No. 2019-2050

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.

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

DEFENDANTS-APPELLANTS ONO PHARMACEUTICAL CO., LTD., TASUKU HONJO, E. R. SQUIBB & SONS, L.L.C., AND BRISTOL-MYERS SQUIBB COMPANY'S COMBINED PETITION FOR PANEL REHEARING AND REHEARING EN BANC

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August 27, 2020

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CERTIFICATE OF INTEREST

Counsel for Defendants-Appellants Ono Pharmaceutical Co., Ltd., Tasuku Honjo, E. R. Squibb & Sons, L.L.C., and Bristol-Myers Squibb Company certifies the following:

1. Represented Entities. Fed. Cir. R. 47.4(a)(1). Provide the full names of all entities represented by undersigned counsel in this case.

Ono Pharmaceutical Co., Ltd., Tasuku Honjo, E. R. Squibb & Sons, L.L.C., Bristol-Myers Squibb Company

2. Real Party in Interest. Fed. Cir. R. 47.4(a)(2). Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.

Not applicable.

3. Parent Corporations and Stockholders. Fed. Cir. R. 47.4(a)(3). Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.

E. R. Squibb & Sons, L.L.C. is a wholly owned subsidiary of Bristol-Myers Squibb Company

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

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5. Related Cases. Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). See also Fed. Cir. R. 47.5(b).

Dana-Farber Cancer Institute, Inc. v. Bristol-Myers Squibb Co. et al., No. 1:19-cv-11380-PBS (D. Mass.)

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

None.

Dated: August 27, 2020

/s/ Seth P. Waxman

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Based on my professional judgment, I believe the panel decision is contrary to the following decisions of the Supreme Court of the United States or this Court: *O'Reilly v. Morse*, 56 U.S. (15 How.) 62 (1853); *Eli Lilly & Co. v. Aradigm Corp.*, 376 F.3d 1352 (Fed. Cir. 2004); *Board of Education ex rel. Board of Trustees of Florida State University v. American Bioscience, Inc.*, 333 F.3d 1330 (Fed. Cir. 2003); *Garrett Corp. v. United States*, 422 F.2d 874 (Ct. Cl. 1970).

Based on my professional judgment, I also believe this appeal requires an answer to the following precedent-setting questions of exceptional importance:

1. Whether the panel erred in adopting a bright-line rule that the novelty and non-obviousness of an invention over alleged contributions to conception are "not probative" of whether those alleged contributions were significant to conception.

2. Whether the panel erred in holding that alleged contributions to the conception of an invention can be "significant" even though the content of the alleged contributions was publicly disclosed before the date of conception.

/s/ Seth P. Waxman
SETH P. WAXMAN

INTRODUCTION

Appellants (collectively, "BMS") appealed a judgment adding Dr. Gordon Freeman and Dr. Clive Wood as inventors on six patents directed to groundbreaking new treatments for cancer (the "Honjo Patents"). In affirming, the panel committed two significant legal errors that warrant rehearing en banc.

First, the panel erroneously adopted a bright-line rule that the novelty and non-obviousness of an invention over alleged contributions to the conception of that invention are "not probative" of whether those contributions were significant to conception. Op. 12. To be a joint inventor, a person must make a "significant" contribution to conception, as "measured against the dimension of the full invention." *Fina Oil & Chem. Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997). Here, most of Dr. Freeman's and Dr. Wood's alleged contributions were in the prior art, and the Honjo Patents issued in spite of, not because of, those contributions. But the panel held that "joint inventorship does not depend on whether a claimed invention is novel or nonobvious over a particular researcher's contribution." Op. 12. Indeed, the panel held that "[t]he novelty and nonobviousness of the claimed inventions" over prior art disclosing the putative inventors' contributions are "not probative of whether" those contributions were significant to conception. *Id*. That bright-line rule conflicts with decisions of this Court and the Supreme Court.

Second, the panel erroneously held that alleged contributions can be "significant" contributions to conception even if the content of the alleged contributions was disclosed publicly—and thus free for all to use—before the date of conception. Op. 12-13.

These legal errors blur the line between collaboration and co-inventorship in a way that makes it difficult for parties to collaborate for a limited purpose without opening the door to claims of joint inventorship directed to their separate work. This will chill cooperation across laboratories and invite future litigation. Given the ever-increasing complexity of biopharmaceutical research, the ability to collaborate freely ensures that the best science is applied to address serious unmet medical needs. If collaborators contribute significantly to an inventive concept, they deserve to be co-inventors of any resulting patent. The panel's decision, however, disconnects the significance of a contribution from its inventiveness and thereby eliminates an important safeguard against an unending chain of purported co-inventors laying claim to patent rights that turn out to be valuable. Because the panel's legal errors involve questions of substantial importance and will impact the Court's inventorship jurisprudence going forward, the Court should grant en banc rehearing to correct them.

Separately, panel rehearing is warranted based on errors that conflict with undisputed facts and the district court's factual findings. All parties and the district

court agreed on one critical fact that the panel ignored: the conception date for the Honjo patents was October 27, 2000, after Dr. Honjo's lab ran and saw the results of *in vivo* mouse experiments. Appx75. Before this date, as the district court found, there was no more than an "idea and hope" that the PD-1/PD-L1 pathway might play "some role" in treating cancer. *Id*. The *in vivo* experiments—in which neither Dr. Freeman nor Dr. Wood played a part—provided the crucial data that allowed Dr. Honjo to form the "definite and permanent idea" that the methods he ultimately patented "could treat cancer." Appx75-76. Yet the panel rejected Defendants' argument that the prior work of Drs. Freeman and Wood was too far removed from the patented methods of treating cancer to warrant joint-inventor status by reasoning that the *in vivo* experiments were "not required" for conception and that such "verification that an invention actually works is part of its reduction to practice," not conception. The panel could not have reached these conclusions if it recognized the undisputed October 27, 2000 conception date. That factual error thus infected the panel's determination that Drs. Freeman and Wood made significant contributions to conception.

In addition, in holding that Dr. Freeman made significant contributions to the conception of U.S. Patent 8,728,474, the panel incorrectly stated that "Dr. Freeman connected the 292 sequence to PD-1," *see* Op. 15, in contravention of the district court's factual finding that Dr. Freeman "did not know [292] was a ligand for PD-

1." Appx95. The panel further ignored that Dr. Freeman was not even the first to discover the 292 sequence. These errors undermine the panel's holding.

BACKGROUND

Dr. Tasuku Honjo revolutionized cancer treatment and earned the 2018 Nobel Prize for his groundbreaking work using the human immune system to treat cancer. The Honjo Patents claim methods of treating cancer by administering antibodies that bind to either the PD-1 receptor or its ligand.

In the early 1990s, Dr. Honjo discovered and characterized PD-1 on a T cell, a specialized immune-system cell. Op. 4; Appx14. He also developed antibodies against PD-1. Appx14-15. Together with Dr. Nagahiro Minato, Dr. Honjo conducted "knockout" mouse experiments, using mice that do not express PD-1, to discover that (1) PD-1 serves as a brake on the immune system, and (2) the brake is activated when PD-1 binds to certain proteins, called PD-1's "ligands." Op. 4; Appx15. As a result, Dr. Honjo hypothesized that altering the PD-1 signal could have therapeutic applications for treating cancer. Appx15-16.

In September 1998, Dr. Honjo asked Dr. Wood of the Genetics Institute to help identify PD-1's ligand. Op. 4; Appx19-20. Separately, in July 1998, Dr. Freeman, a researcher at Dana-Farber, located an amino acid sequence he called "292" from a human ovarian tumor while searching the public BLAST database. Op. 4-5; Appx20-21. Dr. Freeman was unable to identify 292's receptor or to find

its function, so he enlisted Dr. Wood's help. Appx21-22. As the district court found, when Dr. Freeman sent 292 to Dr. Wood, Dr. Freeman "did not know it was a ligand for PD-1." Appx95. Dr. Wood discovered that 292 (renamed PD-L1) and PD-1 bound together, and he informed Dr. Honjo that he had identified a ligand for PD-1. Appx24-25.

In November 1999, Drs. Freeman and Wood filed a provisional patent application disclosing, among other things: Dr. Freeman's finding 292 in the public database; Dr. Wood's identification of 292 as a ligand of PD-1; Dr. Wood's research regarding the PD-1/PD-L1 pathway; and the concept that antibodies can block the PD-1/PD-L1 interaction. Op. 5; Appx31-32. Their application did not list Dr. Honjo as an inventor. Op. 5; Appx31.

In 1999 and 2000, Drs. Honjo, Wood, and Freeman and sixteen others wrote a journal article documenting their discoveries concerning PD-L1 and the PD-1/PD-L1 pathway. Op. 6; Appx32. In a final round of edits, Dr. Freeman added a statement that "PD-L1 is also expressed in some cancers, as three [expressed sequence tags] are from human ovarian tumors. This raises the possibility that some tumors may use PD-L1 to inhibit an antitumor immune response." Appx33; Op. 6. The article published on October 2, 2000. Op. 6; Appx33.

Meanwhile, Dr. Freeman separately asked David Dorfman, a pathologist at the Brigham and Women's Hospital, to test normal and tumor tissues for PD-L1

expression. Op. 6; Appx34. Dr. Dorfman selected the tissues to test and reported to Dr. Freeman in March and April 2000 that he had found PD-L1 was highly expressed in normal cells and on various tumors. Op. 6; Appx34.

In early 2000, ***before*** learning about Dr. Dorfman's test results or seeing the sentence Dr. Freeman added to the article, Dr. Honjo's lab began to run *in vivo* tumor experiments to study whether blocking PD-1 could be used to treat cancer. Appx38; Op. 6. Neither Dr. Freeman nor Dr. Wood was involved in those experiments. On September 1, 2000, Dr. Yoshiko Iwai of Dr. Honjo's lab reported results revealing a connection between tumor growth and the PD-1/PD-L1 pathway. Appx40. On October 27, 2000, Dr. Iwai presented a second round of *in vivo* results, demonstrating that PD-L1-expressing tumors grew less quickly in PD-1 knockout mice than in mice expressing PD-1. Appx43.

It is undisputed that, upon seeing the results from these *in vivo* experiments, Dr. Honjo and his Japanese colleagues conceived of the invention underlying the Honjo patents on October 27, 2000. Appx75-76; Appx43. As the district court found, seeing the results of the *in vivo* experiments allowed Dr. Honjo to form the "'definite and permanent idea' that blocking the PD-1/PD-L1 pathway using antibodies could treat cancer." Appx75. Before those experiments, when it came to treating cancer there was nothing more than speculation—initially by Dr. Honjo before working with Drs. Wood or Freeman, Appx15-16, and then later by Dr.

Freeman, Appx33; Op. 6. It was only with additional information, gleaned through *in vivo* experiments accounting for the complexity of a living animal, that it became possible to move from speculation to the definite and permanent idea claimed in the Honjo patents. *See* Appx2034.

In 2002, Dr. Honjo and Ono Pharmaceutical filed a Japanese patent application, claiming methods of treating cancer by blocking the PD-1 receptor from binding to its ligands. Appx45. They later filed an international patent application claiming those same cancer-treatment methods. Appx46. The Honjo Patents all claim priority from those applications. Op. 7. The Honjo Patents issued over the November 1999 provisional application filed by Drs. Freeman and Wood. Op. 10.

In 2015, Dana-Farber filed this action, alleging that Drs. Freeman and Wood should be added as inventors of the Honjo Patents. The district court determined that Dana-Farber had "not produced clear and convincing evidence that Dr. Freeman or Dr. Wood came up with" the idea of blocking the PD-1/PD-L1 pathway as a method of treating cancer, Appx90, but nonetheless concluded that Drs. Freeman and Wood were inventors due to what the district court believed were significant contributions to conception, Appx104.

The panel affirmed, holding that the "novelty and nonobviousness of the claimed inventions over [Drs. Freeman and Wood's] provisional application are not probative of … whether each researcher's contributions were significant to their

conception." Op. 12. The panel also held that a contribution can be "significant," so as to warrant joint inventorship, even where the information contributed was public knowledge at the time the invention was conceived. Op. 13.

Addressing Dr. Iwai's *in vivo* experiments, the panel held they were "not required" for conception and that such "verification that an invention actually works is part of its reduction to practice." Op. 11-12. The panel did not reconcile this conclusion with the undisputed October 27, 2000 conception date. Finally, the panel held that Dr. Freeman "contributed to the conception of" the '474 patent because he allegedly "connected the 292 sequence to PD-1 and directed important immunohistochemistry experiments[.]" Op. 15.

ARGUMENT

I. REHEARING EN BANC IS WARRANTED

A. The Panel Erred In Adopting A Bright-Line Rule That The Novelty And Non-Obviousness Of Alleged Contributions To Conception Are Not Probative Of Whether Those Contributions Are "Significant"

It is black-letter law that an invention must be novel and non-obvious. Thus, a set of previously known concepts does not by itself constitute an invention. However, if one or more novel and non-obvious elements is added to those previously known concepts, or the known concepts are combined in a novel and non-obvious way, the result may be a patentable invention—and whoever was responsible for the novelty is the rightful inventor. *See Morse*, 56 U.S. at 111

(Samuel Morse was sole inventor of claim to "combination of different elements" even if he derived knowledge of individual elements "from conversation with men skilled in the science"); *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418-419 (2007) (inventions may consist entirely of elements present in prior art if combination thereof is inventive).

It follows that, in assessing whether a putative co-inventor made a "significant" contribution to an invention, courts must consider whether the person actually contributed to that which was inventive. Contributions of already-known or obvious ideas, or ideas that otherwise would not be sufficient to warrant a patent, are, at the very least, less likely to be significant.

The panel denied that basic principle. The Honjo Patents were issued over Dr. Freeman's and Dr. Wood's November 1999 provisional application, which disclosed many of their alleged contributions, including their discoveries concerning the PD-1/PD-L1 pathway. Opening Br. 35-36.[1] Thus, the fact that the Honjo Patents issued over those disclosures shows that the patents' claimed methods of treating cancer "were novel and nonobvious" over them. *Id.* (quoting *American Bioscience*, 333 F.3d at 1340). In rejecting that argument, the panel did not deny that the Honjo

[1] The provisional application did not disclose Dr. Dorfman's results, but the district court correctly concluded that Dr. Freeman's alleged contribution based on those experiments "does not by itself render Dr. Freeman a joint inventor." Appx103.

Patents issued over, and thus were "novel and nonobvious" over, the 1999 provisional application. Rather, the panel announced a broad holding that "joint inventorship does not depend on whether a claimed invention is novel or nonobvious over a particular researcher's contribution." Op. 12. Going even further, the panel announced that "[t]he novelty and nonobviousness of the claimed inventions over the provisional application are ***not probative*** of whether" the material disclosed in that provisional application constitutes a significant contribution to the conception of the Honjo Patents. *Id.* (emphasis added).

BMS is not seeking a bright-line rule that a contribution can never be significant if the invention was novel and non-obvious over that contribution. The only bright-line rule here was the panel's declaration that the novelty and non-obviousness of an invention over a putative contribution are ***irrelevant*** to the significance of that contribution. Indeed, according to the panel's reasoning, the fact that Samuel Morse's combination patent was novel and nonobvious over each of the individual elements he combined should have been "not probative" of whether he needed to share inventorship credit. *See Morse*, 56 U.S. at 111. That simply is not the law, as *Morse* shows.

The panel's conclusion also conflicts with prior decisions of this Court. In *American Bioscience*, for example, two scientists had contributed to the claimed anti-cancer compounds by making compounds with similar properties and

conceiving of a method to synthesize the chemical used to create the claimed compounds. 333 F.3d at 1334, 1341. But the scientists had a separate patent on their analogous compounds, and that patent was treated as prior art. *Id.* at 1334 n.4, 1335. This Court rejected the joint inventorship claim, explaining that the "grant" of the new patent over those prior disclosures "itself supports the conclusion that the claimed … compounds … were novel and nonobvious over the prior art, and hence not the invention of" the putative co-inventors. *Id.* at 1335, 1340.

Similarly, in *Garrett*, 422 F.2d 874, this Court's predecessor rejected a co-inventorship claim based on an idea that the Court determined "to be obvious in view of the prior art." *Id.* at 881. The Court thus treated the inventiveness of a putative inventor's contribution as probative of whether that contribution was significant to the conception of an invention.

The Fourth Circuit likewise has held that "the significance of an alleged joint inventor's contribution should be assessed by asking whether the contribution helped to make the invention patentable." *Levin v. Septodont Inc.*, 34 F. App'x 65, 72 (4th Cir. 2002). The *Levin* Court rejected a joint inventorship claim even where the putative inventor's contributions "appear[ed] in the claims of the patent," because those "contributions did not help to make the [claimed invention] patentable." *Id.* at 72-73, 75. Drawing on "basic principles of patent law," the court concluded that it

was "implausible to say that a person who contributed only to the non-novel and/or obvious elements of a claim can be called an inventor." *Id.* at 72-73.

In endorsing this "implausible" holding, the panel conflated ***contributing*** to an invention and ***collaborating*** with an inventor. Op. 12 ("Collaboration and concerted effort are what result in joint inventorship."). Whether Drs. Honjo, Wood, and Freeman collaborated for certain purposes does not determine whether Dr. Wood or Dr. Freeman made significant contributions to the conception of the inventions claimed in the Honjo Patents. Those patents do not claim a biological pathway, but rather particular methods for treating cancer. The work of Dr. Wood and Dr. Freeman was "too far removed from the real-world realization of" that breakthrough, *see Eli Lilly*, 376 F.3d at 1359 (Fed. Cir. 2004)—as demonstrated by the "grant" of the Honjo Patents over the 1999 provisional application's disclosures, *see American Bioscience*, 333 F.3d at 1340. The panel nowhere addressed or even acknowledged this Court's binding precedent in *American Bioscience* or *Garrett*, let alone the Supreme Court's decision in *Morse* or the Fourth Circuit's in *Levin*.

The panel's decision both lowers the bar for inventorship and risks disincentivizing collaboration moving forward. Allowing putative inventors to receive co-inventorship credit for contributing ideas removed from the claimed invention as part of a collaboration undermines the fundamental role of novelty and non-obviousness in patent law. By categorically denying the "probative" value of

an invention's novelty and non-obviousness over alleged contributions, the panel opened the courthouse door to post hoc claims based on mere collaboration. Indeed, if "[c]ollaboration and concerted effort" alone give rise to joint inventorship, as the panel indicated, Op. 12, scientists may reduce or avoid collaborations for fear that collaborating on one subject may inadvertently lead to shared credit for other achievements. This could stunt the "the progress of… useful Arts." *See* U.S. Const. Art. I, § 8, cl. 8.

B. The Panel Erred By Holding That Alleged Contributions To Conception Can Be "Significant" Even If They Were Publicly Disclosed Before The Date Of Conception

This Court has held that "[a] contribution of information in the prior art cannot give rise to joint inventorship because it is not a contribution to conception." *Eli Lilly*, 376 F.3d at 1362. Although in *Eli Lilly* the information in question was already in the public domain at the time it was contributed, the rule must be the same when the information is not yet public at the time of contribution but becomes so before the time of conception. Because "[c]onception is the touchstone to determining inventorship," *Fina Oil*, 123 F.3d at 1473, the facts that exist at the time of conception are what matter for determining whether an idea qualifies as inventive. If a putative co-inventor's contribution is publicly known at the time of conception, it cannot be inventive and thus cannot be a significant contribution.

In categorically rejecting this conclusion, the panel disregarded *Maatuk v. Emerson Electric, Inc.*, 781 F. App'x 1002 (Fed. Cir. 2019) (nonprecedential). There, the information contributed by the putative co-inventor was confidential when it was initially shared but became public knowledge before conception. *Id.* at 1006. The Court correctly held that those alleged contributions, which "were disclosed in the prior art" when the named inventors "conceived" of the patented invention, could not be significant. *Id.* That holding reflects the basic rule that co-inventorship requires a contribution significant to the ***conception*** of the claimed invention. Where information contributed by a putative co-inventor is free for all to use at the time of conception, it cannot represent a significant contribution to a new invention.

Here, the overwhelming majority of alleged contributions by Drs. Freeman and Wood were published before conception of the Honjo Patents. Opening Br. 38-39. The Court should grant rehearing en banc to correct the panel's incorrect legal conclusion.

II. THE PANEL'S FACTUAL ERRORS WARRANT PANEL REHEARING

Identifying the moment of conception is crucial to assessing a co-inventorship claim because, as noted, "[c]onception is the touchstone to determining inventorship." *Fina Oil*, 123 F.3d at 1473. Here, the date of conception is uncontested: October 27, 2000. Appx75. That is when Dr. Iwai presented the

results of the *in vivo* knockout mouse studies that, as the district court correctly found, allowed Dr. Honjo and his Japanese colleagues to move beyond "hope" and form the "definite and permanent idea" that blocking the PD-1/PD-L1 pathway would be an effective method of treating cancer. Appx75. Dr. Iwai's *in vivo* experiments thus not only predated, but also played the key role in giving rise to, the conception of the Honjo Patents.

The significance to conception of Dr. Iwai's *in vivo* experiments demonstrates that Dr. Honjo's previous collaboration with Drs. Freeman and Wood was too far removed from conception to have yielded significant contributions. Dr. Iwai's experiments represented a giant leap over the prior work on the PD-1/PD-L1 pathway, advancing the state of knowledge from a mere hypothesis to a definite and permanent idea of cancer treatment.

The panel rejected this argument by concluding the *in vivo* studies were "not required" for conception and that such "verification that an invention actually works is part of its reduction to practice." Op. 11-12. But those conclusions conflict with the undisputed October 27, 2000 conception date. They also conflict with this Court's own precedent recognizing that, for some inventions in unpredictable arts, experimentation *is* required for conception to be complete. *E.g.*, *Hitzeman v. Rutter*, 243 F.3d 1345, 1357 (Fed. Cir. 2001) ("When a research plan requires extensive

research before the inventor can have a reasonable expectation that the limitations of the count will actually be met, complete conception has not occurred.").

Had the panel accepted the undisputed conception date, it would have been forced to confront the significance of Dr. Iwai's experiments and, by extension, the relative insignificance of the prior work of Drs. Freeman and Wood to conception of these patents. Instead, the panel based its holding on a clear factual error.

Separately, the panel directly contradicted the district court's factual findings when it concluded that Dr. Freeman's contributions were significant in part because he "connected the 292 sequence to PD-1." Op. 15. Dr. Freeman merely located 292; as the district court found, when he sent 292 to Dr. Wood, Dr. Freeman "did not know it was a ligand for PD-1." Appx95. Dr. Wood then discovered the connection between 292 and PD-1 without further assistance from Dr. Freeman. Appx79. The record is thus clear that Dr. Freeman did ***not*** "connect[] the 292 sequence to PD-1."

Compounding the error, the panel nowhere acknowledged Dr. Freeman was not even the first to locate 292. As the district court found, Dr. Lieping Chen of the Mayo Clinic, not Dr. Freeman, first discovered 292. Appx79. The panel thus erred by crediting Dr. Freeman as a co-inventor of the '474 patent based on an alleged contribution that was neither significant nor original.

CONCLUSION

Rehearing en banc or panel rehearing should be granted.

Respectfully submitted,

/s/ Seth P. Waxman

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August 27, 2020

ADDENDUM

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,

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

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.

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

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

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.

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.

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

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

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.

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. Youssefyeh*, 849 F.2d 581, 584 n.1 (Fed. Cir. 1988)). While Dr. Iwai's work provided important *in vivo* data, *in vivo*

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

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

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

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.

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

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