

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

**PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 8,008,449 B2**

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Exhibits

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1001	U.S. Patent No. 8,008,449 B2 (“the ’449 patent”)
1002	Declaration of Dr. Gérard Zurawski (“Zurawski Decl.”)
1003	<i>Curriculum vitae</i> of Dr. Gérard Zurawski
1004	List of Materials Considered by Dr. Gérard Zurawski
1005	U.S. Patent No. 7,595,048 (“the ’048 patent”)
1006	Ishida et al., <i>Differential expression of PD-L1 and PD-L2, ligands for an inhibitory receptor PD-1, in the cells of lymphohematopoietic tissues</i> , Immunology letters 84.1 (2002): 57-62. (“Ishida 1992”)
1007	Iwai et al., <i>Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade</i> , 99(19) Proc. Nat. Acad. Sci. 12293 (2002) (“Iwai 2002”)
1008	Ohigashi et al., <i>Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer</i> , Clinical cancer research 11.8 (2005): 2947-2953. (“Ohigashi 2005”)
1009	Greenwald et al., <i>The B7 family revisited</i> , Annual review of immunology 23 (2005): 515. (“Greenwald 2005”)
1010	Hirano et al., <i>Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity</i> , Cancer research 65.3 (2005): 1089-1096. (“Hirano 2005”)
1011	<i>Bristol-Myers Squibb Company et al v. AstraZeneca Pharmaceuticals LP et al.</i> , C.A. No. 22-cv-00346 (D. Del.), D.I. No. 78-5
1012	PCT Publication No. WO 01/14557 A1 (“WO ’557”)
1013	Stern, M., and R. Herrmann, <i>Overview of monoclonal antibodies in cancer therapy: present and promise</i> , Critical reviews in oncology/hematology 54.1 (2005): 11-29. (“Stern 2005”)
1014	List of approved Antibodies from The Antibody Society
1015	Vaughan et al., <i>Human Antibodies by Design</i> , Nature Biotechnology 16 (1998): 535-539.
1016	Hoogenboom et al., <i>Antibody phage display technology and its applications</i> , Immunotechnology 4 (1998): 1-20. (“Hoogenboom 1998”)
1017	File History For U.S. Patent No. 8,008,449 B2 (“’449 patent File History”)
1018	PCT Publication No. WO 06/121168 A1 (“WO ’168”)
1019	U.S. Provisional Patent Application No. 60/679,466

1020	U.S. Provisional Patent Application No. 60/738,434
1021	U.S. Provisional Patent Application No. 60/748,919
1022	European Patent No. EP2161336 B1 (“EP ’336”)
1023	Notice of Intent to Grant Application No. 09013687.0, dated February 25, 2013
1024	Merck & Co., Inc.’s April 30, 2014 Notice of Opposition of European Patent No. EP2161336 B1
1025	Novartis AG’s April 25, 2014 Notice of Opposition of European Patent No. EP2161336 B1
1026	4-Antibody AG’s April 29, 2014 Notice of Opposition of European Patent No. EP2161336 B1
1027	Janssen Biotech, Inc.’s April 30, 2014 Notice of Opposition of European Patent No. EP2161336 B1
1028	Declaration of Jennifer Mataraza, dated April 28, 2014, submitted on behalf of Novartis AG in Opposition of European Patent No. EP2161336 B1
1029	Declaration of Robert J. Bloch, dated April 29, 2014, submitted on behalf of Merck & Co., Inc. in Opposition of European Patent No. EP2161336 B1
1030	European Patent No. EP2161336 B1 Amended claims with annotations, dated February 16, 2015
1031	European Patent Opposition Division March 2, 2017 Decision To maintain European Patent No. EP2161336 B1 in amended form
1032	<i>Bristol-Myers Squibb Company et al v. AstraZeneca Pharmaceuticals LP et al.</i> , C.A. No. 22-cv-00346 (D. Del.), D.I. No. 79
1033	PCT Publication No. WO 4/056875 A1 (“WO ’875”)
1034	PCT Publication No. WO 17/011666 A1 (“WO ’666”)
1035	Holm et al., <i>CD4+ CD25+ regulatory T cells: I. Phenotype and physiology</i> , <i>Apmis</i> 112.10 (2004): 629-41. (“Holm 2004”)
1036	Thornton, Angela M., and Ethan M. Shevach, <i>CD4+ CD25+ immunoregulatory T cells suppress polyclonal T cell activation in vitro by inhibiting interleukin 2 production</i> , <i>The Journal of experimental medicine</i> 188.2 (1998): 287-296. (“Thornton and Shevach 1998”)
1037	Gavin et al., <i>Homeostasis and anergy of CD4+ CD25+ suppressor T cells in vivo</i> , <i>Nature immunology</i> 3.1 (2002): 33-41. (“Gavin 2001”)
1038	Cai et al., <i>PD-1 ligands, negative regulators for activation of naive, memory, and recently activated human CD4+ T cells</i> , <i>Cellular immunology</i> 230.2 (2004): 89-98. (“Cai 2004”)

1039	Response to Examination report, dated April 4, 2012, in European Patent Application No. 09013687.0-2405
1040	Daugherty, Ann L., and Randall J. Mrsny, <i>Formulation and delivery issues for monoclonal antibody therapeutics</i> , Advanced drug delivery reviews 58.5-6 (2006): 686-706. (“Daugherty 2006”)
1041	Bindon et al., <i>Human monoclonal IgG isotypes differ in complement activating function at the level of C4 as well as C1q</i> , The Journal of experimental medicine 168.1 (1988): 127-142. (“Bindon 1988”)
1042	Conrath et al., <i>Camel single-domain antibodies as modular building units in bispecific and bivalent antibody constructs</i> , Journal of Biological Chemistry 276.10 (2001): 7346-7350. (“Conrath 2001”)
1043	Lindhofer et al., <i>Bispecific antibodies target operationally tumor-specific antigens in two leukemia relapse models</i> , (1996): 4651-4658. (“Lindhofer 1996”)
1044	Maynard, Jennifer, and George Georgiou, <i>Antibody engineering</i> , Annual review of biomedical engineering 2.1 (2000): 339-376. (“Maynard 2000”)
1045	Zurawski et al., <i>The Primary Binding Subunit of the Human Interleukin-4 Receptor Is Also a Component of the Interleukin-13 Receptor</i> , Journal of Biological Chemistry 270.23 (1995): 13869-13878. (“Zurawski 1995”)
1046	Parks et al., <i>Flow cytometry and fluorescence-activated cell sorting</i> , Fundamental immunology 781 (1989). (“Parks 1989”)
1047	PÉREZ, De La Lastra, and B. E. R. G. Van Den, <i>Epitope mapping of 10 monoclonal antibodies against the pig analogue of human membrane cofactor protein (MCP)</i> , Immunology 96.4 (1999): 663-670. (“Perez 1999”)
1048	Tosi et al., <i>Quantitative immunofluorescent assay of full-length, recombinant CD4 in solution and mapping of its epitopes</i> , Journal of Fluorescence 1.2 (1991): 141-146. (“Tosi 1991”)
1049	Sims et al., <i>Effect of platelet activation on the conformation of the plasma membrane glycoprotein IIb-IIIa complex</i> , Journal of Biological Chemistry 266.12 (1991): 7345-7352. (“Sims 1991”)
1050	Product information for Anti-Human PDCD1 Recombinant Antibody (PD1-17) (CAT#: TAB-0961CL) available at https://www.creativebiolabs.net/Anti-PDCD1-Therapeutic-Antibody-27649.htm

1051	Product Information for Anti-PD-1 [PD1-28], Human IgG1, Lambda Absolute Antibody (PD1-28) (Product #: Ab02652-10.0) <i>available at</i> https://absoluteantibody.com/product/anti-pd-1-pd1-28
1052	Flamar et al., <i>Non-covalent Assembly of Anti-Dendritic Cell Antibodies and Antigens for Evoking Immune Responses in vitro and in vivo</i> , Journal of Immunology 189(5) (2012): 2645-2655.
1053	Product information for Q15116 PDCD1_HUMAN <i>available at</i> https://www.uniprot.org/uniprotkb/Q15116/entry
1054	Product information for CHOgro® High Yield Expression System <i>available at</i> https://www.mirusbio.com/products/transfection/chogro-high-yield-expression-system
1055	Product information for Fluorescent Protein Labeling Kits <i>available at</i> https://www.thermofisher.com/order/catalog/product/A20173
1056	Vaswani, et al., Humanized antibodies as potential therapeutic drugs, Annals of Allergy, Asthma, & Immunology, Volume 81 (1998); 105-119.
1057	GenBank® Accession No. BC074740.2, GI No. 50960296, "Homo sapiens programmed cell death 1, mRNA (cDNA clone MGC:103817 Image:30915198), complete cds
1058	U.S. Patent No. 9,580,505 ("the '505 patent")
1059	U.S. Patent No. 9,580,507 ("the '507 patent")
1060	Staerz et al., <i>Hybrid antibodies can target sites for attack by T cells</i> , Nature 314 (1985) 628-631
1061	Perez et al., <i>Specific targeting of cytotoxic T cells by anti-T3 linked to anti-target cell antibody</i> , Nature 316 (1985) 354-356
1062	Staerz and Bevan, <i>Hybrid hybridoma producing a bispecific monoclonal antibody that can focus effector T-cell activity</i> , Proc. Natl. Acad. Sci. USA 83 (1986), 1453-57
1063	Staerz and Bevan, <i>Use of anti-receptor antibodies to focus T-Cell activity</i> , Immunology Today 7 (1986) 241-245
1064	April 10, 2012 Proposed Claims, European Patent No. EP2161336 B1
1065	Novartis AG's April 25, 2014 Arguments in Support of Opposition of European Patent No. EP2161336 B1
1066	4-Antibody AG's April 29, 2014 Arguments in Support of Opposition of European Patent No. EP2161336 B1
1067	Janssen Biotech, Inc.'s April 30, 2014 Arguments in Support of Opposition of European Patent No. EP2161336 B1
1068	Vector information for pIRES2 DsRed-Express2 Vector

1069	Janeway CA Jr et al. <i>Immunobiology: The Immune System in Health and Disease</i> . 5th edition. New York: Garland Science; 2001. The structure of a typical antibody molecule. Available at https://www.ncbi.nlm.nih.gov/books/NBK27144/ (“Janeway 2001”)
1070	Wang et al., <i>In vitro</i> characterization of the anti-PD-1 antibody nivolumab, BMS-936558, and in vivo toxicology in non-human primates, <i>Cancer Imm Res</i> , 2(9): (2014) 846-56 (“Wang 2014”)

TABLE OF AUTHORITIES

Page(s)

Cases

<i>Abbott Labs. v. Geneva Pharms., Inc.</i> , 182 F.3d 1315 (Fed. Cir. 1999)	36
<i>AbbVie Inc. v. Mathilda and Terence Kennedy Inst. of Rheumatology Trust</i> , 764 F.3d 1366 (Fed. Cir. 2014)	60
<i>Acoustic Tech., Inc. v. Itron Networked Sols., Inc.</i> , 949 F.3d 1366 (Fed. Cir. 2020)	55
<i>Advanced Bionics, LLC v. MED-EL Elektromedizinische Gerate BmbH</i> , IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020).....	63
<i>Allergan, Inc. v. Sandoz, Inc.</i> , 726 F.3d 1286 (Fed. Cir. 2013)	54
<i>Alza Corp. v. Mylan Labs., Inc.</i> , 464 F.3d 1286 (Fed. Cir. 2006)	54, 55
<i>Atlas Powder Co. v. IRECO, Inc.</i> , 190 F.3d 1342 (Fed. Cir. 1999)	36
<i>Becton, Dickinson & Co. v. B. Braun Melsungen AG</i> , IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017)	63
<i>Connell v. Sears, Roebuck & Co.</i> , 722 F.2d 1542 (Fed. Cir. 1983)	60
<i>Dana-Farber Cancer Institute, Inc. v. Ono Pharmaceutical Co., et al.</i> , Case No. 15-cv-13443, D.I. 11 (D. Mass.)	1
<i>Dann v. Johnston</i> , 425 U.S. 219 (1976).....	50
<i>DyStar Textilfarben GmbH v. C.H. Patrick Co.</i> , 464 F.3d 1356 (Fed. Cir. 2006)	54

<i>EnOcean GmbH v. Face Int’l Corp.</i> , 742 F.3d 955 (Fed. Cir. 2014)	23
<i>Fox Factory, Inc. v. SRAM, LLC</i> 944 F.3d 1366 (Fed. Cir. 2019)	61, 62
<i>Galderma Labs., L.P. v. Tolmar, Inc.</i> , 737 F.3d 731 (Fed. Cir. 2013)	61
<i>Johns Hopkins Univ. v. CellPro, Inc.</i> , 152 F.3d 1342 (Fed. Cir. 1998)	60
<i>J.T. Eaton & Co. v. Atlantic Paste & Glue Co.</i> , 106 F.3d 1563 (Fed. Cir. 1997)	62
<i>In re Kahn</i> , 441 F.3d 977 (Fed. Cir. 2006)	54
<i>Ex Parte Kubin</i> , 83 U.S.P.Q.2d 1410, 2007 WL 2070495 (Bd. Pat. App. & Interferences 2007)	59
<i>Leapfrog Enters., Inc. v. Fisher-Price, Inc.</i> , 485 F.3d 1157 (Fed. Cir. 2007)	61
<i>Medichem, S.A. v. Rolabo, S.L.</i> , 437 F.3d 1157 (Fed. Cir. 2006)	50
<i>MEHL/Biophile Int’l Corp. v. Milgraum</i> , 192 F.3d 1362 (Fed. Cir. 1999)	27
<i>In re O’Farrell</i> , 853 F.2d 894 (Fed. Cir.1988)	50, 55
<i>Ormco Corp. v. Align Tech., Inc.</i> , 463 F.3d 1299 (Fed. Cir. 2006)	61
<i>Perfect Web Techs., Inc. v. InfoUSA, Inc.</i> , 587 F.3d 1324 (Fed. Cir. 2009)	55
<i>Pfizer, Inc. v. Apotex, Inc.</i> , 480 F.3d 1348 (Fed. Cir. 2007)	56

<i>Phillips v. AWH Corp.</i> , 415 F.3d 1303 (Fed. Cir. 2005)	19, 20
<i>Sanofi-Aventis U.S. LLC v. Immunex Corp.</i> , IPR2017-01884, Paper 14 (PTAB Feb. 15, 2018).....	65
<i>Schering Corp. v. Geneva Pharms.</i> , 339 F.3d 1373 (Fed. Cir. 2003)	26, 36
<i>SmithKline Beecham Corp. v. Apotex Corp.</i> , 403 F.3d 1331 (Fed. Cir. 2005)	32, 37
<i>Teva Pharms. Int’l GmbH v. Eli Lilly & Co.</i> , 8 F.4th 1349 (Fed. Cir. 2021)	63
<i>Tokai Corp. v. Easton Enters., Inc.</i> , 632 F.3d 1358 (Fed. Cir. 2011)	61
<i>Toro Co. v. Deere & Co.</i> , 355 F.3d 1313 (Fed. Cir. 2004)	36

Statutes

35 U.S.C. § 102	4, 24
35 U.S.C. § 103	4, 50, 59
35 U.S.C. § 282(b)	19
35 U.S.C. § 325(d)	63, 64, 65

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37 C.F.R. § 42.8(b)	4, 5
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37 C.F.R. § 42.103	4
37 C.F.R. § 42.100(b)	19, 21
37 C.F.R. § 42.101	4
37 C.F.R. § 42.102(a).....	4

37 C.F.R. § 42.104	4
83 Fed. Reg. 197, 51340-51359 (Oct. 11, 2018)	19
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Dana-Farber Cancer Institute, Inc. (“Dana-Farber” or “Petitioner”) requests *inter partes* review (“IPR”) of claims 1, 7-9, 12-16, and 21-23 (the “Challenged Claims”) of U.S. Patent 8,008,449 (“the ’449 patent”) owned by E.R. Squibb & Sons, L.L.C. and Ono Pharmaceuticals Co., Ltd. (“Patent Owner”).

I. INTRODUCTION

The discovery of anti-programmed cell death protein 1/ligand 1 (“PD-1/PD-L1”) antibodies is disclosed in U.S. Patent No. 7,595,048 and its relatives (now known as the “Honjo-Freeman Patents”), whose inventors include Dr. Gordon Freeman of Dana-Farber, a non-profit research hospital dedicated to advancing the understanding, diagnosis, treatment, cure, and prevention of cancer. This Nobel Prize-winning discovery was groundbreaking; it won industry acclaim for revolutionizing cancer therapeutics¹ and spurred Bristol-Myers Squibb Co. (“BMS”)², Merck & Co., Sanofi, Novartis AG, AstraZeneca Pharmaceuticals LP, and others to invest in commercializing antibodies targeting the PD-1/PD-L1

¹ Other awards included the 2014 William B. Coley Award and the 2017 Warrant Alpert Foundation Prize, both shared with Dr. Freeman.

² Upon information and belief, Patent Owner E.R. Squibb & Sons, L.L.C., is a wholly owned subsidiary of BMS. *Dana-Farber Cancer Institute, Inc. v. Ono Pharmaceutical Co., et al.*, Case No. 15-cv-13443, D.I. 11 (D. Mass.).

pathway. The discoveries of Dr. Freeman and others set the stage for this new frontier in cancer therapeutics. But the Challenged Claims are not an advancement over the Honjo-Freeman Patents. Rather, the Challenged Claims, directed to antibodies that can be administered in performing the treatment methods described in the Honjo-Freeman Patents, represent BMS's attempt to obtain exclusionary rights over prior art anti-human PD-1 antibodies to which it made no inventive contribution.

The '449 patent's specification discloses seven human monoclonal anti-PD-1 antibodies: 17D8, 2D3, 4H1, 5C4, 4A11, 7D3, and 5F4. Those are the *only* anti-PD-1 antibodies disclosed in the '449 patent. Yet the claims of the '449 patent are not confined to those antibodies. The '449 patent claims *any* isolated human monoclonal antibody ("mAb") that *cross-competes* for binding to the variable regions of the seven recited PD-1 antibodies. The inventors of the '449 patent were not the first to discover anti-PD-1 antibodies or human anti-PD-1 antibodies; the prior art already disclosed and taught numerous human monoclonal anti-PD-1 antibodies that cross-compete with, at least, antibody 5C4 of the '449 patent.³ As Petitioner's expert, Dr. Gerard Zurawski, explains, the prior art thus

³ Antibody 5C4 is also known as nivolumab, which BMS commercializes as Opdivo®.

anticipates many of the Challenged Claims. Other Challenged Claims that are not anticipated are nothing more than obvious alterations to the antibodies disclosed by the prior art.

Patent Owner seeks to remove from the public domain what was already known in the prior art—a sub-genus of anti-PD-1 antibodies that bind PD-1 and cross-compete with one or more of the recited reference antibodies. This functional sub-genus of antibodies that Patent Owner now seeks to claim is *prima facie* obvious over the known genus of anti-PD-1 antibodies. The Challenged Claims do not set out any structural characteristics of the claimed cross-competing antibodies (let alone novel structures) to distinguish them from antibodies known in the art, nor do they identify any unexpected results across the breadth of the sub-genus of unspecified cross-competing antibodies to overcome a finding of obviousness.

Dana-Farber seeks cancellation of the Challenged Claims to extinguish the cloud of improperly extended monopoly rights purporting to cover any anti-PD-1 antibody that cross-competes with the disclosed reference antibodies. As a cancer institute, Dana-Farber has an interest in ensuring that BMS does not extend the period of exclusivity conferred by the Honjo-Freeman Patents to later-claimed antibodies used in the patented cancer treatment methods that BMS did not invent.

II. BASIS FOR THE PETITION AND MANDATORY NOTICES**A. Identification of Challenge under 37 C.F.R. § 42.104(b)(1) & (2)**

Petitioner requests *inter partes* review on the following grounds:

Ground	Claims	Basis	Prior Art
1	1, 7-8, 12-14 and 21-23	35 U.S.C. § 102	WO '875
2	14-16	35 U.S.C. § 103	WO '875
3	9	35 U.S.C. § 103	WO '875 in view of WO '557
4	1, 7-9, 12-16, and 21-23	35 U.S.C. § 103	WO '875 in view of WO '557

The bases for the petition are described in greater detail below and in the declaration of Dr. Gerard Zurawski. (EX1002).

B. Grounds for Standing under 37 C.F.R. § 42.104(a)

Petitioner certifies the '449 patent is available for *inter partes* review, *see* 37 C.F.R. § 42.102(a), and that it is not barred or estopped from requesting an *inter partes* review on the grounds identified herein. *See* 37 C.F.R. § 42.101.

C. Fees under 37 C.F.R. §§ 42.15(a) and 42.103

Fees under 37 C.F.R. § 42.15(a) are being paid concurrently herewith. Counsel for Petitioner authorizes the U.S. Patent and Trademark Office to charge Deposit Account no. 502778.

D. Real Party-in-Interest under 37 C.F.R. § 42.8(b)(1)

The Real Party-in-Interest is Dana-Farber Cancer Institute, Inc.

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

Petitioner and Patent Owner are engaged in litigation in which Petitioner asserts state law claims concerning Patent Owner's unfair methods of competition relating to patents co-owned by Petitioner and Patent Owner in *Dana-Farber Cancer Institute, Inc. v. Bristol Myers Squibb, Co., et al.*, C.A. No. 19-cv-11380-PBS (D. Mass.). Petitioner's complaint was filed following judgment for Petitioner on inventorship claims establishing that Dana-Farber scientist Dr. Gordan Freeman and a second researcher were co-inventors of pioneering discoveries concerning the administration of PD-1 and PD-L1 antibodies to treat cancer, as claimed in the Honjo-Freeman Patents. *See Dana Farber Cancer Institute, Inc. v. Ono Pharm. Co.*, 379 F. Supp. 3d 53 (D. Mass. 2019), *aff'd*, 964 F.3d 1365 (Fed. Cir. 2020).

Petitioner also identifies *Dana-Farber Cancer Institute, Inc. v. Bristol-Myers Squibb, Co.*, Case No. IPR2023-00252 (PTAB) (U.S. Patent No. 10,138,299) and *Dana-Farber Cancer Institute, Inc. v. Bristol-Myers Squibb, Co.*, Case No. IPR2023-00249 (PTAB) (U.S. Patent No. 10,323,092).

F. Lead and Backup Counsel and Service Information under 37 C.F.R. §§ 42.8(b)(3) & (4)

Petitioner is contemporaneously filing a power of attorney for the following counsel:

Lead	Back-Up
Amanda K. Antons, Ph.D. (Reg. No. 65,236) Dechert LLP 35 West Wacker Drive, Suite 3400 Chicago, IL, 60601-1608 Telephone: 312-646-5800 Facsimile: 312-646-5858 Email: amanda.antons@dechert.com	Katherine A. Helm, Ph.D. (<i>pro hac vice</i> to be applied for) Noah M. Leibowitz (<i>pro hac vice</i> to be applied for) Dechert LLP Three Bryant Park 1095 Avenue of the Americas, New York, NY, 10036-6797 Telephone: 212-698-3500 Facsimile: 212-698-3599 Email: khelm@dechert.com Email: noah.leibowitz@dechert.com

Please send all correspondence to the lead counsel at the address shown above. Petitioner consents to service by e-mail at the following address: d-fci@dechert.com.

III. PERSON OF ORDINARY SKILL IN THE ART (POSA)

The POSA 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.

IV. STATE OF THE ART

A. Technical Field

The '449 patent is directed to anti-PD-1 monoclonal antibodies ("mAbs") that bind to PD-1.

1. PD-1

Programmed cell death protein 1 (PD-1), a member of the immunoglobulin gene superfamily, is a receptor that is found on the surface of T cells and B cells. EX1006, 57; EX1007, 12293; EX1002, ¶37. PD-1 has two ligands, PD-L1 and PD-L2, which are expressed on antigen-presenting cells and various types of tumor cells. EX1007, 12293; EX1008, 2947, EX1002, ¶38. When PD-L1 or PD-L2 bind to PD-1, T-cell activity is inhibited. EX1007, 12293; EX1009, 515; EX1002, ¶38. In normal cells, the PD-1/PD-L1 or PD-L2 interaction prevents T-cells from launching an immune response against those cells. *Id.* PD-L1 overexpression by tumor cells, however, suppresses the proliferation, cytokine production, and cytotoxic activity of T-cells, effectively inhibiting the body's immune response to malignant tumor cells. EX1007, 12293-95; EX1002, ¶38.

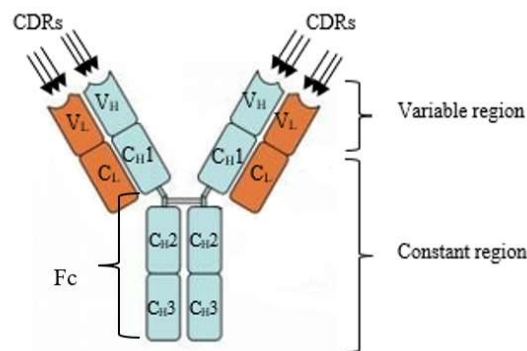
Inhibiting the binding of PD-1 to PD-L1 with an anti-PD-1 mAb impairs the growth of tumors in mice via T cell activation. EX1010, 1089, 1093; EX1002, ¶39. Thus, it was known in the art that developing an anti-PD-1 antibody to obstruct the interaction of PD-1 with its ligands would be important in the field of cancer therapy. *Id.*

U.S. Patent No. 7,595,048 (“the ’048 patent”)⁴ describes the groundbreaking discovery of Dana-Farber and others in identifying the relationship between PD-1, PD-L1, and cancer and conceiving a new method for treating cancer that involves modulating that relationship. EX1005 describes that anti-PD-1 antibodies “can be manufactured using a partial protein of the extracellular region of PD-1.” EX1005, 5:24-25. Honjo-Freeman ’048 discloses methods of treating cancers in human subjects using anti-PD-1 antibodies and provides at least one example of an anti-PD-1 antibody. *Id.*, 10:37-38 (noting that inventors “invented” an “anti-PD-1 antibody”), 11:1-12; EX1002, ¶40. Honjo-Freeman ’048 teaches that its anti-PD-1 antibodies “inhibit[] . . . PD-1 function” and suppress cancer growth. EX1005, 10:34-59. In addition to the teachings of Honjo-Freeman, as noted below, International PCT Publication No. WO 01/14557 A1 (“WO ’557”), discloses the methods for preparation of “fully human antibodies” against “PD-1” that were prepared by assessing antibody reactivity to PD-1 or a fusion protein comprising at least an immunogenic portion of the extracellular domain. EX1012 at Example 9.

⁴ While the Honjo-Freeman ’048 patent published after the ’449 patent’s priority date of May 9, 2005, the Honjo-Freeman ’048 patent’s priority date is years before this date. *See* EX1005.

2. Monoclonal Antibodies

Antibodies are Y-shaped protein molecules that are made up of two heavy chains and two light chains. EX1013, 13; EX1002, ¶41. 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), each 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 have more constant amino acid sequences. *Id.* The Fc region of an antibody, which is not involved in antigen binding specificity, is formed by the constant regions of the two heavy chains and determines the isotype of the antibody (e.g., IgA, IgD, IgE, IgG, or IgM). *Id.*



As of May 9, 2005, it was understood that mAbs were a promising therapeutic approach for treating diseases in humans. By this time, at least 12

therapeutic mAbs were approved for human use by the U.S. Food and Drug Administration. EX1014; EX1002, ¶42. Thus, it was known in the art that developing a mAb against an antigen known to be involved in a human disease was a promising and well-established therapeutic approach. *Id.*

3. Isolating Antibodies

As of the critical date of the '449 patent, the techniques for screening candidate antibodies and making human antibodies were routine and well-known. EX1002 ¶43. Antibodies are discovered and isolated in a number of different ways, including by phage display and using transgenic mice. EX1015, 536-38; EX1002, ¶43. These methods were well known in the art for initial antibody screens. EX1016; EX1002, ¶¶43-45. 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. EX1002, ¶43. After the initial antibody screen, additional testing and engineering may be needed to further optimize and refine an antibody for therapeutic use. *Id.*

A POSA would expect to screen numerous candidate antibodies having different sequences and structures to identify and characterize mAbs with desired properties. *Id.*, ¶44. 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; EX1002, ¶44.

4. Antibody Competition Assays

Numerous techniques were known and 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. EX1002, ¶46.

As of May 9, 2005, several competition assays were known to POSAs. 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); EX1002, ¶47. 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. EX1002, ¶47.

V. THE '449 PATENT

A. Priority

The '449 patent issued from Application No. 11/913,217, filed on Jan. 29, 2009, and 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).

B. Prosecution History

Patent Owner's initial application sought broad claims directed to *any* isolated human mAb that binds to PD-1. On October 31, 2007, Patent Owner filed a preliminary amendment. EX1017, 7. As amended, claim 1 claimed the following:

An isolated human monoclonal antibody, or an antigen-binding portion thereof; wherein the antibody binds to PD-1 and wherein the antibody exhibits at least one of the following properties:

- a) binds to human PD-1 with a K_d of $1 \times 10^{-7}M$ or less;
- b) does not substantially bind to human CD28, CTLA-4 or ICOS;
- c) increases T-cell proliferation in a Mixed Lymphocyte Reaction (MLR) assay;
- d) increases interferon-gamma production in an MLR assay;
- e) increases interleukin-2 (IL-2) secretion in an MLR assay.

EX1017, 7.

This broad claim would cover any isolated human mAb that binds to PD-1 and exhibits any one of five functional properties.

Patent Owner's amendment also included a number of other claims, including proposed claim 8 that would cover any isolated human mAb, or an antigen-binding portion thereof, which cross-competes for binding to PD-1 with antibodies having any of seven recited variable regions. EX1017, 7-8. Proposed claim 8 recited the following:

An isolated human monoclonal antibody, or antigen-binding portion thereof, wherein the antibody cross-competes for binding to PD-1 with a reference antibody, wherein the reference antibody is selected from the group consisting of:

- a) an antibody comprising a human heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1 and a human light chain variable region comprising the amino acid sequence of SEQ ID NO: 8;
- b) an antibody comprising a human heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2 and a human light chain variable region comprising the amino acid sequence of SEQ ID NO: 9;
- c) an antibody comprising a human heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 3 and a human light chain variable region comprising the amino acid sequence of SEQ ID NO: 10;
- d) an antibody comprising a human heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 4 and a human light chain variable region comprising the amino acid sequence of SEQ ID NO: 11;

- e) an antibody comprising a human heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 5 and a human light chain variable region comprising the amino acid sequence of SEQ ID NO: 12;
- f) an antibody comprising a human heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 6 and a human light chain variable region comprising the amino acid sequence of SEQ ID NO: 13; and
- g) an antibody comprising a human heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 7 and a human light chain variable region comprising the amino acid sequence of SEQ ID NO: 14.

Id.

Eventually, a slightly amended version of this claim would become claim 1 of the '449 patent. *Compare* EX1017, 7-8 *with* EX1001, cl.1. The antibody comprising a human heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 4 and a human light chain variable region comprising the amino acid sequence of SEQ ID NO: 11 is antibody 5C4⁵ of the '449 patent, also known as nivolumab. EX1002, ¶54.

On August 9, 2010, the Examiner issued a Restriction Requirement pursuant to 35 U.S.C. §§ 121, 372. EX1017, 1656. The Examiner reasoned that while various proposed claims were drawn to an anti-PD-1 antibody, other claims were directed to nucleic acids encoding anti-PD-1 antibodies, transgenic mice

⁵ 5C4 is specifically claimed by, e.g., claims 2 and 3 of the '449 patent.

expressing an anti-PD-1 antibody, and methods of treatment with an anti-PD-L1 antibody. *Id.*, 1656-57. In response to this Restriction Requirement, Patent Owner cancelled various claims, including original claim 1, and attempted to traverse the Examiner's Restriction Requirement. *Id.*, 1673. In the alternative, Patent Owner stated that if the Examiner maintained the Restriction Requirement, Patent Owner intended to prosecute the claims drawn to an antibody to PD-1, and to compositions and immunoconjugates of said antibody. *Id.*

The Examiner did not find Patent Owner's traversal persuasive and made the Restriction Requirement final, resulting in the withdrawal of a number of claims that were not targeted to anti-PD-1 antibodies. *Id.*, 1687. The Examiner then proceeded to evaluate the remaining pending claims, including pending cross-competition claim 8. *Id.* The Examiner deemed various claims, including claim 8, allowable without further discussion. *Id.*, 1692.

The Examiner rejected other pending claims (106-112) as failing to meet the enablement requirement under 35 U.S.C. § 112. In the Examiner's view, the specification was "enabling for an antibody wherein the sequences of the six CDRs are defined," but the specification did not "reasonably provide enablement for an antibody wherein the sequences of recited CDRs are from different antibodies." *Id.*, 1688-89. The Examiner, however, did not explain why that rationale did not apply equally to pending claim 8, which sought broad coverage of any anti-PD-1

antibody with any sequence—including CDRs not described by the specification—so long as it cross-competes with any one of several categories of reference antibodies. *Id.*

In response, Patent Owner amended various claims, including the claims that the Examiner previously determined were allowable. Patent Owner characterized its amendments to these claims as “primarily [of] an editorial nature.” *Id.*, 1834. Patent Owner then withdrew claims 106-107 and 111-112 in light of the Examiner’s rejection and amended claims 108-110 to specifically recite that the claimed antibodies contain all six defined CDR domains disclosed in the specification. *Id.*, 1835-36.

A Notice of Allowance issued, without comment, on April 22, 2011. *Id.*, 1847-48.

The ’449 patent issued on August 30, 2011. *Id.*, 1885.

VI. PROCEEDINGS BEFORE THE EUROPEAN PATENT OFFICE

Patent Owner has a history of seeking claims directed to *any* anti-PD-1 antibody that cross-competes with certain reference antibodies despite the prior disclosure of such antibodies in the prior art. In fact, Patent Owner was previously challenged on similar claims in proceedings before the European Patent Office regarding counterpart “Korman” patents. When those claims were challenged by way of opposition in the European Patent Office, Patent Owner promptly cancelled

the claims that purported to cover any anti-PD-1 antibody that cross-competes with nivolumab.

Specifically, in the European Patent Office (“EPO”), Patent Owner prosecuted European Patent No. EP2161336 B1, another patent naming Alan Korman as inventor and claiming priority to the same PCT application and three provisional applications as the ’449 patent. On February 25, 2013, the EPO communicated its intent to grant a patent with similar cross-competition claims:

1. An isolated monoclonal antibody, or antigen-binding portion thereof, comprising:
 - a) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 18;
 - b) a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID No: 25;
 - c) a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID No: 32;
 - d) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID No: 39;
 - e) a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID No: 46; and
 - f) a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID No: 53;wherein the antibody specifically binds human Programmed Death 1 (PD-1) protein.
2. The antibody of claim 1, comprising:

- a) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 4; and
 - b) a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 11;
- wherein the antibody specifically binds human PD-1.

3. A monoclonal antibody, or antigen binding portion thereof, wherein the antibody *cross-competes* for binding to PD-1 with the antibody of claim 1 or 2.

See EX1064, cls. 1-3 (emphasis added); EX1023, 1.

In other words, claim 3, as proposed by Patent Owner, was directed to a mAb that cross-competes for binding to PD-1 with an antibody defined by the six CDRs of 5C4—a claim that is strikingly similar to the claims Patent Owner obtained here.

In response, numerous third-parties, including Novartis AG, 4-Antibody AG, Janssen Biotech, Inc., and Merck & Co, Inc., opposed this broad cross-competition claim. See EXS1024-1027. Novartis AG, for example, argued that Claim 3 lacked novelty over “antibody PD1-17” in WO ’875, the same reference relied upon in this petition. EX1065, 1. Novartis AG submitted a sworn statement from a Senior Investigator at Novartis Institutes of Biomedical Research, who conducted a competition assay between PD1-17, disclosed in WO ’875, and mAb 5C4, as described in the patent. EX1028, ¶¶1-17. Both the flow cytometry and Biacore data showed that PD1-17 cross-competes with 5C4 for binding to human

PD-1. *Id.*, ¶17. 4-Antibody AG and Janssen Biotech, Inc. argued the same.

EX1066, 14 (arguing lack of novelty over WO 2004/056875 A1); EX1067, 2-8, 21 (same). Similarly, in opposition to EP No. 2161336 B1, Merck submitted a declaration by Robert J. Bloch that tested various commercially available antibodies for cross-competition to nivolumab, which is antibody 5C4. EX1029, ¶169.

Patent Owner did not respond to these arguments *at all*. Instead, Patent Owner amended its claims to cancel claim 3, the claim that purported to cover any anti-PD-1 antibody that cross-competes with nivolumab. EX1030, 79. Eventually, the EPO maintained the patent in amended form without the anticipated or non-inventive cross-competition claim.

VII. CLAIM CONSTRUCTION

The Challenged Claims must be “construed using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b),” *i.e.*, the *Phillips* standard. 37 C.F.R. § 42.100(b); 83 Fed. Reg. 197, 51340-51359 (Oct. 11, 2018); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005). Petitioner and Dr. Zurawski have applied this standard.

A. Expressly Defined Limitations**1. “human monoclonal antibody”**

Each of the Challenged Claims are directed to a “human monoclonal antibody, or an antigen-binding portion thereof.” EX1001, cl. 1. The specification explicitly defines the term “human monoclonal antibody,” and such definition should be used by the Board when construing this term. EX1001, 16:33-36; EX1002, ¶62; *Phillips*, 415 F.3d at 1316 (“[T]he inventor’s lexicography governs.”). The specification states that the term “human monoclonal antibody” means “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. The term “human monoclonal antibody” should be construed to mean the same.

2. “isolated”

Each of the Challenged Claims are also directed to an “*isolated* human monoclonal antibody.” EX1001, cl. 1 (emphasis added). The specification also expressly defines what an “isolated” antibody is—an antibody 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 bind antigens other than PD-1).” EX1001, 16:3-7; EX1002, ¶63.

3. “pharmaceutically acceptable carrier”

Claim 7 of the ’449 patent includes a “pharmaceutically acceptable carrier.”

EX1001, cl. 7. This is also expressly defined by the specification of the ’449 patent: a “pharmaceutically acceptable carrier” means “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; EX1002, ¶¶64.

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

In the absence of an express definition, such as those above, claim terms are given their ordinary and customary meaning, as would have been understood by a POSA at the time of the alleged invention, 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).

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 by, as demonstrated by, for example, Biacore analysis, ELISA analysis, or flow cytometry.” EX1002, ¶¶66-67. 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); EX1002, ¶68.

Thus, the '449 patent describes how to measure the inhibition of an antibody to bind its target (e.g., PD-1) by a test antibody using one of BIAcore, 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. EX1002, ¶69.

Patent Owner has taken a consistent position with respect to the claim construction of the limitation “cross-competes for binding to PD-L1 with a reference antibody,” which also appears in U.S. Patent Nos. 9,580,505 and 9,580,507. EX1032, D.I. No. 79 at 6; EX1011, D.I. 78-5 at 3; EX1002, ¶70. 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.” *Id.*

VIII. STATE OF THE PRIOR ART

A. WO '875

International PCT Publication No. WO 2004/056875 A1 (“WO '875”), a PCT application filed by Wyeth and Cambridge Antibody Technology, published on July 8, 2004. EX1033. It is prior art pursuant to pre-AIA § 102(a). In addition, WO '875 was filed on December 23, 2002, designated the United States (“US”) in its international application, and published under PCT Article 21(2) in English. *Id.* WO '875 is thus also prior art under pre-AIA § 102(e)(1). *See* MPEP § 2136; *see also EnOcean GmbH v. Face Int’l Corp.*, 742 F.3d 955, 957 n.3 (Fed. Cir. 2014) (“[s]ince the Burrow reference was filed on or after November 29, 2000, designated the United States, and was published in English, it is available as prior art as of its PCT filing date.”)⁶

⁶ MPEP § 2316 explains that the “prior art date of a reference under pre-AIA 35 U.S.C. 102(e) may be the international filing date if the international filing date was on or after November 29, 2000, the international application designated the United States, and the international application was published by the World Intellectual Property Organization (WIPO) under the Patent Cooperation Treaty (PCT) Article 21(2) in the English language.”

WO '875 is entitled “Antibodies against PD-1 and Uses Therefor.” EX1033,

1. It describes that “PD-1 is 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.” *Id.*, [006]. It further states that “a need exists to provide safe and effective therapeutic methods for immune disorders such as . . . cancer. . . . Modulation of the immune responses in these disorders can be accomplished by manipulation of the PD-1 pathway.” *Id.*, [009]; EX1002, ¶72.

WO '875's invention provides antibodies that can act as “antagonists of PD-1, thereby modulating immune responses regulated by PD-1.” EX1033, [010]; EX1002, ¶73. Its disclosure further “provides anti-PD-1 antibodies that comprise novel antigen-binding fragments.” *Id.* As WO '875 discloses, these anti-PD-1 antibodies are capable of “specifically binding to PD-1, including human PD-1,” “block[ing] PD-1 interactions with its natural ligand(s),” or both. *Id.* Compositions comprising these antibodies can be “used to treat or prevent immune disorders by virtue of increasing or reducing the T cell response mediated by TcR/CD28.” EX1033, [012].

WO '875 further discloses “[n]on-limiting illustrative embodiments of the antibodies,” including mAbs “PD1-17, PD1-28, PD1-33, PD1-35, and PD1-F2.” *Id.*, [011]; EX1002, ¶74. It also discloses the DNA and Amino Acid Sequences of

the V_H and V_L Domains and CDRs of each of these anti-PD-1 antibodies. EX1033, Table 1, Sequence Listing; EX1002, ¶74. WO '875 also describes that its “antibodies specifically bind an epitope within the extracellular domain of human PD-1,” and the “predicted extracellular domain” sequence. EX1033, [046]. The “antibodies of the invention [of WO '875] bind to the PD-L-binding domain of PD-1.” *Id.*; EX1002, ¶¶74-76.

B. WO '557

International PCT Publication No. WO 01/14557 A1 (“WO '557”), a PCT application filed by Dana-Farber Cancer Institute Inc. and Genetics Institute, Inc., published on March 1, 2001. EX1012. It is prior art pursuant to pre-AIA § 102(b).

WO '557 is a patent application entitled “PD-1, a Receptor for B7-4, and Uses Therefor.” EX1012. WO '557 teaches the production of human mAbs to PD-1, and that such antibodies to PD-1 can be made using conventional techniques and identifies those techniques. *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”); 50:23-56:3 (monoclonal techniques); EX1002, ¶79. WO '557 uses the term “antibody” to also refer to “antigen-binding portion[s]” of antibodies. EX1012, 21:1-4 (“[t]he term ‘antibody’ as used herein also includes an ‘antigen-binding portion’ of an antibody”). WO '557 also teaches POSAs how to detect anti-PD-1 antibodies

using conventional assays, and that 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; EX1002, ¶80.

WO '557 further describes how the administration of an anti-PD-1 antibody that blocks interactions between PD-1 and PD-L1 can be used to treat human patients. EX1012, 4:28-32; 82:18-24; 82:11-12; 135:24-27; EX1002, ¶80.

Specifically, it discusses how the “prevention of an inhibitory signal (e.g., by using a non-activating antibody against PD-1) in immune cells leads to upmodulation of immune cell responses (and resulting upmodulation of an immune response).”

EX1012, 9:27-10:2; EX1002, ¶80. WO '557 discloses the preparation of “fully human antibodies” against “PD-1” that were prepared by assessing antibody reactivity to PD-1 or a fusion protein comprising at least an immunogenic portion of the extracellular domain. EX1012, Example 9; EX1002, ¶80.

IX. GROUND 1: CLAIMS 1, 7-8, 12-14, AND 21-23 ARE UNPATENTABLE AS ANTICIPATED BY WO '875

A patent is invalid for anticipation “if a single prior art reference discloses each and every limitation of the claimed invention.” *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). A prior art reference can “anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference.” *Id.* at 1377. The doctrine of inherent anticipation “does not require

that a person of ordinary skill in the art at the time would have recognized the inherent disclosure.” *Id.*; *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999) (“Where . . . the result is a necessary consequence of what was deliberately intended, it is of no import that the article’s authors did not appreciate the results.”).

A. Overview of Anticipation Based on WO ’875

WO ’875 anticipates claims 1, 7-8, 12-14, and 21-23 of the ’449 patent. These claims cover *any* isolated human mAb that cross-competes for binding to PD-1 with any of the antibodies having one of the seven recited variable regions. EX1001, cl. 1. 5C4, also known as nivolumab, comprises a heavy chain variable region comprising SEQ ID NO:4 and a light chain variable region comprising SEQ ID NO:11 of the recited reference antibodies in the Challenged Claims. EX1002, ¶¶ 94-96, 119. WO ’875 discloses a number of isolated human mAbs, including PD1-17 and PD1-28. *Id.*, ¶74. Dr. Zurawski obtained these two antibodies disclosed by WO ’875 and tested them for cross-competition with nivolumab, i.e., 5C4, for binding to PD-1. *Id.*, ¶¶87-93. The results of those experiments demonstrate that both of the PD1-17 and PD1-28 antibodies disclosed by WO ’875 cross-compete with 5C4 for binding to PD-1. *Id.*, ¶¶99-118, 120. As such, their disclosure in WO ’875 inherently anticipates claims 1, 7-8, 12-14, and 21-23 of the ’449 patent.

B. Claims 1, 7-8, 12-14, and 21-23 Are Anticipated by WO '875**1. Claim 1**

Claim 1 of the '449 patent requires an “isolated human monoclonal antibody, or an antigen-binding portion thereof” that “cross-competes for binding to PD-1” with an antibody comprising one of seven recited human heavy chain variable regions and human light chain variable regions, including the 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.

For the reasons explained in detail herein, claim 1 is unpatentable as anticipated by WO '875.

a) “An isolated human monoclonal antibody, or an antigen-binding portion thereof”

WO '875 discloses an “isolated human monoclonal antibody, or an antigen-binding portion thereof.” EX1001, cl. 1. WO '875 states that its “disclosure provides antibodies that can act as agonists and/or antagonists of PD-1, thereby modulating immune responses regulated by PD-1.” EX1033, [010]. It further describes that its invention “provides anti-PD-1 antibodies that comprise novel antigen-binding fragments.” *Id.* It provides “[n]onlimiting illustrative embodiments of the antibodies . . . as PD1-17, PD1-28, PD1-33, PD1-35, and PD1-F2.” *Id.*, [011]; EX1002, ¶¶122-23.

The anti-PD-1 antibodies disclosed by WO '875 are “isolated human monoclonal antibodies, or an antigen-binding portion thereof.” EX1001, cl. 1. Example 7 discloses 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]; EX1002, ¶122. And claim 7 of WO '875 claims a “human” antibody comprising the amino acid sequence of PD1-17, PD1-28, PD1-33, PD1-35, or PD1-F2. EX1033, cl. 7, [042] (“DNA and amino acid sequences of anti-PD-1 antibodies, their scFv fragment, VH and VL domains, and CDRs are set forth in the Sequence Listing and are enumerated as listed in Table 1”); EX1002, ¶122. The '449 patent defines the term “human monoclonal antibody” as “refer[ing] to 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. Consistent with the '449 patent, WO '875 states that its “disclosure provides novel CDRs *derived from human immunoglobulin gene libraries.*” EX1033, [041] (emphasis added); EX1002, ¶123. Indeed, the sequences of the antibodies disclosed by WO '875 are DNA and amino acid sequences from human immunoglobulin sequences. *See* EX1033, Sequence Listing.

WO '875 also discloses “isolated” mAbs, or an antigen-binding portion thereof. EX1002, ¶124. WO '875 discloses that after 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, [081]; EX1002, ¶124. WO ’875 states that its “[a]ntigen-binding fragments . . . may be isolated and/or purified from their natural environment, in substantially pure or homogenous form.” EX1033, [072]. WO ’875 defines “isolated” to refer to a molecule that “is substantially free of its natural environment.” EX1002, ¶125. The ’449 patent similarly 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 antigens other than PD-1).” EX1001, 16:3-7. It goes on to state that an “isolated antibody may be substantially free of other cellular material and/or chemicals.” *Id.*, 16:10-12. Consistent with this definition, WO ’875 discloses an “isolated” antibody. EX1002, ¶125.

Thus, WO ’875 discloses an “isolated human monoclonal antibody, or an antigen-binding portion thereof,” as used in claim 1 of the ’449 patent.

b) “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”**

WO '875 discloses human mAbs—specifically, the PD1-17 and PD1-28 antibodies—that cross-compete for binding to PD-1 with at least one of the claimed reference antibodies in Claim 1 of the '449 patent. The antibody identified in the '449 patent as “5C4” comprises the recited heavy and light chain variable regions (SEQ ID NO: 4 and 11, respectively) identified in Claim 1, and corresponds to nivolumab. *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 (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))”). Although WO '875 does not expressly state that PD1-17 and PD1-28 cross-compete for binding to PD-1 with 5C4, cross-competition is an inherent

property of an antibody.⁷ EX1002, ¶127. Thus, testing can demonstrate that PD1-17 and PD1-28 inherently cross-compete with at least one of the reference antibodies. EX1002, ¶¶128-129; *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005) (“[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference.”).

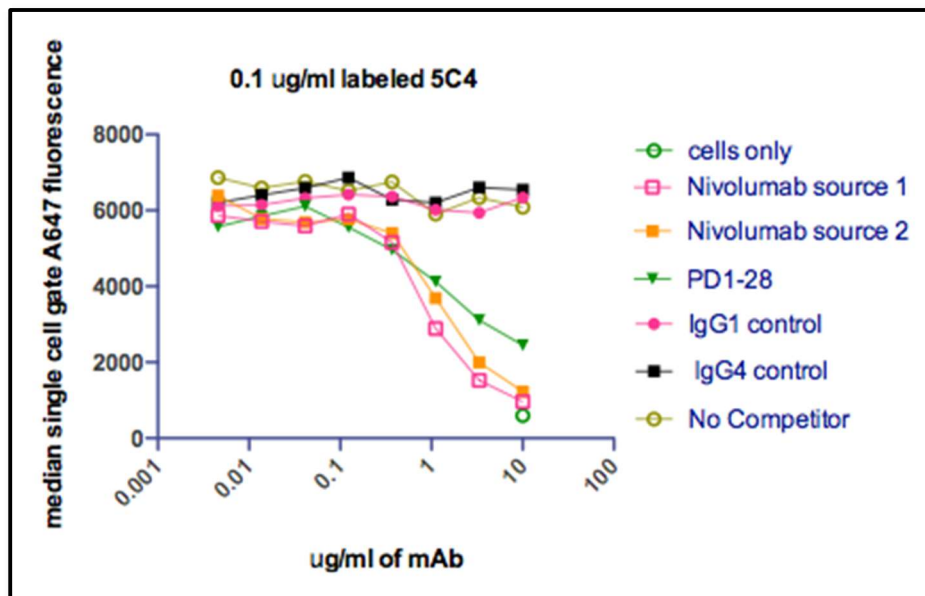
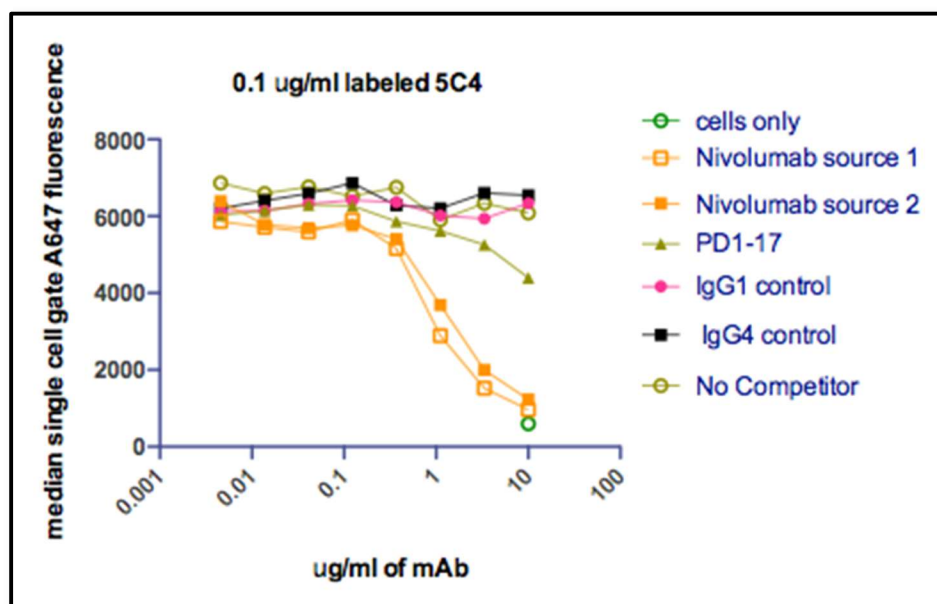
Dr. Gerard Zurawski, an Investigator at the Baylor Institute for Immunology Research (“BIIR”) and co-director of BIIR, is a trained molecular biologist who specializes in the immune system. EX1002, ¶10. He has over 30 years of industry experience as a researcher and teacher in molecular biology and protein engineering. *Id.*, ¶¶6-11. He has authored or co-authored more than 100 peer-reviewed journal articles relating to various vaccines and antibodies and has taught graduate courses in immunology, including on therapeutic antibodies. *Id.*, ¶12.

⁷ Indeed, WO ’875 could not have expressly disclosed the ability of its anti-PD-1 antibodies to cross-compete with antibody 5C4 as the filing of WO ’875 predates the disclosure of antibody 5C4. *Compare* EX1033 (WO ’875 international filing date December 22, 2003) *with* EX1001 (earliest provisional 60/679,466 (EX1019) filed May 9, 2005 that disclosed 5C4).

Dr. Zurawski confirmed that both the PD1-17 and PD1-28 antibodies disclosed by WO '875 necessarily cross-compete with reference antibody 5C4. EX1002, ¶¶99-118. Antibody 5C4 of the '449 patent qualifies as a reference antibody within claim 1 as its human heavy chain variable region comprises amino acids having the sequence set forth in SEQ ID NO: 4 and its human light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 11. *See* EX1001, 9:50-61, Figs. 4A-4B. Reference antibody 5C4 corresponds to BMS's product nivolumab, an anti-PD-1 antibody. EX1002, ¶¶94-96. Dr. Zurawski obtained samples of antibodies PD1-17 and PD1-28 and the claimed reference antibody 5C4 (nivolumab). *Id.*, ¶¶87-93. Utilizing routine mass spectrometry techniques, Dr. Zurawski confirmed that the sample mAbs PD1-17 and PD1-28 he obtained have the same amino acid sequence as the PD1-17 and PD1-28 antibodies disclosed by WO '875. *Id.*

Dr. Zurawski then performed various tests for cross-competition, consistent with the teachings of the '449 patent's specification. The tests showed that both antibodies disclosed in WO '875 cross-compete for binding to PD-1 with reference antibody 5C4. *Id.*, ¶¶48-50, 81-86, 99-118. The '449 patent provides examples of competition assays that may be used to assess cross-competition, 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. It then states

that “[f]or example, BIAcore analysis, ELISA assays or flow cytometry may be used to demonstrate cross-competition with the antibodies of the current invention.” *Id.*, 26:34-36. Thus, the ’449 patent confirms what the POSA already knew—that any of these techniques may be used to demonstrate cross-competition, although other standard PD-1 binding assays could also be used to show cross-competition. EX1002, ¶¶ 67-70. Consistent with the specification of the ’449 patent, Dr. Zurawski conducted cross-competition experiments using standard flow cytometry techniques. EX1002, ¶¶ 81-86, 99-118. CHO-S (Chinese Hamster Ovary) cells were transfected with a vector carrying a human PD-1 cDNA insert. *Id.*, ¶ 100-102. After obtaining CHO cells that express PD-1, Dr. Zurawski conducted flow cytometry experiments with nivolumab, i.e., antibody 5C4, and antibodies PD1-17 and PD1-28. The results of these experiments are depicted in the figure below, and demonstrate that both antibodies PD1-17 and PD1-28 necessarily cross-compete with nivolumab for binding to PD-1. EX1002, ¶¶ 107-118.

FIGURE 1 – PD1-28**FIGURE 2 – PD1-17**

The results are clear—both PD1-17 and PD1-28 cross-compete for binding to PD-1 with reference antibody 5C4. *Id.* Specifically, PD1-28 inhibited nivolumab binding to PD-1 in a strict competitive experiment by 68% at the 10

ug/ml concentration and by 56% at the 3.3 ug/ml concentration. PD1-17 inhibited nivolumab binding to PD-1 by 45% at the 10 ug/ml condition and by 37% at the 3.3 ug/ml condition.

Thus, Dr. Zurawski's testing demonstrates that the PD1-17 and PD1-28 antibodies disclosed in WO '875 inherently anticipate claim 1 of the '449 Patent. *See Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320 (Fed. Cir. 2004) (“[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention.”). This experimental evidence establishes inherency even if it was not understood as of the priority date that the PD1-17 and PD1-28 antibodies would cross-compete with reference antibody 5C4. It is well-established law that an inherent property need not be known before the priority date and can be shown by post-priority date evidence. *See Schering Corp.*, 339 F.3d at 1377 (allowing expert testimony with respect to post-critical date clinical trials to show inherency); *see also Abbott Labs. v. Geneva Pharms., Inc.*, 182 F.3d 1315, 1319 (Fed. Cir. 1999) (“If a product that is offered for sale inherently possesses each of the limitations of the claims, then the invention is on sale, whether or not the parties to the transaction recognize that the product possesses the claimed characteristics.”); *Atlas Powder Co. v. IRECO, Inc.*, 190 F.3d 1342, 1348-49 (Fed. Cir. 1999) (“Because ‘sufficient aeration’ was

inherent in the prior art, it is irrelevant that the prior art did not recognize the key aspect of [the] invention An inherent structure, composition, or function is not necessarily known.”); *SmithKline Beecham Corp.*, 403 F.3d at 1343-44 (“inherent anticipation does not require a person of ordinary skill in the art to recognize the inherent disclosure in the prior art at the time the prior art is created.”).

Thus, as illustrated by Dr. Zurawski’s experiments, two antibodies expressly disclosed by WO ’875—PD1-17 and PD1-28—cross-compete with reference antibody 5C4 for binding to PD-1 and therefore inherently anticipate claim 1 of the ’449 patent.

2. Claim 7

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.

WO ’875 anticipates this claim. As explained above, *see supra* §IX.B.1, WO ’875 inherently anticipates claim 1 by disclosing isolated human mAbs that cross-compete with nivolumab, i.e., antibody 5C4, for binding to PD-1. Claim 7 adds only a limitation that the antibody be in a composition with a “pharmaceutically acceptable carrier.” EX1001, cl. 7.

The specification of the ’449 patent defines a “pharmaceutically acceptable carrier” to mean “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. WO ’875 also discloses the use of a “pharmaceutically acceptable carrier.” EX1033, [098] (“Pharmaceutical 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).”); EX1002, ¶132. WO ’875 further notes that it is “preferable to include isotonic agents” and that the “carrier can be a solvent or dispersion medium.” *Id.* Thus, WO ’875 anticipates claim 7 by disclosing an antibody composition including a “pharmaceutically acceptable carrier.”

3. Claim 8

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.

WO ’875 anticipates this claim. As explained above, *see supra* §IX.B.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 8 adds only the claim element further requiring 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. Consistent with the ’449 patent, WO ’875 also discloses that “[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]; EX1002, ¶133-35. Thus, WO ’875 anticipates claim 8 by disclosing an immunoconjugate comprising an antibody of claim 1 linked to a therapeutic agent.

4. Claim 12

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. WO ’875 anticipates this claim.

It was well-known that regulatory T cells act to suppress CD4+CD25-T cells and the body’s immune response, and play an important role in preventing autoimmunity. EX1002, ¶138; *see also* EX1035, 629 (explaining that “regulatory CD4+CD25+T cells (Treg 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”). WO ’875 explains 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.”). Enhanced IL-2 production inhibits the suppression of CD4+CD25-T cells by Treg cells. EX1002, ¶139; *see also* EX1036, 288 (“The 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.”). Thus, the increased production of IL-2 by PD1-17 and PD1-28, as taught by WO ’875, will necessarily inhibit the natural suppression of CD4+CD25-T cells by regulatory T cells. EX1002, ¶139.

Additionally, because the PD1-17 and PD1-28 antibodies will bind the PD-1 expressed on Treg cells themselves, the antibodies will thereby block PD-1/PD-L1 interactions that mediate regulatory T cells’ suppressive effects. EX1002, ¶140. Regulatory T cells constitutively express PD-1 as one mechanism by which they inhibit and suppress CD4+CD25-T cells. 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”). Indeed, it was known that the “PD-1 molecules expressed by Treg cells are critical for the regulation of peripheral tolerance and autoimmunity.” EX1035, 634. By blocking the PD-1 pathway for regulatory T cells, PD1-17 and PD1-28 will again

necessarily inhibit the natural suppression of CD4+CD25-T cells by those regulatory T cells, i.e., CD4+CD25+T cells. EX1002, ¶¶140-41.

5. Claim 13

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.

WO '875 anticipates this claim. As explained above, *see supra* §IX.B.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 13 further requires that the antibody or antigen-binding portion thereof “enhance[] the antigen specific-memory response to a tumor or a pathogen.” EX1001, cl.13. The '449 patent does not explicitly define the phrase “antigen specific-memory response,” even though it uses the term in various locations. 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 tumor or pathogen cells that the immune system previously encountered. EX1002, ¶144.

This element is disclosed by WO '875. *Id.*, ¶145 WO '875 states that its described 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]. It was known that PD-1:PD-L1 acts as 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.”); EX1002, ¶146. Thus, WO ’875 teaches the use of its antibodies to enhance the immune memory response to a specific antigen, e.g., tumor or pathogen.

6. Claim 14

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.

WO ’875 anticipates this claim. As explained above, *see supra* §IX.B.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.

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, 83:11-52; EX1002, ¶149-50. 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 the “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. EX1002, ¶150. 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. EX1002, ¶151.

The anti-PD-1 antibodies of WO '875, including PD1-17 and PD1-28, would also confer “persistent immunity” to tumor relapse. EX1002, ¶152-53. These anti-PD-1 antibodies cross-compete for binding to PD-1 with the reference antibodies of claim 1, as shown by Dr. Zurawski’s experiments, which are also the same antibodies directly claimed by claims 2 and 3. EX1002, ¶153. Even though

Example 19 used a different anti-PD-1 mouse antibody than those of claims 1-3, these results show that anti-PD-1 antibodies, by producing a PD-1 blockade, confer “persistent immunity” to tumor relapse. The antibodies of WO ’875, including PD1-17 and PD1-28 also bind to PD-1, including the *same* epitope as the other antibodies referenced in claims 1-3. *Id.* The effector functions of any antibody, e.g., conferring persistent immunity, are an inherent characteristic of the antibody itself. *Id.* 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. *Id.*

7. Claim 21

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. SEQ ID NO: 3 and SEQ ID NO: 10 of the ’449 patent set forth the heavy chain and light chain variable regions of anti-PD-1 mAb 4H1. EX1001, Fig. 3A, 3B, 19:20-30. WO ’875 anticipates this claim.

As explained above, *see supra* §IX.B.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. Thus, WO '875 discloses isolated human antibodies that compete for binding to PD-1. While the '449 patent does not explicitly define the term “cross-competes,” Patent Owner’s prior statements regarding related patents are informative on this issue. During prosecution of related patent No. EP2161336 B1, before the European Patent Office, Patent Owner stated that “antibodies that bind to the same epitope on PD-1 have the ability to cross-compete for binding to PD-1.” EX1039, 1. Specifically, Patent Owner relied on data from “competitive binding experiments” that “demonstrated that four monoclonal antibodies described in the present application (17D8, 2D3, 4H1 and 7D3) compete with antibody 5C4 according to claims 1 and 2 for binding to PD-1.” EX1039, 1, Annex. Patent Owner’s experiments are consistent with the methods described in the '449 patent as well as Dr. Zurawski’s methods of showing cross-competition between antibody 5C4 with PD1-17 and PD1-28 for binding to PD-1. EX1002, ¶128.

Because, as Patent Owner’s experiments showed, antibody 4H1 competes with antibody 5C4, and because the disclosed anti-PD-1 antibodies of WO '875, including PD1-17 and PD1-28, cross-compete with 5C4 and bind to the ligand binding domain of PD-1, they will necessarily cross-compete with the 4H1

antibody. EX1002, ¶¶156-57. WO '875 discloses that its described antibodies bind the extracellular domain of human PD-1, and that they specifically bind within the PD-L1-binding domain of PD-1. EX1033, [046] (“the antibodies specifically bind an epitope within the extracellular domain of human PD-1” and “antibodies of the invention bind to the PD-L-binding domain of PD-1”), cl. 5 (claiming an antibody that “specifically binds to the extracellular domain of PD-1”); cl. 6 (“antibody inhibits the binding of PD-L to PD-1”). Dr. Zurawski’s experiments show that the prior art antibodies compete with nivolumab (antibody 5C4) for binding to PD-1. *See supra* §IX.B.1.b. Patent Owner’s evidence submitted to the EPO shows that antibody 4H1 also competes with nivolumab for binding to PD-1. EX1039, Annex. The '449 patent further explains that when two antibodies cross-compete, they bind to the same epitope:

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, 26:36-42 (emphasis added).

Consequently, Patent Owner’s evidence submitted to the EPO shows that 4H1 and nivolumab (antibody 5C4) bind to the same epitope, and Dr. Zurawski’s experiments show that PD1-17 and PD1-28 bind to the same epitope as nivolumab

(antibody 5C4). Thus, the prior art antibodies 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. EX1002, ¶157.

The Examples of WO '875 further confirm that its antibodies bind within the PD-L1 binding domain of PD-1. The ELISA assay in Example 6 as well as Figure 3 demonstrate that PD1-17, PD1-28, PD1-33, PD1-35, and PD1-F2 inhibit binding of PD-L1 to PD-1. EX1033, [0119]-[120]. WO '875 discloses that those antibodies “block PD-1/PD-L1 interaction” while two other antibodies, J110 and PD1-30 “did not inhibit the binding of PD-L1 to PD-1.” *Id.* In Example 7, WO '875 further teaches that the antibodies that blocked the PD-1/PD-L1 interaction—PD1-17, PD1-28, PD1-33, and PD1-35—bind to a distinct site on human PD-1 from the J110 antibody that did not block the PD-1/PD-L1 interaction. *Id.*, [0121]-[0122]. WO '875 teaches that “the tested anti-PD-1 antibodies bind to at least two distinct epitopes: one recognized by J110 and J116, and the other one recognized by PD1-17, PD1-28, PD1-33, and PD1-35.” *Id.*, [0122]. Accordingly, WO '875 discloses anti-PD-1 antibodies, including PD1-17 and PD1-28, which necessarily bind to the ligand binding domain of PD-1, as described in paragraph [046]. *Id.*, [046]. The WO '875 antibodies will therefore cross-compete with the 4H1 antibody as they bind to the same ligand-binding domain of PD-1.

8. Claim 22

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.

WO '875 anticipates this claim. As explained above, *see supra* §IX.B.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. SEQ ID NO: 4 and SEQ ID NO: 11 set forth the heavy chain and light chain variable regions of anti-PD-1 mAb 5C4, as disclosed by the '449 patent. EX1001, Fig. 3A, 3B, 19:20-30. Thus, for the same reasons that WO '875 anticipates claim 1, the reference also inherently anticipates claim 22. EX1002, ¶159.

9. Claim 23

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.

WO '875 anticipates this claim. As explained above, *see supra* §§IX.B.1, IX.B.3, WO '875 inherently anticipates claims 1 and 8 by disclosing an

immunoconjugate containing isolated human antibodies that cross-compete with nivolumab, i.e., antibody 5C4, for binding to PD-1 linked to another therapeutic agent. The only additional claim element in claim 23 is an “immunoconjugate” that links the antibody of claim 1 to “a therapeutic agent” that “is a cytotoxin or a radioactive isotope.” EX1001, cl. 8. 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. WO ’875 likewise discloses that “[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]; EX1002, ¶¶160-61.

Thus, WO ’875 discloses that its anti-PD-L1 antibodies, including those that anticipate claim 1, can form part of an immunoconjugate when linked to another therapeutic agent, including a cytotoxin or radiotoxin. Claim 23 is thus anticipated by WO ’875.

X. GROUND 2: CLAIMS 14-16 ARE UNPATENTABLE AS OBVIOUS OVER WO ’875

A claim is invalid under 35 U.S.C. § 103(a) if the differences between the claim and the prior art are such that the claimed subject matter would have been obvious to the POSA at the time the invention was made. The “mere existence of differences between the prior art and an invention does not establish the

invention's nonobviousness.” *Dann v. Johnston*, 425 U.S. 219, 230 (1976). The gap between the prior art and the claimed invention may not be “so great as to render the [claim] nonobvious to one reasonably skilled in the art.” *Id.*

Obviousness is a legal conclusion and a proper analysis under § 103 requires the consideration of:

(1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1164 (Fed. Cir. 2006).

A reasonable expectation of success does not require a certainty of success. *See In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988) (“Obviousness does not require absolute predictability of success [A]ll that is required is a reasonable expectation of success.”).

A. Claim 14

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 explained above, *see supra* §IX.B.6, the antibodies of WO '875 would

anticipate this claim. However, even if they did not, the POSA would have found this claim obvious in light of WO '875 and the general knowledge of the POSA. EX1002, ¶166.

The POSA would have been motivated to pursue anti-PD-1 antibodies that do not just treat tumors in the short-term, but also provide persistent immunity to tumors after treatment concludes. EX1002, ¶167. The POSA would have understood that tumors often relapse and that treatments that provide immunity for longer periods of time would be used to prevent or at least delay the progression of relapse. *Id.*, ¶168. 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 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 of the '449 patent. *See supra* §IX.B.6; EX1002, ¶151. The POSA would have understood that e.g., modifying the antibody isotype (*e.g.*, IgG1 vs. IgG3), modifying specific amino acids in the Fc region, making a bispecific antibody, modifying the CDRs amino acid sequences to increase epitope binding affinity can all be done to induce and change the nature of the resulting immune response. EX1002, ¶168.

B. Claims 15 and 16

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.

Claims 15 and 16 are obvious in light of WO '875. As explained above, *see supra* §IX.B.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.

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.

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.

EX1002, ¶¶164-65. “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. EX1002, ¶¶172-74. 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.”).

The POSA thus would have 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.1.b, *supra*), to generate anti-PD-1 IgG4 antibodies that would also inherently cross-compete for targeting the ligand-binding region of PD-1.

XI. GROUND 3: CLAIM 9 IS UNPATENTABLE AS OBVIOUS OVER WO '875 IN VIEW OF WO '557

A. Motivation to Combine

“Motivation to combine may be found in many different places and forms.” *Allergan, Inc. v. Sandoz, Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013); *see also Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1294 (Fed. Cir. 2006) (the motivation to combine can be supported by expert testimony regarding knowledge of the POSA at the time of invention). A motivation to modify or combine the prior art “may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.” *DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006). And a “motivation to combine the relevant prior art teachings does not have to be found explicitly in the prior art.” *In re Kahn*, 441 F.3d 977, 987-88 (Fed. Cir. 2006).

Here, the POSA would have been motivated to combine the teachings of WO '875 and WO '557. Both references disclose the use of anti-PD-1 antibodies to treat tumors and are thus directed towards the same issue the POSA would be concerned with—the development of anti-PD-1 antibodies to treat cancer, pathogens, or other medical conditions that may be responsive to anti-PD-1

treatment. EX1002, ¶176; *Acoustic Tech., Inc. v. Itron Networked Sols., Inc.*, 949 F.3d 1366, 1375 (Fed. Cir. 2020) (“The motivation to combine prior art references can come from the knowledge of those skilled in the art, from the prior art reference itself, or from the nature of the problem to be solved.”); *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1294 (Fed. Cir. 2006) (the motivation to combine can be supported by expert testimony regarding knowledge of the POSA at the time of invention); *see also Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1329 (Fed. Cir. 2009) (motivation to combine may be found based on “need or problem known in the field of endeavor at the time of the invention and addressed by the patent”). The POSA reviewing WO ’875 would be interested in identifying additional compositions and means of formulating and administering its disclosed anti-PD-1 antibodies to patients. EX1002, ¶176. The POSA would have thus reviewed WO ’557 and identified its teachings regarding bispecific antibodies. *Id.*, ¶176. As explained further below, *see infra* §XI.3, the POSA would have found each of these teachings useful and would have been motivated to combine those teachings with the antibodies disclosed in WO ’875.

B. Reasonable Expectation of Success

The POSA would have also reasonably expected success in combining the teachings of WO ’875 and WO ’557. *In re O’Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988) (“Obviousness does not require absolute predictability of success

[A]ll that is required is a reasonable expectation of success.”); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Both references disclose anti-PD-1 antibodies that achieved success in the Examples of each reference. *See supra* §§VIII.1, VIII.2. The POSA would have understood that the teachings regarding the compositions of WO ’557 would be just as likely to apply to the anti-PD-1 antibodies of WO ’875. EX1002, ¶178. As explained further below, as to each additional limitation disclosed by WO ’557 the POSA would have reasonably expected success in combining these additional disclosures with the disclosed antibodies of WO ’875. *See infra* §XI.3.

C. Claim 9

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.

Claim 9 is obvious over WO ’875 in view of WO ’557. As explained above, *see supra* §IX.B.1, antibodies PD1-17 and PD1-28 of WO ’875 anticipate claim 1 of the ’449 patent. In view of the teachings of WO ’557, the POSA would have been motivated to modify those antibodies in anti-PD-1 bispecific antibodies containing the anti-PD-1 antibodies of WO ’875. WO ’557 describes the use of

bispecific molecules comprising an anti-PD-1 antibody linked to a second functional moiety with a different binding specificity:

In 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*, e.g., on a T cell, a B cell, or a myeloid cell. In one embodiment, such an antibody, in addition to comprising a PD-1 binding site can further comprise a binding site which binds to a molecule which is in proximity to an activating or inhibitory receptor, e.g., B-cell antigen receptor, a T-cell antigen receptor, or an Fc receptor in order to target the molecule to a specific cell population. For example, a CD3 antigen, a T-cell receptor chain, LFA-1, CD2, CTLA-4, immunoglobulin, B cell receptor, Ig alpha, Ig beta, CD22, or Fc receptor could be used. *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.*

EX1012, 76:9-21 (emphasis added).

The POSA would have been motivated to create a bispecific molecule in light of WO '875 and its disclosed anti-PD-1 antibodies. It was well-known prior

to the critical date that bispecific antibodies could provide an even more effective means of treating tumors due to their ability to bind 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”). Consistent with what was well-known to the POSA, WO ’557 teaches that a bispecific molecule would not only block PD-1/PD-L1 binding, but would also *recruit* other immune cells to target the tumor. *See supra* §XI.3. The POSA thus would have been motivated to achieve this effect and combine these teachings from WO ’875 and WO ’557.

The POSA also would have reasonably expected success in creating a bispecific antibody. As the specification of the ’449 patent admits, 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. WO ’557 describes the procedures for making bispecific antibodies, and incorporates various other prior art publications that describe well-known methods of

constructing bispecific antibodies by chemical means and hybridoma technology.

EX1012, 55:24-56:8; EX1002, ¶178.

XII. GROUND 4: THE CHALLENGED CLAIMS ARE UNPATENTABLE AS OBVIOUS OVER WO '875 IN VIEW OF WO '557

Each of the Challenged Claims are, alternatively, obvious over WO'875 in view of WO '557. The Challenged Claims are directed to nothing more than a sub-genus of a known set of antibodies that bind PD-1—a sub-genus of anti-PD-1 antibodies that cross-compete with the seven recited reference antibodies.

EX1002, ¶¶182-84. But an applicant cannot generate a new reference antibody within a known genus of antibodies and then claim a sub-genus of antibodies that happen to cross-compete with the newly generated reference antibody; although the structure of the reference antibody may be new, the sub-genus, which is not structurally limited, is not. Rather, “[a] single, obvious species, within a claimed genus renders the claimed genus unpatentable under § 103.” *Ex Parte Kubin*, 83 U.S.P.Q.2d 1410, 2007 WL 2070495 (Bd. Pat. App. & Interferences 2007), *aff'd*, 561 F.3d 1351 (Fed. Cir. 2009) (precedential). That is particularly true here, where the prior art already taught the use of anti-PD-1 antibodies and the epitope of PD-1. *See supra* at 26 (citing EX1012). For the reasons set forth in Grounds 1-3, the prior art discloses, expressly or inherently, each and every limitation of the Challenged Claims. *See* §§IX, X, XI. 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* §XI.3.

Thus, the Challenged Claims directed to a broad sub-genus of anti-PD-1 antibodies that cross-compete with one of the seven recited reference antibodies, are *prima facie* obvious over the anti-PD-1 antibodies described by WO '875 and WO '557. In the absence of unexpected results stemming from the cross-competition of the claimed anti-PD-1 antibodies, the Challenged Claims are obvious. *See Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1357 n. 21 (Fed. Cir. 1998) (“[a]nticipation is the epitome of obviousness”) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)).

Here, Patent Owner has presented no unexpected properties, let alone across the breadth of the Challenged Claims, to justify an inventive selection of the cross-competing sub-genus over the prior art anti-PD-1 antibodies disclosed in WO '875 and WO '557. *See AbbVie Inc. v. Mathilda and Terence Kennedy Inst. of Rheumatology Trust*, 764 F.3d 1366, 1378-81 (Fed. Cir. 2014) (“A species contained in a previously patented genus may be patentable if the species manifests unexpected properties or produces unexpected results.”). Nor has the Patent Owner identified any common structural features among the claimed antibodies to distinguish the antibodies that are disclosed in WO '875 and WO '557.

For these reasons, the Challenged Claims are obvious.

XIII. SECONDARY CONSIDERATIONS CANNOT REBUT THE STRONG SHOWING OF OBVIOUSNESS

It is Patent Owner’s burden to establish secondary considerations of nonobviousness to overcome Petitioner’s strong *prima facie* showing of obviousness. As here, where a strong *prima facie* obviousness showing exists, the Federal Circuit has repeatedly held that secondary considerations may not dislodge the primary conclusion of obviousness. *See, e.g., Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007). Notably, there is no evidence of the claimed invention achieving unexpected results. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013).

With respect to commercial success, any showing of commercial success is irrelevant where it is due to what was *already disclosed* in the prior art—here, human anti-PD-1 mAbs that inhibit binding to PD-1. *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011) (“If commercial success is due to an element in the prior art, no nexus exists.”). Because “the feature that creates the commercial success was known in the prior art, the success is not pertinent.” *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006). WO ’875 disclosed anti-PD-1 antibodies that cross-compete with an antibody (5C4) having the recited variable heavy and light chain regions for binding to PD-1—the allegedly novel aspect of the invention. Any evidence regarding the commercial success of the claim is thus irrelevant. *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d

1366, 1373 (Fed. Cir. 2019) (secondary considerations must be limited to the features of the claimed invention in order to prove nexus and patentee must show that evidence of secondary considerations is the direct result of the unique characteristics of the patent claims).

A party cannot “demonstrate commercial success, for purposes of countering the challenge of obviousness, unless it can show that the commercial success of the product results from the claimed invention.” *J.T. Eaton & Co. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). Here, the challenged claims are not directed to nivolumab, i.e., Opdivo®. The claims are broadly directed to *any* human anti-PD-1 mAb that *functionally* cross-competes for binding to PD-1 with any one of multiple reference antibodies, one of which is nivolumab. To demonstrate a nexus, Patent Owner must show that what is commercially successful is “coextensive with the patented invention.” *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019). To be coextensive, the product “*is* the invention disclosed and claimed.” *Id.* (emphasis in original). Here, it is not. The challenged claims are far broader in that they encompass any human anti-PD-1 mAb that cross-competes with nivolumab (or various other reference antibodies), not nivolumab itself. The claims are not commensurate or coextensive with nivolumab and there can thus be no nexus between the claims and Opdivo® or any product that has achieved commercial success. Moreover, due to the broad

nature of these functional claims, any other features in Opdivo® that are unclaimed would undermine any contention that there is a nexus to the claims. *See Teva Pharms. Int’l GmbH v. Eli Lilly & Co.*, 8 F.4th 1349, 1362-63 (Fed. Cir. 2021) (stating that “[a] claim to ‘anything that works’ hardly has a nexus to any particular product”).

XIV. DISCRETIONARY DENIAL IS NOT WARRANTED

Under 35 U.S.C. § 325(d), the Board uses a two-part framework to evaluate whether to institute: (1) whether the same or substantially the same art or arguments were previously presented to the Office; and (2) if the first part is satisfied, whether the Petition has demonstrated that the Office erred in a manner material to the patentability of the challenged claims. *See Advanced Bionics, LLC v. MED-EL Elektromedizinische Gerate BmbH*, IPR2019-01469, Paper 6 at 6-11 (PTAB Feb. 13, 2020) (precedential). As explained in *Advanced Bionics*, factors (a), (b), and (d) from *Becton, Dickinson* relate to whether the art and arguments presented are the same or substantially the same as those previously presented to the Office. And factors (c), (e), and (f) “relate to whether the petitioner has demonstrated a material error by the Office” in its prior consideration of the art or arguments. *Id.* at 10; *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph) (“*Becton, Dickinson*”) (explaining that the PTAB

considers the following non-exclusive factors when evaluating discretion under § 325(d): (a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (d) the extent of the overlap between the arguments made during examination and the manner in which a Petitioner relies on the prior art or a Patent Owner distinguishes the prior art; (e) whether a Petitioner has pointed out sufficiently how the Examiner erred in its evaluation the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petitioner warrant reconsideration of the prior art or arguments.).

Patent Owner only disclosed WO '875 in an IDS after the Examiner determined that the cross-competition claims were allowable. EX1017, 1685, 1661, 1709. Patent Owner also disclosed WO '557 in an IDS amongst numerous other references. *Id.*, 809. But the Examiner never issued any rejection based on either reference. Nor could a rejection have been issued then. Neither reference discloses experimental data regarding cross-competition with nivolumab, and the Examiner did not have the means to test the antibodies. *See supra* n.7. This Petition addresses *cross-competition* claims and issues regarding inherent anticipation. The Petition presents experimental evidence demonstrating the

inherent cross-competition of anti-PD-1 mAbs disclosed in WO '875 that was not before the Examiner. *See* EX1002, ¶¶99-118. This evidence, which was unavailable during prosecution, establishes that prior art antibodies meet every limitation of numerous claims in the '449 patent and, in combination with other routine disclosures, render other claims obvious. Thus, a rejection under § 325(d) would be inappropriate.

Indeed, in *Sanofi-Aventis U.S. LLC v. Immunex Corp.*, IPR2017-01884, Paper 14 at 12 (PTAB Feb. 15, 2018), the Board rejected an argument that a petition should be denied under § 325(d). The Board stated that “[b]ecause the Examiner did not have the benefit of Petitioner’s additional experimental evidence relating to competition, we are not persuaded that the same or substantially the same prior art or arguments were previously presented to the Office.” *Id.* The same is true here. Because the evidence contained in Dr. Zurawski’s declaration was not before the Examiner, the Board should decline to exercise its discretion to deny institution under § 325(d). The Examiner did not have the experimental evidence now before the Board regarding the inherent cross-competition of the disclosed anti-PD-1 antibodies of WO '875 and any § 325(d) argument should be rejected.

XV. CONCLUSION

Based on the foregoing and the accompanying expert declaration of Dr. Zurawski submitted herewith, the Challenged Claims are anticipated and/or rendered obvious over the prior art cited herein. Petitioner has established a reasonable likelihood of prevailing on each Ground.

Dated: February 6, 2023

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Certification of Word Count

I certify that the Petition for *Inter Partes* Review filed herewith has a word count of 13,682 words, as determined by the Microsoft Word word-processing software used to create this paper. The above word count excludes the table of contents, exhibit list, the certificates of service and word count, and mandatory notices.

Dated: February 6, 2023

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Certification of Service

I certify that true and correct copies of the foregoing *Inter Partes* Review of U.S. Patent No. 8,008,449 B2 and Exhibits 1001-1070 were served on February 6, 2023 via FedEx to the attorneys of record for U.S. Patent No. 8,008,449 B2 as evidenced on Patent Center on February 6, 2023, namely:

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