SEQ ID Nos. 3 and 10 refers to anti-PD-1 monoclonal antibody 4H1. EX1001, Fig. 3A, 3B, 19:20-30. It is my opinion that WO '875 anticipates this claim.

155. As explained above, *see supra* Section X.A.1, WO '875 anticipates claim 1 by disclosing isolated human monoclonal antibodies, PD1-17 and PD1-28, that cross-compete with reference antibody 5C4 for binding to PD-1. Because these antibodies specifically bind to PD-1, including the same epitope of PD-1 as

reference antibody 5C4, it is my opinion that they will necessarily cross-compete with antibody 4H1 as well.

156. WO '875 states that its antibodies “specifically bind an epitope within the extracellular domain of human PD-1.” EX1033, [046]. It further notes that its antibodies “bind to the PD-L-binding domain of PD-1.” *Id.* Patent Owner has previously admitted, before the European Patent office, that “antibodies that bind to the same epitope on PD-1 have the ability to cross-compete for binding to PD-1.” EX1039, 2. Before the European Patent Office, Patent Owner submitted additional data from “competitive binding experiments” which demonstrated that antibody 4H1 “compete[s] with antibody 5C4.” EX1039 at 1, Annex. Those experiments are consistent with the methods described by the Examples of the '449 patent as well as with my experiments that show the cross-competition of PD1-17 and PD-28 with antibody 5C4 for binding to PD-1.

157. Thus, Patent Owner’s evidence shows that antibody 4H1 competes with antibody 5C4 for binding to PD-1. At the same time, my experiments demonstrate that the prior art antibodies, PD1-17 and PD1-28, also cross-compete with antibody 5C4 for binding to PD-1. Thus, the antibodies of WO '875, because they compete with 5C4 for binding, must bind to the same epitope or overlapping

epitope on PD-1 as 4H1, or sterically hinder 4H1, and will necessarily cross-compete for binding with 4H1.

8. Claim 22

158. Claim 22 of the '449 patent claims an “antibody, or antigen-binding portion thereof of claim 1, wherein the reference antibody or reference antigen-binding portion thereof comprises: (a) a human heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 4; and (b) a human light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 11.” EX1001, cl. 22.

159. For the same reasons discussed above regarding claim 1, WO '875 anticipates this claim. SEQ ID Nos. 4 and 11 set forth the amino acid sequences of the heavy chain and light chain variable regions of anti-PD-1 monoclonal antibody 5C4. EX1001, Fig. 3A, 3B, 19:20-30. Thus, because PD1-17 and PD1-28 both cross-compete with antibody 5C4 for binding to PD-1, *see supra* Section IX.B, WO '875 anticipates this claim.

9. Claim 23

160. Claim 23 of the '449 patent claims “[t]he immunoconjugate of claim 8, wherein the therapeutic agent is a cytotoxin or a radioactive isotope.” EX1001, cl. 23; *see also id.*, Dec. 20, 2011 Certificate of Correction. It is my opinion that WO '875 anticipates this claim.

161. As explained above, *see supra* Section X.A.1, WO '875 anticipates claims 1 and 8 by disclosing an immunoconjugate containing isolated human monoclonal antibodies, PD1-17 and PD1-28, that cross-competes with reference antibody 5C4 for binding to PD-1 linked to another therapeutic agent. The only additional element of claim 23 is that the “therapeutic agent” must be a “cytotoxin or a radioactive isotope.” EX1001, cl. 23.

162. WO '875 teaches this additional limitation. WO '875 states that the “[a]nti-PD1 antibodies described herein can be linked to another functional molecule, e.g., another peptide or protein (albumin, another antibody, etc.), toxin, radioisotope, cytotoxic or cytostatic agents.” EX1033, [063]. Thus, WO '875 teaches that its anti-PD-1 antibodies, including PD1-17 and PD1-28, can form part of an immunoconjugate when linked to a cytotoxin or radioisotope.

B. Claims 14-16 Are Unpatentable as Obvious Over WO '875

163. It is also my opinion that 14-16 are rendered obvious by WO '875 in view of the knowledge of the POSA. At a high-level, these claims depend from claim 1 which is anticipated by WO '875, as explained above. *See supra* Section X.A.1. Claim 15 further requires that the “antibody or antigen-binding portion thereof is an IgG4 isotype” and claim 16 further requires that the antibody or antigen-binding portion of claim 15 “has neither ADCC activity nor CDC

activity.” EX1001, cls. 15-16. ADCC refers to antibody-dependent cellular cytotoxicity and CDC refers to complement dependent cytotoxicity.

164. Both of these additional elements were routine adjustments made by the POSA who would have been motivated to generate an IgG4 isotype that has neither ADCC nor CDC activity. The POSA would have been motivated to generate IgG4 anti-PD-1 antibodies that cross-compete with reference antibodies that target the ligand binding region of PD-1 to adjust the effector function of the antibodies. *See* EX1056, 106 (“Selection of the desired human antibody heavy chain isotypes is often based on the desired effector functions for a specific therapeutic application.”). Specifically, it was known that IgG4 heavy chains do not mediate ADCC and CDC. *See* EX1040, 688 (“In general, IgG1 and IgG3 antibodies are effective at initiating ADCC while IgG2 readily fixes complement but is poor at inducing ADCC. IgG4 appears to be inefficient at both ADCC and CDCC.”).

165. Because it was known that the IgG4 isotype does not mediate ADCC and CDC, the POSA would have been motivated to modify the IgG1 heavy chains of PD1-17 and PD1-28 to generate antibodies of the IgG4 isotype. The POSA would have understood that this would generate an antibody that also binds to PD-

1, but would have reduced ADCC and CDC activity. The POSA would want reduced ADCC and CDC activity in cases where cytotoxicity is undesirable.

1. Claim 14

166. Claim 14 of the '449 patent claims an “antibody or antigen-binding portion thereof of any one of claims 1, 2, and 3, wherein the antibody or antigen-binding portion thereof confers a persistent immunity to tumor relapse.” EX1001, cl. 14. As I explained above, *see supra* X.A.1, the antibodies of WO '875 would anticipate this claim. However, even if they did not, it is my opinion that the POSA would have found this claim obvious in light of WO '875 and the general knowledge of the POSA.

167. The POSA would have been motivated to pursue anti-PD-1 antibodies that did not just treat tumors in the short-term, but also provided persistent immunity to tumors after treatment concluded.

168. The POSA would have understood that tumors often relapse and that treatments which provide immunity for longer periods of time could be used to prevent or at least delay the progression of relapse. Thus, even if the anti-PD-1 antibodies of WO '875, including PD1-17 and PD1-28, did not provide persistent immunity to tumor relapses (which they would), the POSA would have understood that they could be modified, and or administered in a modified regimen, to induce an immune response that could be long-lasting and provide “persistent immunity”

to tumor relapse for at least the 18-day time period identified in Example 19. *See supra* Section X.A.6. The POSA would have understood that modifying the antibody isotype (*e.g.*, IgG1 vs. IgG3), modifying specific amino acids in the Fc region, making a bispecific antibody, modifying the amino acid sequences of the CDRs to increase epitope binding affinity can all be done to modify the properties of the antibody to induce and change the nature of the resulting immune response.

2. Claims 15 and 16

169. Claim 15 of the '449 patent claims an “antibody or antigen-binding portion thereof of any one of claims 1, 2, and 3, wherein the antibody or antigen-binding portion thereof is an IgG4 isotype.” EX1001, cl. 15. Claim 16 of the '449 patent claims an “antibody or antigen-binding portion thereof of claim 15, wherein the antibody or antigen-binding portion thereof has neither ADCC activity nor CDC activity.” EX1001, cl. 16.

170. It is my opinion that claims 15 and 16 are obvious in light of WO '875. As I explained above, *see supra* Section X.A.1, WO '875 inherently anticipates claim 1 by disclosing isolated human antibodies that cross-compete with nivolumab, *i.e.*, antibody 5C4, for binding to PD-1. Claim 15 further requires that the “the antibody or antigen-binding portion thereof is an IgG4 isotype.” EX1001, cl. 15.

171. First, this additional element is disclosed by WO '875. It discloses that the antigen-binding domain of its antibodies “may have attached all or part of an immunoglobulin heavy chain derived from any antibody isotope, e.g., IgG, IgA, IgE, and IgM and any of the isotope sub-classes, which include but are not limited to, IgG1 and IgG4.” EX1033, [043]. While PD1-17 and PD1-28 are IgG1, it would have been obvious to modify the heavy chain to IgG4.

172. Specifically, the POSA would have been motivated to generate IgG4 anti-PD-1 antibodies that cross-compete with reference antibodies that target the ligand binding region of PD-1 to adjust the effector function of the antibodies. “Selection of the desired human antibody heavy chain isotypes is often based on the desired effector functions for a specific therapeutic application.” EX1056, 106, (Table 2). For example, it was well known that the antibody-dependent cellular cytotoxicity (“ADCC”) activity of an anti-PD-1 antibody is related to its Fc region. EX1001, 13:63-67. It was also long known that IgG4 heavy chains do not mediate antibody-dependent cellular cytotoxicity (“ADCC”) and complement dependent cytotoxicity (“CDC”). *Id.*; EX1040, 688 (“In general, IgG1 and IgG3 antibodies are effective at initiating ADCC while IgG2 readily fixes complement but is poor at inducing ADCC. IgG4 appears to be inefficient at both ADCC and CDCC.”). Thus, the POSA would have been motivated to modify the IgG1 heavy chains of

PD1-17 and PD1-28 to IgG4 to generate an antibody that binds PD-1, but has different functional characteristics, such as reduced ADCC and CDC activity. In cases where cytotoxicity is not wanted, IgG4 would be desired. *Id.*, EX1041, 136 (“When the efficiency for lysis was measured by antibody titer, the hierarchy between isotypes (human IgG1 > rat IgG2b > human IgG3 > human IgG2 > human IgG4 > human IgE) was identical for different complement sources.”).

173. It is my opinion that the POSA would have thus been motivated to modify the teachings of WO '875, including its disclosed IgG1 antibodies PD1-17 and PD1-28, which cross-compete (*see* IX.B, *supra*), to generate anti-PD-1 IgG4 antibodies that would also inherently cross-compete for targeting the ligand-binding region of PD-1.

174. It is also my opinion that the POSA would have had a reasonable expectation of success in modifying the teachings of WO '875, including its disclosed IgG1 antibodies PD1-17 and PD1-28, which cross-compete (*see* Section IX.B, *supra*), to generate anti-PD-1 IgG4 antibodies that would also inherently cross-compete for targeting the ligand-binding region of PD-1. It was understood by the POSA that the CDRs of an IgG1 antibody can be used with the Fc IgG4 and maintain antibody binding specificity.

C. Claim 9 is Unpatentable as Obvious Over WO '875 in view of WO '557

175. It is also my opinion that claim 9 is rendered obvious by WO '875 in view of WO '557. Claim 9 also depends from claim 1 which is anticipated by WO '875, as explained above. *See supra* Section X.A.1. Claim 9 further requires a “bispecific molecule” comprising the antibody of claim 1 “linked to a second functional moiety having a different binding specificity than said antibody, or antigen-binding portion thereof.” EX1001, cl. 9.

176. The POSA would have been motivated to combine the teachings of WO '557 with WO '875. Both references disclose the use of anti-PD-1 antibodies to treat tumors and are directed to the same issue that the POSA would have focused on, namely, the development of anti-PD-1 antibodies to treat cancer, pathogens, or other medical conditions that could be responsive to anti-PD-1 treatment. The POSA reviewing WO '875 would be interested in identifying additional compositions and means of formulating and administering the disclosed anti-PD-1 antibodies. The POSA, in doing so, would have reviewed WO '557 and identified its helpful teachings regarding bispecific molecules—which could further improve the therapeutic profile of the anti-PD-1 antibody.

177. With respect to a bispecific molecule, it was well-known by the POSA that bispecific antibodies could provide a more effective means of treating tumors

as they can target two different antigens. *See* EX1042, 7346 (“[b]ispecific antibody constructs have a great potential in therapeutic and diagnostic applications where cross-linking of unrelated antigens is required”); EX1043, 4651 (in experiments, “[c]ompared with the parental antibodies, the bsAbs [bispecific antibodies] markedly reduced tumor mortality”); EX1044, 357 (“[b]ispecific antibodies can be very useful for therapeutic applications because they offer a means to recognize an infected cell via one binding site while providing a second binding factor to recruit cytotoxic lymphocytes”). The POSA thus understood that a bispecific antibody could not only block PD-1/PD-L1 binding, but could also recruit other immune cells to target the tumor as taught by WO ’557. The POSA would have thus been motivated to combine this teaching from WO ’557 with the anti-PD-1 antibodies of WO ’875.

178. The POSA would have also reasonably expected success in creating a bispecific antibody with the antibodies of WO ’875. Techniques for creating bispecific antibodies were routine and well known in the art. WO ’557 describes well known methods of constructing bispecific antibodies by chemical means and hybridoma technology. EX1012, 55:24-56:8 (citing EX1060, 628; EX1061, 354; EX1062, 1453; EX1063, 241). Patent Owner explains that the “bispecific molecules of the present invention can be prepared by conjugating the constituent

binding specificities . . . *using methods known in the art.*” EX1001, 44:22-25 (emphasis added).

179. As noted above, claim 9 of the ’449 patent claims a “bispecific molecule comprising the antibody, or antigen-binding portion thereof, of any one of claims 1, 2, 3, and 4-5, linked to a second functional moiety having a different binding specificity than said antibody, or antigen-binding portion thereof.”

EX1001, cl. 9. It is my opinion that this claim is obvious due to the combination of WO ’875 with WO ’557.

180. As explained above, *see supra* Section X.A.1, WO ’875 anticipates claim 1 by disclosing isolated human monoclonal antibodies, PD1-17 and PD1-28, that cross-compete with reference antibody 5C4 for binding to PD-1. WO ’557 teaches the POSA to modify those antibodies into anti-PD-1 bispecific antibodies containing the effective anti-PD-1 antibodies of WO ’875. WO ’557 describes the benefits of using bispecific molecules comprising an anti-PD-1 antibody linked to a second functional moiety having a different binding specificity. It explains that “[i]n one embodiment of the invention, an activating antibody used to stimulate PD-1 activity is a bispecific antibody. For example, such an antibody can comprise a PD-1 binding site and another binding site which targets a cell surface receptor on an immune cell.” EX1012, 76:9-21. It further goes on to state that:

“Such antibodies (or other bispecific agents) are art recognized and can be produced, e.g., as described herein. Selection of this second antigen for the bispecific antibody provides flexibility in selection of cell population to be targeted for inhibition.” *Id.*

181. As explained above, *see supra* paragraphs 176-177, the POSA would have been motivated to combine these teachings with WO '875's antibodies with a reasonable expectation of success. It is thus my opinion that this claim is obvious.

D. The Challenged Claims Are Unpatentable As Obvious Over WO '875 in view of WO '557

182. It is also my opinion that all of the Challenged Claims referenced above are also obvious over WO '875 in view of WO '557. As discussed above, both WO '875 and WO '557 disclose, either expressly or inherently, every limitation of the Challenged Claims. Thus, to the extent any of the claims are not anticipated by these references, it is my opinion that the POSA would have found them to be obvious.

183. I understand that disclosure of a species prior to the critical date renders the claimed genus unpatentable as obvious. The Challenged Claims are directed to a sub-genus of a known set of antibodies that bind PD-1. That sub-genus specifically being anti-PD-1 antibodies that cross-compete with one of the seven recited reference antibodies. More specifically, the anti-PD-1 antibodies,

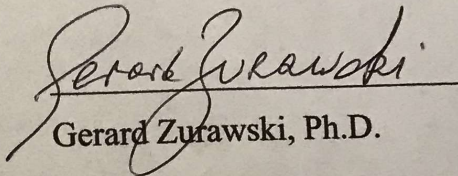
PD1-17 and PD1-28 do cross-compete with reference antibody 5C4 in binding to PD-1. Thus, the species PD1-17 and PD1-28 render obvious the genus of the Challenged Claims.

184. For the same reasons as set forth in Ground 3, the POSA would have been motivated with a reasonable expectation of success in combining the disclosures of WO '875 and WO '557 to arrive at the claimed antibodies of the '449 patent. *See* ¶¶176-178, *supra*.

XI. CONCLUSION

185. I 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 that these statements were made with knowledge that willful false statements and the like are made punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code.

Dated: Feb 3 2023

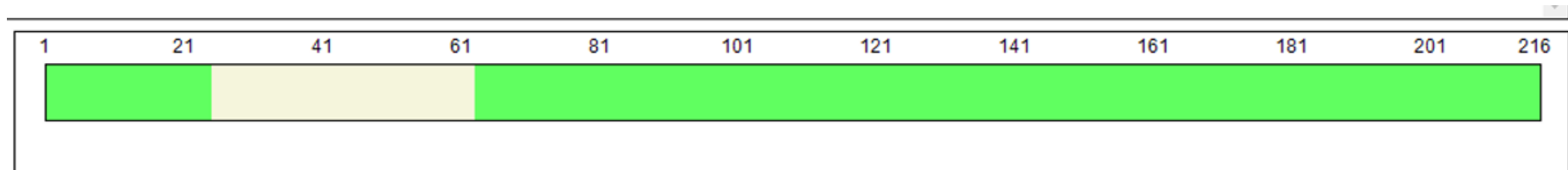

Gerard Zurawski, Ph.D.

APPENDIX A

PD1-17 Heavy Chain



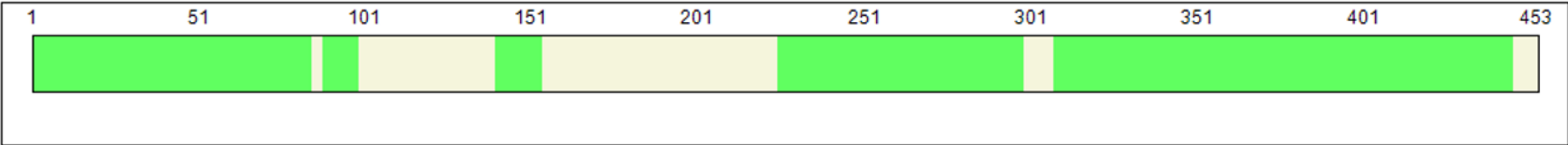
PD1-17 Light Chain



Sequence	Modification List
	1 11 21 31 41 51 61 71 81 91
Modifications BBBBB	1 O C C 1 NF 11 MLTQPHSV 21 SESPGKTVTI 31 SCTRSSGSIA 41 SNSVQWYQQR 51 PGSSPTTVIY 61 EDNQRP 71 SGVP 81 DRFSGSIDSS 91 SNSASLTVSG 101 LKTEDEADYY 111 CQSSDSSAVV
Modifications BBBBB	101 C C 101 FGSGTKLTVL 111 GQPKAAPSVT 121 LFPPSSEELQ 131 ANKATLVCLI 141 SDFYPGAVTV 151 AWKADSSPVK 161 AGVETTTPSK 171 QSNKYAASS 181 YLSLTPEQWK 191 SHRSYSCQVT
Modifications BBBBB	201 C 201 HEGSTVEKTV 211 APTECS

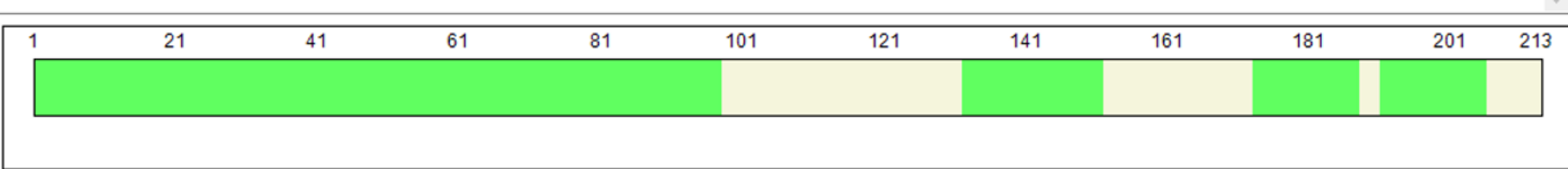
APPENDIX B

PD1-28 Heavy Chain



Sequence	Modification List
1	112131415161718191
Modifications	1A C O O O C
sp	EVQLVQSGAE VKKPGASVKV SCKASGYRFT SYGISWVRQA PGQGLEWMGW ISAYNGNTNY AQLQGRVTM TTDSTNTAY MELRSLRSDD TAVYYCARDA
Modifications	101 C
sp	DYSSGSGYWG QGTLVTVSST VSSASTKGPS VFPLAPCSRS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTPVSSSLG
Modifications	201 C C C O C
sp	TQTYICNVNH KPSNTKVDKR VEPKSCDKTH TCPPCPAPEL LGGPSVFLEP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE
Modifications	301 C C
sp	QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKQPR EPQVYTLPPS RDELTKNQVS LTCLVKGFYP SDIAVEWESN GPENNYKTT
Modifications	401 C O
sp	PPVLDSGSE FLYSKLTVDK SRWQGNVFS CSVMHEALHN HYTKSLSLG PGK

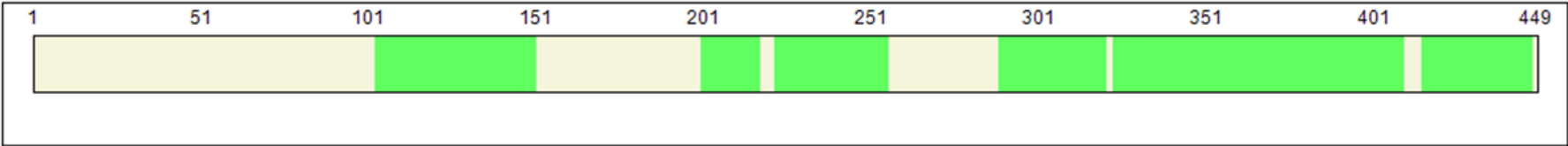
PD1-28 Light Chain



Sequence		Modification List										
		1	11	21	31	41	51	61	71	81	91	
Modifications	1A											
sq		SYELTQPPSV	SVSPGQTARI	TCSGDALPKQ	YAYWYQQKPG	QAPVMVIYKD	TERPSGIPER	FSGSSSGTKV	TLTISGVQAE	DEADYYCQSA	DNSITYRVFG	
Modifications	101											
sq		GGTKVTVLQQ	PKAAPSVTLF	PPSSEELQAN	KATLVCLISD	FYPGAVTVAW	KADSSPVKGV	ETTTPSKQSN	NKYAASSYLS	LTPEQWKSHR	SYSCQVTHEG	
Modifications	201											
sq		STVEKTVAPT	ECS									

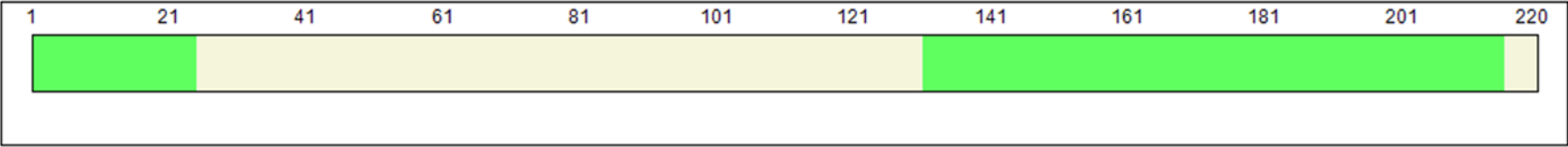
APPENDIX C

Nivolumab Source 1 Heavy Chain



Sequence		Modification List									
		1	11	21	31	41	51	61	71	81	91
Modifications	1										
FFFFF		QVQLVQSGVE VKKPGASVKV SCKASGYTFT NYMYWVRQA PQQGLEWMGG INPSNGGTNF NEKFKNRVTL TDSSTTTAY MELKSLQFDD TAVYYCARRD									
Modifications	101										
FFFFF		YRFDMGFDYW QGTTTVTVSS ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT									
Modifications	201										
FFFFF		YTCNVDHKPS NTKVDKRVES KYGPPCPPCP APEFEGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY									
Modifications	301										
FFFFF		RVSVSLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK QPREPQVYT LPPSQEEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTTPPVLDS									
Modifications	401										
FFFFF		DGSFFLYSRL TVDKSRWQEG NVFSCSVME ALHNHYTQKS LSLSLGKAS									

Nivolumab Source 1 Light Chain



Sequence		Modification List										
		1	11	21	31	41	51	61	71	81	91	
Modifications	1	C										
EEEE		EIVLTQSPAT	LSLSPGERAT	LSCRASKGVS	TSGYSYLHWY	QOKPGQAPRL	LIYLASYLES	GVPARFSGSG	SGTDFTLTIS	SLEPEDFAVY	YCQHSRDLPL	
Modifications	101	C										
EEEE		TFGGGTKVEI	KRIVAAPSVF	IFPPSDEQLK	SGTASVVCLL	NNFYPREAKV	QWKVDNALQS	GNSQESVTEQ	DSKDSTYSLS	STLTLSKADY	EKKHKVYACEV	
Modifications	201											
EEEE		THQGLSSPVT	KSFNRGECAS									