

United States Court of Appeals for the Federal Circuit

DANA-FARBER CANCER INSTITUTE, INC.,
Plaintiff-Appellee

v.

**ONO PHARMACEUTICAL CO., LTD., TASUKU
HONJO, E.R. SQUIBB & SONS, L.L.C., BRISTOL-
MYERS SQUIBB COMPANY,**
Defendants-Appellants

2019-2050

Appeal from the United States District Court for the
District of Massachusetts in No. 1:15-cv-13443-PBS,
United States District Judge Patti B. Saris.

Decided: July 14, 2020

DONALD ROSS WARE, Foley Hoag LLP, Boston, MA, argued for plaintiff-appellee. Also represented by SARAH S. BURG, BARBARA A. FIACCO.

SETH P. WAXMAN, Wilmer Cutler Pickering Hale and Dorr LLP, Washington, DC, argued for defendants-appellants. Also represented by STEVEN JARED HORN, THOMAS SAUNDERS; MATTHEW TYMANN, Los Angeles, CA; DIANNE B. ELDERKIN, STEVEN D. MASLOWSKI, MATTHEW A. PEARSON,

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Akin, Gump, Strauss, Hauer & Feld, LLP, Philadelphia,
PA.

Before NEWMAN, LOURIE, and STOLL, *Circuit Judges*.

LOURIE, *Circuit Judge*.

Ono Pharmaceutical Co. Ltd., Tasuku Honjo, E.R. Squibb & Sons, L.L.C., and Bristol-Myers Squibb Co. (collectively, “Ono”) appeal from the judgment of the United States District Court for the District of Massachusetts after a bench trial ordering that Dr. Gordon Freeman and Dr. Clive Wood be added to U.S. Patents 7,595,048 (“the ’048 patent”), 8,168,179 (“the ’179 patent”), 8,728,474 (“the ’474 patent”), 9,067,999 (“the ’999 patent”), 9,073,994 (“the ’994 patent”), and 9,402,899 (“the ’899 patent”) as co-inventors. *Dana-Farber Cancer Inst., Inc. v. Ono Pharm. Co.*, 379 F. Supp. 3d 53 (D. Mass. 2019) (“*Decision*”). Because we conclude that the district court did not err in its inventorship determination, we affirm.

BACKGROUND

This appeal presents an inventorship dispute over groundbreaking work in the field of cancer treatment. Each patent at issue claims a method of treating cancer by administering antibodies targeting specific receptor-ligand interactions on T cells.

The human immune system comprises many different cell types, but two types of those cells are relevant here: dendritic cells and T cells. Dendritic cells detect pathogens and present antigens—proteins from a pathogen or tumor—to T cells. T cells have a variety of functions but, as relevant here, are responsible for processing information to develop an immune response in the body using receptors on their surfaces. The primary receptor on a T cell, the T cell receptor, can bind to antigens to activate an immune response. But a signal sent to a T cell receptor will not

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activate the T cell unless a ligand binds to one of its co-stimulatory receptors, such as CD28. CD28 has two ligands, B7-1 and B7-2, which are expressed in dendritic cells that have detected infection or cancer. For a T cell to activate an immune response, two things must happen: (1) an antigen on a dendritic cell must bind to the T cell receptor, and (2) a B7 ligand on the dendritic cell must bind to the CD28 receptor on the T cell. In the absence of an infection or cancer, dendritic cells do not express B7 ligands on their surface thus blocking an immune response. B7 ligands also bind to an inhibitory receptor called CTLA-4, which is only expressed in highly activated T cells. B7 ligands bind more tightly to CTLA-4 than to CD28, so if both receptors are being expressed, CTLA-4 prevents the B7 ligands from activating the T cell through the CD28 receptor.

The discovery behind the present patents was the existence of an inhibitory receptor on T cells, PD-1, and that, when PD-1 binds to one of its ligands, either PD-L1 or PD-L2, the T cell is inhibited and does not attack the cell expressing the ligand. Expression of the PD-1 ligands in healthy cells generally shields them from attack, but some tumor cells can also express the ligands, allowing them to circumvent an immune response. The patents in this case capitalize on the discovery of the PD-1 receptor-ligand interaction. Each claim recites uses of antibodies that target either the PD-1 receptor or its PD-L1 ligand, blocking the receptor-ligand interaction. By blocking the interaction, the use of the inventions in effect stimulates the immune response against tumor cells that would otherwise have been hidden by their expression of the PD-L1/L2 ligands.

The appeal raises the question whether Drs. Freeman and Wood should be deemed inventors of the subject matter of the '048, '179, '474, '999, '994, and '899 patents alongside Dr. Tasuku Honjo. Essential to this determination is a recounting of each researcher's work and the nature of their collaboration.

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Dr. Honjo, a professor at Kyoto University's medical school, discovered the PD-1 receptor in the early 1990s. He isolated its DNA sequence and began working with the protein in mouse models with Dr. Nagahiro Minato, a colleague studying tumor immunology. Using knockout mice (wherein the PD-1 gene is not expressed), they discovered that mice without PD-1 showed symptoms typical of autoimmune disease, suggesting that the receptor was involved in immune-system inhibition. Based on its structure, Dr. Honjo believed at that time that PD-1 was in the same family of proteins as the inhibitory receptor CTLA-4. Drs. Honjo and Minato submitted their research for publication, and their work was published in *Immunity* in August 1999.

In mid-1998, Dr. Honjo enlisted a graduate student, Dr. Yoshiko Iwai, to conduct studies on PD-1 with knockout mice and human tumor cell lines. Dr. Iwai found binding of the PD-1 protein in a variety of cells, including in tumor cells, but she did not identify the molecule that was binding to the receptor. She also recognized that her experiments may have yielded false positives because she used a specific fusion protein. Her work did not continue at that time because she took a leave of absence because of illness.

In September 1998, Dr. Honjo met with representatives from Ono, now an assignee of Dr. Honjo's rights in the instant patents, and the Genetics Institute, who connected him to Dr. Wood, a researcher at Genetics Institute. They discussed Dr. Honjo's work with PD-1, and Dr. Wood agreed to collaborate with Dr. Honjo to find the PD-1 ligand. Dr. Wood believed that the PD-1 receptor could be a candidate for antibody therapy development, and accordingly Dr. Honjo shared with him PD-1 reagents and a confidential draft of the *Immunity* article.

In July 1998, Dr. Freeman, a researcher at Dana-Farber, was studying novel B7 ligands. He ran a search in the BLAST database for a sequence of 208 amino acids that

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forms part of the binding portion of the B7-1 molecule. The search yielded 12 results—two of which were from human ovarian tumors—and Dr. Freeman began to investigate the sequence further, titling it “292” after its label in the database.

At this point, the timelines converge. Drs. Wood, Freeman, and Honjo began sharing information directly. Drs. Wood and Freeman began working together to determine whether PD-1 binds to 292, and Dr. Wood informed Dr. Honjo that it does. The three dubbed 292 “PD-L1” and ran further experiments. Dr. Wood sent Dr. Honjo plans for a journal article, and Dr. Honjo sent Dr. Wood anti-PD-1 antibodies for further experimentation. Dr. Freeman emailed Dr. Honjo for the first time at this point, discussing the possibility of a research collaboration on the PD-1/PD-L1 pathway.

The collaboration culminated in a meeting in Cambridge, Massachusetts in October 1999. At the meeting, Dr. Wood disclosed that PD-1 and CTLA-4 had similar structures and that PD-L1 antibodies inhibited the PD-1/PD-L1 interaction. Dr. Freeman disclosed that 292 was from a human ovarian tumor and that PD-L1 shares 20% of its amino acid sequence with B7-1 and B7-2 but does not bind to either CD28 or CTLA-4. Dr. Honjo disclosed his unpublished knockout mouse data indicating that PD-1 inhibits the immune response.

After the meeting, the three began exchanging reagents. Dr. Honjo ran in vitro experiments on the pathway indicating that it inhibited the immune response, using knockout mouse cells as a control. Drs. Freeman and Wood filed a provisional patent application disclosing modulation of the immune response via activating or blocking the PD-1/PD-L1 pathway, but did not list Dr. Honjo as an inventor.

In the fall of 1999, Dr. Freeman conducted a second BLAST search and identified another B7-like molecule that shares 38% of its protein structure with PD-L1. Over

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the next year, Dr. Freeman conducted a number of experiments on this ligand, which he labeled PD-L2.

In January 2000, Dr. Freeman asked Dr. David Dorfman, a pathologist at the Brigham and Women's Hospital, and Dr. Julia Brown, a new postdoctoral researcher, to test both normal and tumor tissues and determine whether PD-L1 was expressed by them. Dr. Dorfman studied numerous cell lines and found high PD-L1 expression in tumors, including squamous cell carcinoma of the tongue, breast lobular carcinoma, lung and colon adenocarcinoma, and anaplastic large cell lymphoma. These immunohistochemistry results were not published until 2003.

In March 2000, Dr. Freeman emailed Dr. Honjo to tell him about PD-L2 and to send its sequence. Drs. Honjo, Freeman, and Wood then worked on a journal article documenting their discoveries concerning PD-L1, and, in a final round of edits in April 2000, Dr. Freeman added a sentence to the paper stating that PD-L1 was also expressed in cancers and that some tumors may use PD-L1 to inhibit an antitumor immune response. This article was published in the *Journal of Experimental Medicine* on October 2, 2000.

Drs. Wood, Freeman, and Minato all separately developed antibody candidates. In March 2000, Drs. Wood and Honjo presented results of their PD-1/PD-L1 collaborative research at a conference. Dr. Iwai also resumed her knockout mice studies. By May 2000, Drs. Wood, Freeman, and Honjo were discussing their development of anti-PD-L1 antibodies and the possible use of those antibodies in treating cancer.

In June 2000, Dr. Honjo learned of the 1999 provisional application filed by Drs. Wood and Freeman, and challenged his exclusion as an inventor. By September, the three had met again in Cambridge and Drs. Wood and Freeman presented the results of their research on PD-L2. Dr. Honjo presented some new data from Dr. Iwai's knockout mice.

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In October, Dr. Iwai had generated data suggesting that mouse melanoma tumors expressing PD-L1 grow faster than tumors without PD-L1 expression. Ono identifies October 2000 as the date Drs. Honjo, Iwai, and Minato conceived the claimed inventions. As more data were generated by the Iwai experiments, Dr. Honjo stopped sharing results with Drs. Freeman and Wood. The three met one final time in April 2001.

Meanwhile, Dr. Honjo's attorneys were pursuing his inventorship claim, but Genetics Institute, the assignee of Drs. Freeman and Wood's patents, and its attorneys declined to voluntarily add him to their patents. Genetics Institute stated that Dr. Honjo could pursue his inventorship claim at the PTO. Inventorship of those patents is not at issue here.

In 2002, Dr. Honjo then filed his own patent application in Japan, disclosing results from Drs. Honjo, Iwai, and Minato's experiments. Each patent at issue in this case claims priority from Dr. Honjo's Japanese patent application; none include Drs. Freeman and Wood as inventors. Because Dr. Freeman is an employee of Dana-Farber, Dana-Farber is presumably the assignee of any rights he has as an alleged inventor of any of the patents in suit. Pfizer, which purchased Genetics Institute, is presumably the assignee of any rights Dr. Wood has in the patents, but Pfizer has transferred its potential interest in the patents to Ono. None of these relationships is at issue here.

Dr. Freeman allegedly learned about the '048 patent in 2010 but did not pursue litigation until 2015. Dr. Wood may have known of the patents but did not get involved until Dana-Farber filed this suit on behalf of Dr. Freeman. In 2018, Dr. Honjo won the Nobel Prize in Physiology or Medicine, and it is not without interest that in his acceptance speech he credited Dr. Freeman as a major collaborator in his work.

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The parties' inventorship dispute began in the United States District Court for the District of Massachusetts. Dana-Farber brought suit alleging that Drs. Freeman and Wood should be added as inventors on Dr. Honjo's patents. Dana-Farber presented an eight-point theory justifying Drs. Freeman and Wood's inventorship: (1) Dr. Freeman found the 292 sequence; (2) Drs. Freeman and Wood jointly disclosed PD-L1; (3) Drs. Freeman and Wood discovered that PD-1/PD-L1 binding inhibits T cell activation; (4) Dr. Freeman contributed the idea of treating cancer by blocking the pathway in his April 2000 edits to the researchers' journal article; (5) Dr. Freeman provided reagents that Dr. Iwai used in her mouse model; (6) Dr. Freeman, through Dr. Dorfman, discovered that human PD-L1 is expressed across a number of tumors; (7) Drs. Freeman and Wood discovered PD-L2; and (8) Drs. Freeman and Wood developed relevant antibodies.

In a 111-page opinion, the district court considered each of Dana-Farber's points. Ultimately, the court credited Drs. Freeman and Wood's discovery of the PD-L1 ligand, Dr. Wood's discovery that PD-1/PD-L1 binding inhibits the immune response, Drs. Freeman and Wood's discovery that anti-PD-1 and anti-PD-L1 antibodies can block the pathway's inhibitory signal, and Dr. Freeman's immunohistochemistry experiments confirming PD-L1 expression in various tumors as contributions significant to the conception of all six patents.

Ono appealed, and we have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

District courts may order the correction of patent inventorship by the U.S. Patent and Trademark Office "on notice and hearing of all parties concerned." 35 U.S.C. § 256(b). "[A] valid patent requires correct inventorship." *In re VerHoef*, 888 F.3d 1362, 1365 (Fed. Cir. 2018), *as amended* (May 7, 2018). Inventorship is a question of law

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reviewed de novo, but the district court's underlying findings of fact are reviewed for clear error. *Vapor Point LLC v. Moorhead*, 832 F.3d 1343, 1348 (Fed. Cir. 2016) (citing *Gen. Elec. Co. v. Wilkins*, 750 F.3d 1324, 1329 (Fed. Cir. 2014) and then *Trovan, Ltd. v. Sokymat SA, Irori*, 299 F.3d 1292, 1301 (Fed. Cir. 2002)).

35 U.S.C. § 116(a) provides the standard for joint inventorship:

When an invention is made by two or more persons jointly, they shall apply for patent jointly and each make the required oath, except as otherwise provided in this title. Inventors may apply for a patent jointly even though (1) they did not physically work together or at the same time, (2) each did not make the same type or amount of contribution, or (3) each did not make a contribution to the subject matter of every claim of the patent.

Ono challenges the district court's decision on two bases: (1) the district court's legal analysis of conception, and (2) the district court's factual findings regarding inventorship. We address each argument in turn.

A

Ono argues that as a matter of law the district court erred by relying on contributions of Drs. Freeman and Wood that were too far removed from the claimed subject matter of the patents; it also argues that these contributions were made public and were hence in the prior art before the alleged conception. In Ono's view, the patents claim specific methods of treating cancer using PD-1 or PD-L1 blocking antibodies, and Drs. Honjo and Minato discussed the possible use of PD-1 for treating cancer in October 2000 in conjunction with data received from Dr. Iwai's knockout mice experiments. Thus, Ono submits, these experiments, performed independently of Drs. Freeman or Wood, were what led directly to the conception of the

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claimed inventions, and the previous work was at most speculative because it was not *in vivo*. Ono also notes that the patents were issued over Drs. Freeman and Wood's 1999 provisional application as evidence that the patents claim treatments that were novel and nonobvious over Drs. Freeman's and Wood's alleged contributions.

Ono also argues that Drs. Freeman's and Wood's alleged inventive contributions should be deemed irrelevant to inventorship because their work with Dr. Honjo was published in October 2000 in the *Journal of Experimental Medicine* before conception of the patented inventions. Ono urges us to adopt a legal rule that once a contribution is made public, it "no longer qualifies as a significant contribution to conception." Appellants' Br. 39.

Dana-Farber responds that Ono offers an erroneous view of the law. According to Dana-Farber, Ono's rule would require each joint inventor to individually have conceived the complete invention and have participated in a particular moment of conception, which is inconsistent with law.

We agree with Dana-Farber. Ono asks us to adopt an unnecessarily heightened inventorship standard. "[A] joint invention is simply the product of a collaboration between two or more persons working together to solve the problem addressed." *Fina Oil & Chem. Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997) (citing *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1227 (Fed. Cir. 1994)). To be a joint inventor, one must:

- (1) contribute in some significant manner to the conception or reduction to practice of the invention,
- (2) make a contribution to the claimed invention that is not insignificant in quality, when that contribution is measured against the dimension of the full invention, and
- (3) do more than merely explain to the real inventors well-known concepts and/or the current state of the art.

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Pannu v. Iolab Corp., 155 F.3d 1344, 1351 (Fed. Cir. 1998); *quoted in VerHoef*, 888 F.3d at 1366. There is no “explicit lower limit on the quantum or quality of inventive contribution required for a person to qualify as a joint inventor.” *Eli Lilly & Co. v. Aradigm Corp.*, 376 F.3d 1352, 1358 (Fed. Cir. 2004) (quoting *Fina Oil*, 123 F.3d at 1473). “People may be joint inventors even though they do not physically work on the invention together or at the same time, and even though each does not make the same type or amount of contribution.” *Burroughs Wellcome*, 40 F.3d at 1227 (citing 35 U.S.C. § 116).

Ono attacks the inventorship case for Drs. Freeman and Wood on the ground that they failed to participate in certain experiments that led to the conception of the claimed invention, but the statute and our case law make clear that joint inventors need not contribute to all aspects of a conception. *See, e.g., Eli Lilly*, 376 F.3d at 1359–59; 35 U.S.C. § 116(a). That Drs. Freeman and Wood were not present for or participants in all the experiments that led to the conception of the claimed inventions does not negate their overall contributions throughout their collaboration with Dr. Honjo.

Ono’s argument that work from Drs. Honjo, Freeman, and Wood’s collaboration was too speculative until the October 2000 knockout mice studies is likewise misguided. Conception is the touchstone of the joint inventorship inquiry, *Sewall v. Walters*, 21 F.3d 411, 415 (Fed. Cir. 1994), and conception is complete when an idea is definite and permanent enough that one of skill in the art could understand the invention, *Burroughs Wellcome*, 40 F.3d at 1228. An inventor need not know, however, that an invention will work for its intended purpose in order for conception to be complete, as verification that an invention actually works is part of its reduction to practice. *Id.* (citing *Applegate v. Scherer*, 332 F.2d 571, 573 (CCPA 1964) and *Oka v. Youssefye*, 849 F.2d 581, 584 n.1 (Fed. Cir. 1988)). While Dr. Iwai’s work provided important *in vivo* data, *in vivo*

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verification is not required for a conception to be definite and permanent. *See In re Isaacs*, 347 F.2d 887, 889 (CCPA 1965) (holding that *in vivo* testing was not required to establish utility for claims to interferon). Moreover, the record is clear that Dr. Iwai's work was conducted *after* Dr. Freeman had shown expression of PD-L1 in human tumors and Dr. Honjo had shown that PD-L1 expression causes tumor growth, so as a factual matter, PD-L1's potential utility in treating human cancers was developed jointly with Dr. Freeman before Dr. Iwai's work.

Ono also argues that the Honjo patents were issued over Drs. Freeman and Wood's 1999 provisional patent application, so the latter contributions were thus not significant to the dispute over inventorship of Dr. Honjo's patents. As a factual matter, it is unclear that Drs. Freeman and Wood's contributions to the inventions are co-extensive with the disclosure of their provisional application. Regardless, joint inventorship does not depend on whether a claimed invention is novel or nonobvious over a particular researcher's contribution. Collaboration and concerted effort are what result in joint inventorship. *Eli Lilly*, 376 F.3d at 1359. The novelty and nonobviousness of the claimed inventions over the provisional application are not probative of whether the collaborative research efforts of Drs. Honjo, Freeman, and Wood led to the inventions claimed here or whether each researcher's contributions were significant to their conception.

Ono also urges us to hold categorically that research made public before the date of conception of a total invention cannot qualify as a significant contribution to conception of the total invention. Such a rule would ignore the realities of collaboration, especially that collaboration generally spans a period of time and may involve multiple contributions. It is certainly true that simply informing another about the state of the prior art does not make one a joint inventor. *Hess v. Advanced Cardiovascular Sys., Inc.*, 106 F.3d 976, 981 (Fed. Cir. 1997) (holding that

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explaining the state of the art and providing well-known information found in textbooks was insufficient for joint inventorship). But a collaborative enterprise is not negated by a joint inventor disclosing ideas less than the total invention to others, especially when, as here, the collaborators had worked together for around one year prior to the disclosure, and the disclosure occurred just a few weeks prior to conception. Inventorship of a complex invention may depend on partial contributions to conception over time, and there is no principled reason to discount genuine contributions made by collaborators because portions of that work were published prior to conception for the benefit of the public. Earlier publication of an invention is obviously a potential hazard to patentability, but publication of a portion of a complex invention does not necessarily defeat joint inventorship of that invention, and it does not here.

B

Next, Ono raises a series of challenges to the district court's factual analysis for each patent. We begin where Ono focuses the majority of its argument, the '474 patent.

i. '474 patent

Claim 1 of the '474 patent recites a “method for treatment of a tumor in a patient, comprising administering to the patient a pharmaceutically effective amount of an anti-PD-1 monoclonal antibody.” '474 patent col. 25 ll. 13–15. According to Ono, Dr. Freeman's alleged contribution to discovering PD-L1 was locating the 292 sequence in the BLAST database, but he played no meaningful role in the discovery that the PD-1/PD-L1 pathway is inhibitory. Ono also contends that Dr. Freeman's work is not a significant contribution to the invention of the '474 patent because the '474 patent claims rely on anti-PD-1 antibodies, not PD-L1 antibodies.

Ono argues that Dr. Wood likewise should not be credited as a joint inventor on the '474 patent because his work

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on the PD-L1 pathway was not a significant contribution to the claims. Ono submits that the district court overstated Dr. Wood's contributions and that Dr. Wood's work merely confirmed information that Dr. Honjo had already discovered.

Dana-Farber responds that Ono failed to argue that the inventors' contributions differ from patent to patent before the district court. According to Dana-Farber, "the claimed methods are all based on conception of the same core invention: blocking the PD-1/PD-L1 interaction so that the tumor cannot use the pathway to evade immune system attack." Appellees' Br. 41 (emphasis omitted). Dana-Farber cites the district court's fact finding that knowing the structure and function of PD-L1 was essential to all the claimed inventions.

We agree with Dana-Farber, and with the district court, that Drs. Freeman and Wood are joint inventors of the '474 patent. The '474 patent claims use of anti-PD-1 antibodies in treating cancer and does not explicitly mention PD-L1. But PD-1 is just a receptor. Unless one also knows that the PD-1 receptor binds to at least one ligand that inhibits the immune response, such as PD-L1, there would be no reason to use anti-PD-1 antibodies to treat tumors. The '474 patent claims need not explicitly recite PD-L1 for research on PD-L1 to have been a significant contribution to conception of the invention.

The record certainly confirms this reality. The district court credited testimony from Dana-Farber's expert, Dr. Kenneth Murphy, that not all antibodies that bind to a receptor or ligand block the signal. Ono's expert, Dr. Mark Greene, did not contest that Dr. Honjo needed to understand the receptor-ligand interaction to develop effective therapeutic antibodies. But even apart from expert testimony, Dr. Honjo's own efforts underscore the importance of understanding the receptor-ligand relationship to conception. In 1992, Dr. Honjo discovered PD-1 and theorized

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that it played a role in inhibiting the immune response. But despite having this knowledge, Dr. Honjo still enlisted collaboration with the Genetics Institute to search for ligands for PD-1. Even under Ono's view of the facts, knowledge of PD-1 was itself insufficient for Dr. Honjo to conceive of the method claimed in the '474 patent.

It is clear based on the record that Drs. Freeman and Wood both contributed to conception of the '474 patent. Dr. Freeman connected the 292 sequence to PD-1 and directed important immunohistochemistry experiments revealing that several types of tumors express PD-L1. Dr. Wood provided Dr. Honjo with the first confirmation that the PD-1/PD-L1 interaction was inhibitory, supported by experimental data. Drs. Freeman and Wood's work on PD-L1, Dr. Wood's discovery that the PD-1/PD-L1 interaction inhibits the immune response, and Dr. Freeman's discovery of PD-L1 expression by human tumors were significant building blocks upon which the '474 patent is built.

ii. The remaining patents

Each of the remaining patents recites treatment of tumors, lung cancer, or melanoma by administering anti-PD-1 or anti-PD-L1 antibodies. Ono makes arguments about the remaining patents, but each argument depends significantly on our acceptance of its arguments regarding the '474 patent. As we concluded above, discovery of PD-1 in a vacuum was insufficient for conception. Drs. Freeman and Wood's work linking PD-1 to its ligand and expression in tumors was a significant contribution to each of these patents' conception.

Ultimately, the decision in this appeal rests on the extensive factual determinations made by the district court relating to the work performed together by Drs. Wood and Freeman, and Dr. Honjo that were not clearly erroneous, and the court made no errors of law.

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CONCLUSION

We have considered the parties' remaining arguments but find them unpersuasive. Because we conclude that the district court did not err in holding Drs. Freeman and Wood should be included as joint inventors of the '048, '179, '474, '999, '994, and '899 patents, we affirm the district court's conclusions.

AFFIRMED