4 Inventorship Lessons From Fed. Circ.'s Dana-Farber Ruling

By **Siegmund Gutman and Sarah Cork** (September 14, 2020)

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A patent's inventors are presumed to own the patent.[1] Thus, significant business decisions are often predicated on the understanding that a patent's inventors are correctly named. These decisions can run the gamut from licensing or purchasing patent rights and investing in product development to planning strategies in patent infringement litigation.

If a patent's inventorship is later corrected, the consequences can be significant. For example, one potential defense to a claim of infringement is to obtain a license from a putative inventor and seek correction of inventorship under Title 35 of the U.S. Code, Section 256.

The Dana-Farber inventorship litigation, Dana-Farber Cancer Institution Inc. v. Ono Pharmaceutical Co., is a recent successful example of this strategy.[2] Dana-Farber shows how inventorship issues can play out over the course of initial discovery, subsequent research and development and commercialization, and litigation, and its cautionary tale serves as a useful source of practical and strategic pointers to patentees, investors and challengers alike. Four key takeaways are discussed below.

Inventorship rights can arise from partial contributions.

To appreciate the result in Dana-Farber, it is helpful to know its background.[3] As described in Dana-Farber, in the early 1990s, Tasuku Honjo discovered the PD-1 receptor on immune cells, and initial experiments suggested PD-1 could block the immune response. The Honjo team surmised that PD-1 could have a variety of therapeutic applications, but they did not investigate its role in cancer at the time. They also had difficulty identifying the PD-1 ligand, which limited their understanding of the molecular mechanisms of PD-1's activity.[4]

Around that time, Honjo, the Genetics Institute and Ono Pharmaceuticals formed a three-way collaboration to discover novel pharmaceutical products. In 1998, at one of the collaboration's meetings, Honjo asked for help identifying the PD-1 ligand.[5] Clive Wood of the Genetics Institute agreed to help, and Honjo sent him reagents. Observing similarities between PD-1 and another receptor, CTLA-4, Wood thought PD-1 might be bound by a CTLA-4 ligand of the B7 family, but his initial efforts failed to show this.[6]

Around the same time, Gordon Freeman of Dana-Farber was studying novel B7 ligands. He discovered a new ligand, 292, in ovarian tumors, which was of interest because the then-known B7 ligands were expressed on immune cells.[7] As Dana-Farber and the Genetics Institute had an oncology partnership, Freeman reached out to see if the Genetics Institute could help locate 292's receptor.

By the summer of 1999, Wood became involved in Freeman's study. He tested whether PD-1 and 292 bound each other and found that they did, and passed the good news on to Honjo and Freeman. Wood later confirmed that 292 — now called PD-L1 — inhibited the immune response, and Honjo provided him with antibodies to test the blocking of the PD-1/PD-L1 pathway. The three scientists met in October 1999, discussed their findings and agreed to continue the research, including the development of anti-PD-L1 antibodies.[8]

Around this time, the group began to write up their findings. In the spring of 2000, all three worked on a journal article describing the discovery of PD-1 and PD-L1. In editing this manuscript, Freeman proposed that tumors' expression of PD-L1 suggested that the tumors utilize PD-L1 to block an anti-tumor immune response.[9]

In November 1999, Freeman and Wood filed a provisional patent application relating to methods of modulating the immune system via activating or blocking PD-1/PD-L1. They did not name Honjo as a co-inventor.[10]

The scientists began investigating the relationship of the PD-1 pathway to cancer. By early 2000, Freeman and colleagues demonstrated that PD-L1 was expressed on various cancers. Researchers in Honjo's lab began in vivo tumor model studies shortly afterwards. By the fall of 2000, these studies confirmed that tumors expressing PD-L1 grew more quickly than nonexpressing tumors, suggesting that blocking PD-1 can suppress tumor growth. These experiments were not shared with Freeman and Wood, however.[11]

The collaboration ultimately dissolved. In 2002, Honjo and his collaborators filed their own patent application relating to methods of treating cancer via blocking the PD-1/PD-L1 pathway, without naming Freeman or Wood as co-inventors. This 2002 application gave rise to the Honjo patent family at issue in Dana-Farber, which was assigned to Ono.[12]

In 2018, Honjo shared the Nobel Prize for the discovery of treating cancer via inhibiting negative immune regulation by blocking PD-1. In his Nobel lecture, he credited his major outside collaborators, including Freeman.[13]

In 2016, Dana-Farber and Pfizer Inc. (the assignees of Freeman's and Wood's interests in the Honjo patents, respectively) sought correction of the patents' inventorship. They ultimately prevailed and the U.S. District Court for the District of Massachusetts ordered Freeman and Wood to be added as inventors of the Honjo patent family.

On appeal, the major dispute centered around whether the contributions of Freeman and Wood could constitute conception of the Honjo claims. The U.S. Court of Appeals for the Federal Circuit concluded they did and affirmed.

Conception

Ono argued that the efforts of Freeman and Wood did not rise to the level of conception because they did not participate in the Honjo lab's tumor experiments in 2000 (which, according to Ono, led to conception) and that their own contributions were too speculative to constitute conception.

The Federal Circuit disagreed, noting that these arguments required an unnecessarily heightened application of inventorship principles. It observed that joint inventors need not contribute to all aspects of a conception; thus, "[t]hat 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."[14]

It noted that an inventor need not know that an invention will work for its intended purpose in order for conception to be complete, and that in vivo confirmation is not required for conception to be definite and permanent. The court also observed that the Honjo lab's in vivo studies were performed after joint experiments showing PD-L1's potential role in

tumorigenesis, including Freeman's discovery that PD-L1 is expressed in tumors.

Ono also argued that Freeman's and Wood's 1999 provisional application should bar their addition as inventors of the Honjo patent family on the grounds that, because the Honjo patents issued over the provisional, the claimed treatments were novel and nonobvious over Freeman's and Wood's alleged contributions. The court observed in disagreement that "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."[15]

The court also rejected Ono's argument that research made public before the date of conception of a total invention cannot be a significant contribution to the conception. Such a rule, according to the court, "would ignore the realities of collaboration, especially that collaboration generally spans a period of time and may involve multiple contributions."[16]

The court suggested that this inquiry could depend on the circumstances of the public disclosure, however, observing that "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."[17]

It noted that "[i]nventorship 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."[18]

Inventorship

The court also rejected the argument that Freeman's contribution to claims reciting a PD-1 antibody was not meaningful because his work focused instead on the ligand PD-L1. It reasoned that "[u]nless 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," and that the "claims need not explicitly recite PD-L1 for research on PD-L1 to have been a significant contribution to conception of the invention."[19]

The court also noted that, even after discovering PD-1, Honjo sought others' help in order to find ligands, supporting the view that simply knowing about the receptor was insufficient to establish conception of the anti-cancer methods claimed in the Honjo patents.

Practice Points

Dana-Farber exemplifies how inventorship and its attendant rights can arise from collaboration, even if co-inventors work at different times or have different roles on the project. These considerations may be particularly important for early-stage companies, where discoveries are often the product of multiple entities' efforts.

Prepare for research collaborations to dissolve.

Notably, the Dana-Farber collaboration began to break down after Honjo discovered Freeman's and Wood's 1999 provisional application. He sought to be added as an inventor, but the Genetics Institute refused. This led to the souring of relations between Honjo and the Genetics Institute.[13]

Practice Points

It's always possible that a collaboration will end, and sometimes that end will be contentious. In many cases, an agreement covering the venture will govern the various ownership interests. It's advisable to investigate whether any research activities predate a formal agreement, however, and to consider the researchers' employment contracts.

Look for potential co-inventors.

Dana-Farber's suit evidently arose from another competitor's realization that the Honjo patents' inventorship might be incorrect.

In 2015, Freeman discussed his collaboration with Honjo and Wood over PD-1/PD-L1 signaling with Novartis.[20]

At the time, Novartis was developing an anti-PD-1 antibody and anticipated being sued. According to witness testimony, Novartis thought that if it entered into an agreement to license any rights Dana-Farber might have to the Honjo patents, as the assignee of Freeman's rights, and then sued to correct inventorship, it could participate in any settlement Bristol-Myers Squibb Co. might strike with the other companies developing antibodies targeting the PD-1/PD-L1 pathway. Dana-Farber declined to grant Novartis an exclusive license, however.[21]

Practice Points

Patent owners, interested investors, and potential or actual defendants are all well-served to investigate the possibility of unnamed inventors. Much of the relevant information may not be public — in lab notebooks and other records — but, as Dana-Farber shows, early publications and patent applications can be a source for the identification of candidate inventors.

It may be fruitful to search such early records and contact any persons who appear to be involved but are not named inventors, as they may be able to establish the role and contributions of each person and provide further avenues to explore. The inventorship of issued patents, however, is presumed to be correct and a challenger must show clear and convincing evidence otherwise in order to prevail.[22] If a collaborator can't back up his/her claims, this uphill battle may be unwinnable.

Licensing rights of a potential co-inventor can be a cost-effective litigation strategy.

Ono's licensees developed a PD-1 antibody, nivolumab (Opdivo), which was approved in the U.S. in 2014 and has continued to gain approval for use in a variety of cancer types.[23] Notably, Bristol-Myers Squibb spent $3 billion in research and development for nivolumab between 2011 and 2018.[24] Around the same time, other companies were working on anti-PD-1/PD-L1 therapeutic antibodies, including Merck & Co. Inc., which developed a PD-1 antibody named pembrolizumab (Keytruda).

The threat of the Honjo patents had not gone unnoticed. Between 2011 and 2014, Merck sought to invalidate European and U.K. counterparts of the Honjo patent family[25] while the Honjo patents migrated through the U.S. Patent Office. As they issued, Bristol-Myers Squibb began suing competitors in the PD-1/PD-L1 space, including Merck.[26]

In response, Merck sought inter partes review of certain Honjo patents. On the eve of trial in the BMS-Merck litigation, the parties settled the cases and the inter partes reviews.[27] The Merck-BMS settlement, which resolved global litigation concerning Keytruda, carried a $625 million lump sum price tag and ongoing royalties for 10 years.[28] In terminating the inter partes reviews, the parties noted that Dana-Farber was seeking correction of the inventorship of the Honjo patents.[29]

Practice Points

An accused infringer can face threats of expensive litigation, a costly settlement and royalties or damages if liability is found. Dana-Farber shows how a Section 256 action can be a powerful tool to avoid these consequences. In such cases, an exclusive license may not be necessary; even if a putative inventor grants an exclusive license, this license will be effectively a nonexclusive license because the properly-named inventors, and their licensees or assignees, may still hold patent rights.

Relatedly, Dana-Farber underscores that diligence concerning patent inventorship should be an important part of any transaction involving patent rights, including patent licensing diligence or the decision to invest in products derived from a joint research venture.

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[1] Ethicon, Inc. v. U.S. Surgical Corp., 135 F.3d 1456, 1465 (Fed. Cir. 1998) ("[I]n the context of joint inventorship, each co-inventor presumptively owns a pro rata undivided interest in the entire patent, no matter what their respective contributions.") (internal footnote omitted).

[2] Dana-Farber Cancer Inst., Inc. v. Ono Pharm. Co., 964 F.3d 1365 (Fed. Cir. 2020).

[3] Findings of Fact, Conclusions of Law, and Order, Dana-Farber Cancer Inst. Inc. v. Ono Pharm. Co., Civ. No. 15-13443 (D. Mass. May 17, 2019) (D.I. 389) ("FOFCOL").

[4] See, e.g., FOFCOL 14-17.

[5] See, e.g., FOFCOL 17-18.

[6] See, e.g., FOFCOL 18-20.

[7] See, e.g., FOFCOL 21.

[8] See, e.g., FOFCOL 24-29.

[9] See, e.g., FOFCOL 32-33.

[10] See, e.g., FOFCOL 31-32.

[11] See, e.g., FOFCOL 34-35, 43.

[12] See, e.g., FOFCOL 45-47.

[13] See, e.g., FOFCOL 50.

[14] Dana-Farber, 964 F.3d at 1371-72.

[15] 964 F.3d at 1372.

[16] 964 F.3d at 1372.

[17] Id.

[18] Id. at 1372-73.

[19] 964 F.3d at 1373.

[20] See, e.g., FOFCOL 39-40, 45.

[14] See, e.g., FOFCOL 49.

[15] See, e.g., FOFCOL 50.

[16] See Eli Lilly & Co. v. Aradigm Corp., 376 F.3d 1352, 1358 (Fed. Cir. 2004). "The general presumption of patent validity does not pertain to patent applications before they issue," however. Id. at 1365.

[17] FOFCOL 47-48.

[18] See, e.g., FOFCOL 48.

[19] E.g., Complaint ¶¶ 20-21, Bristol-Myers Squibb Co. v. Merck & Co., Inc., Civ. No. 15-560 (D. Del. Jun 30, 2015) (D.I. 1).

[20] E.g., FOFCOL 48.

[21] E.g., Joint Mot. to Terminate Pursuant to 35 U.S.C. § 317, Merck Sharp & Dohme Corp. v. Ono Pharm. Co. Ltd., IPR2016-01218 (P.T.A.B. Jan. 23, 2017) ("Section 317 Mot.").

[22] Press Release: Bristol-Myers Squibb and Ono Pharmaceutical Company Enter Settlement and License Agreement with Merck to Resolve PD-1 Antibody Patent Litigation, Bristol-Myers Squibb (Jan. 20, 2017), https://news.bms.com/press-release/partnering-news/bristol-myers-squibb-and-ono-pharmaceutical-company-enter-settlement-a

[23] Section 317 Mot. 3 n.1.