

UNITED STATES DISTRICT COURT  
DISTRICT OF MASSACHUSETTS

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DANA-FARBER CANCER INSTITUTE, INC., )	)	
	)	
Plaintiff, )	)	
	)	
v. )	)	Civil Action
	)	No. 15-13443-PBS
	)	
ONO PHARMACEUTICAL CO., LTD.; )	)	
TASUKU HONJO; E.R. SQUIBB & SONS, )	)	
L.L.C.; and BRISTOL-MYERS SQUIBB, )	)	
CO., )	)	
	)	
	)	
Defendants. )	)	
_____ )	)	
_____ )	)	

**FINDINGS OF FACT, CONCLUSIONS OF LAW, AND ORDER**

May 17, 2019

Saris, C.J.

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**INTRODUCTION**

Plaintiff Dana-Farber Cancer Institute, Inc. ("Dana-Farber") brings this civil action to correct inventorship of six disputed patents ("the Honjo patents") against Defendants Ono Pharmaceuticals Co., Ltd. ("Ono"); Dr. Tasuku Honjo; E.R. Squibb & Sons, L.L.C.; and Bristol-Myers Squibb, Co. ("BMS"). The Honjo patents claim methods of cancer immunotherapy. Dr. Honjo is the named inventor on these patents together with two colleagues from Kyoto University and a researcher at Ono. Dana-Farber contends that Dr. Gordon Freeman, one of its professors, and Dr. Clive Wood, formerly of the Genetics Institute ("GI"), made significant contributions to the conception of the inventions in the Honjo patents through, among other things, the discovery and characterization of the PD-L1 and PD-L2 ligands, the discovery that the interaction between PD-1 and PD-L1 ("the PD-1/PD-L1 pathway") is inhibitory and could be blocked by antibodies, and the discovery that PD-L1 is expressed in human tumors.<sup>1</sup> Dana-Farber seeks to add Dr. Freeman and Dr. Wood as joint inventors on the Honjo patents. Defendants argue that Dr. Freeman's and

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<sup>1</sup> Because Dr. Wood was involved in the collaboration at issue while he worked at GI, GI intervened in this lawsuit in 2017, as did its parent companies Wyeth LLC and Pfizer Inc. Pfizer, Wyeth, and GI settled with Defendants on the eve of trial.

Dr. Wood's contributions to the inventions are not significant enough to make them joint inventors.

After a bench trial, I find Dana-Farber has presented clear and convincing evidence that Dr. Freeman and Dr. Wood are joint inventors of the six Honjo patents. Dr. Honjo collaborated extensively with both Dr. Freeman and Dr. Wood from at least October 1999<sup>2</sup> until at least September 2000 through numerous meetings, joint authorship of scientific journal articles, written collaboration agreements, and sharing of experimental results and ideas. Indeed, Dr. Honjo himself referred to his work with Dr. Freeman and Dr. Wood as a collaboration on at least six occasions. While the relationship among these three brilliant scientists eventually soured, all three made significant contributions to the inventions. After a review of the extensive record and evaluation of the credibility of the witnesses, I conclude that both Dr. Freeman's and Dr. Wood's contributions were significant in light of the dimension of the full inventions claimed in the six Honjo patents, which are all premised on blocking the inhibitory interaction of the PD-1/PD-L1 pathway to treat tumors that express PD-L1 or PD-L2. Judgment shall enter for Dana-Farber.

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<sup>2</sup> The collaboration between Dr. Wood and Dr. Honjo began in September 1998.

**FINDINGS OF FACT**

**I. Scientific Background**<sup>3</sup>

**A. The Immune System and Receptor-Ligand Signaling**

The immune system is the body's defense against foreign invaders, such as viruses, bacteria, and other pathogens. The immune system works through a network of different types of cells, each with a specific function. Dendritic cells, for example, detect the presence of pathogens and alert the rest of immune system. B cells respond by producing proteins called antibodies that bind to pathogens and neutralize them. The most important immune cells for the purposes of this dispute are T cells. T cells either coordinate the immune system's response to pathogens ("helper" T cells) or eliminate infected or abnormal cells from the body ("killer" or "cytotoxic" T cells). Killer T cells can help prevent cancer from growing in the body. Once the immune system recognizes cancer cells as abnormal, T cells attack the cancer cells in the same way they attack cells infected with viruses and bacteria.

In a healthy person, the immune system activates to fight pathogens and then deactivates to protect healthy cells from immune attack. Disorders of the immune system come in two forms. An individual with a suppressed immune response, such as someone

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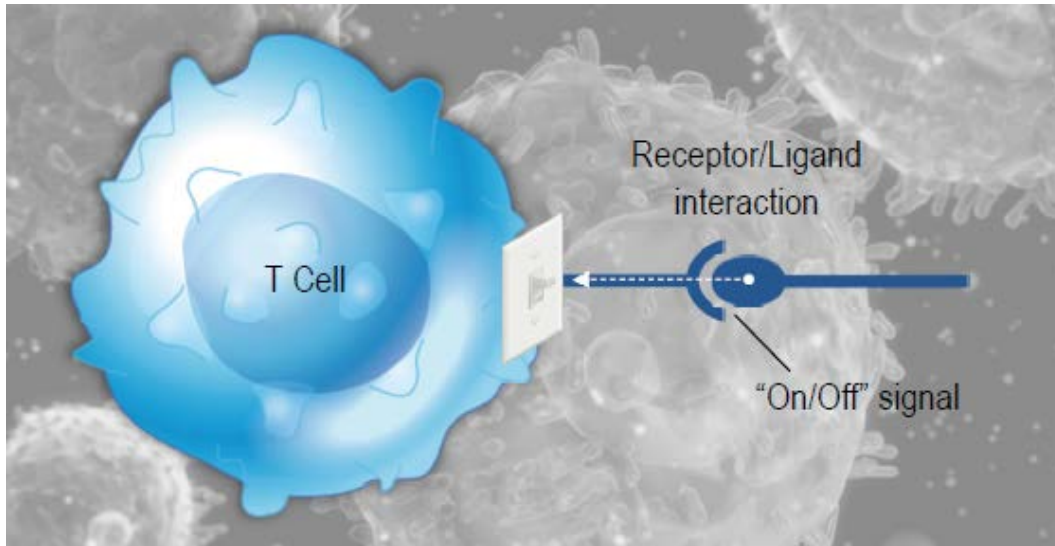
<sup>3</sup> The scientific background is taken from the tutorials the parties provided for the Court (Dkt. Nos. 384-388).

with AIDS, is highly susceptible to infections and other diseases. An overactive immune response, on the other hand, can lead to autoimmune diseases in which the immune system attacks healthy cells.

To maintain a healthy balance, the immune system relies on communication among immune cells and between immune cells and other cells found in the body. Cells can communicate through receptor-ligand interactions. A receptor is a protein located on the cellular membrane that allows the cell to detect and respond to its environment. The receptor receives a signal from outside the cell and then transmits the signal to the internal components of the cell to trigger a response. Ligands are proteins that bind to receptors to initiate signaling. Ligands can be secreted by cells ("cytokines") or found on the cell surface. When a ligand binds to its receptor, it activates the intracellular signaling pathway that tells the cell with the receptor how to respond.

Receptor-ligand interactions play a critical role in regulating the immune system. In the presence of pathogens, some receptors act as accelerators that "upregulate" or "stimulate" immune cells to increase the immune response. To prevent activated immune cells from damaging healthy cells, other receptors act as brakes to "downregulate" or "inhibit" the immune response. The immune system maintains a balance via the

"on-off switches" of receptor-ligand signaling by upregulating when it detects infected or abnormal cells and downregulating once those cells are eliminated.



The primary receptor on a T cell is known as the T cell receptor ("TCR"). The TCR binds to foreign proteins known as antigens, which come from viruses, bacteria, or cancers. In combination with other signals, binding between the TCR and antigen activates the T cell to attack the pathogen.

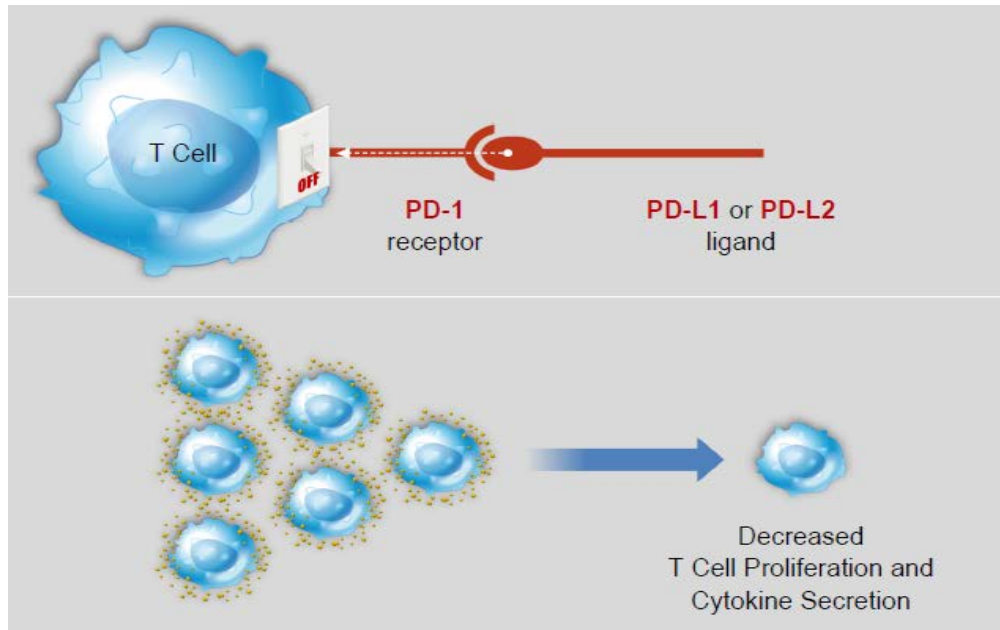
T cells also have other receptors on their surface. For example, a signal sent to the TCR does not activate a T cell unless a ligand binds to one of its co-stimulatory receptors. An important co-stimulatory receptor is called CD28. CD28's two ligands, B7-1 and B7-2, are expressed on dendritic cells that have detected infection or cancer. In order for a T cell to activate, an antigen on the dendritic cell must bind to the TCR on the T cell and a B7 ligand on the dendritic cell must also



bind to the CD28 receptor on the T cell. In the absence of an infection or cancer, the dendritic cell will not express a B7 ligand on its surface; if the TCR on the T cell interacts with the dendritic cell but does not receive a signal through CD28, the T cell will not activate. This requirement for co-stimulation ensures the immune system does not activate unless pathogens are present.

The B7 ligands also bind to an inhibitory receptor called CTLA-4, which is only expressed on highly activated T cells. The B7 ligands bind more tightly to CTLA-4 than CD28. Thus, when a T cell expresses both CD28 and CTLA-4, CTLA-4 prevents the B7 ligands from activating the T cell through the CD28 receptor. CTLA-4 thereby ensures the immune system does not run out of control and harm healthy cells.

The Honjo patents target another inhibitory receptor on T cells known as PD-1. When PD-1 binds to one of its ligands, PD-L1 or PD-L2, the T cell receives an inhibitory signal that prevents it from attacking the cell expressing PD-L1 or PD-L2. Expression of PD-L1 or PD-L2 on healthy cells protects the cells from immune attack. Some tumor cells also express PD-L1 or PD-L2, allowing them to masquerade as healthy cells by activating PD-1 to send an inhibitory signal to T cells.



Because of their importance in the immune system, receptor-ligand interactions are an attractive target for research and therapy. For example, scientists can develop monoclonal antibodies that bind to a specific receptor or ligand. Antibodies are named according to the target protein to which they bind (e.g., anti-PD-1 antibodies). A monoclonal antibody can be designed to trigger a receptor's signal ("agonist") or block a signal either by binding to the ligand or the receptor ("antagonist"). If the receptor-ligand interaction stimulates immune cells, an antagonistic monoclonal antibody decreases the immune response by blocking the stimulation. This can be useful for treating autoimmune diseases. By contrast, if the receptor-ligand interaction inhibits immune cells, an antagonistic monoclonal antibody increases the immune response by blocking

the inhibition. This can be useful for treating viruses or cancer.

The Honjo patents claim methods of treating cancer by using the body's immune system to attack tumor cells, a type of treatment known as cancer immunotherapy. Specifically, the methods involve administering antagonistic monoclonal antibodies that bind to PD-1 or PD-L1 and block the inhibitory interaction between PD-1 and PD-L1/PD-L2. By blocking the signaling pathway, the methods aim to stimulate the immune system to attack the tumor cells.

#### **B. Experimental Methods**

This case also requires understanding how scientists study genes, proteins, and pathways. The Basic Local Alignment Search Tool ("BLAST"), a public database managed by the National Center for Biotechnology Information, contains millions of DNA sequences. Many of these sequences are short fragments of genetic material called "Expressed Sequence Tags" ("ESTs") whose identity, complete sequence, and function are not known. A search through the BLAST database allows scientists to identify new DNA sequences and proteins to study. For example, a scientist can input a reference DNA sequence that encodes a known protein with a known function, and the BLAST search will show ESTs that share similar sequences with the reference DNA. After identifying the full-length sequences, she can then

determine if they encode proteins with similar functions to the known proteins.

Having identified a gene or protein of interest, she can use complementary DNA ("cDNA") and "Fc-fusion proteins" to further study it. cDNA is a DNA sequence that contains only the parts of a gene necessary for encoding a protein. By inserting cDNA into a vector, scientists can cause a wide variety of cells to express a specific protein and then use those cells in experiments. An "Fc-fusion protein" contains a generic "handle" (the "Fc" region) that allows the protein to be easily manipulated and studied apart from the cell. The relevant portion of the amino acid sequence of the protein of interest is attached to the handle. For example, PD-1 fusion protein contains the binding portion of the PD-1 receptor attached to a generic protein handle. The fusion protein can then be used to test whether PD-1 binds to various molecules and whether the expression of PD-1 has an effect on the immune response.

To explore the function and structure of proteins, scientists conduct both in vitro and in vivo experiments. In vitro experiments occur outside of a living organism in test tubes, flasks, and other controlled environments. They allow scientists to learn about a protein without worrying about confounding effects from other molecules within a living organism. For example, mixing T cells expressing a receptor with

cells expressing the receptor's ligand and then observing the number of T cells shows whether the signaling pathway stimulates or inhibits the immune response. Another in vitro experiment, known as immunohistochemistry ("IHC"), involves administering a monoclonal antibody to thin sections of tissue to determine whether the molecule to which the antibody binds is present.

In vivo experiments are conducted using living organisms. Scientists use in vivo experiments to study proteins in their biological context. "Knockout mouse" studies are one type of in vivo experiment. A "knockout mouse" is a mouse without the gene that encodes a particular protein and therefore is unable to make the protein. Observing the characteristics of the knockout mouse reveals the role the protein plays in the organism. For example, if knocking out a gene leads the mouse to have an abnormally active immune system, the protein encoded by that gene likely has an inhibitory effect on the immune system. Mouse tumor models are another type of in vivo experiment used to study cancer. In these experiments, mice are inoculated with tumor cells, and specific signaling pathways or proteins are then blocked in some of the mice. If the tumors grow more or less quickly in the altered mice than in normal mice, the tumor model suggests that the pathway or protein has an effect on tumor growth.

## **II. Discoveries of PD-1 and 292**

### **A. Dr. Honjo Discovers the PD-1 Receptor**

Dr. Tasuku Honjo is a professor at the medical school at Kyoto University. T4-8:22-23, 12:24-25.<sup>4</sup> After receiving his medical degree and PhD in biochemistry in Japan, he came to the United States to work at the Carnegie Institution of Washington in Baltimore, Maryland where he began to study immunology. T4-10:6-24. He then worked at the National Institutes of Health before returning to Japan. T4-11:5-23. He has been a professor at Kyoto University since 1984. T4-12:16-25.

In the early 1990s, Dr. Honjo discovered a new receptor expressed on certain mouse immune cells. T4-14:19-21, 19:10-15; JTX-0320.0001. He named the molecule "PD-1" because he believed the receptor was involved in programmed cell death, a process by which the body kills off old cells when new cells generate. T4-16:10-17:6. He published his discovery in 1992. T4-16:1-9; JTX-0320.0001. Dr. Honjo isolated the human DNA sequence for the gene that encodes PD-1 and, along with researchers from another Japanese University, developed antibodies against both mouse and

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<sup>4</sup> Record citations are to the trial transcripts (e.g., "T4" is the transcript from the fourth day of trial), deposition transcripts submitted in lieu of live testimony (e.g., "Honjo Depo" is the transcript submitted from Dr. Honjo's deposition), or a document from the joint exhibit list (e.g., "JTX-0320"). Pincites for transcripts are to the page and line numbers, and pincites for exhibits are to the page number.

human PD-1 to help study its function. T4-20:15-21:1, 22:2-23:5; Iwai Depo. 41:25-43:3; JTX-0272.0001; JTX-0373.0001; JTX-0429.0011. In 1996, he published another article describing the expression of PD-1 in mouse cells and the PD-1 fusion protein he was using to study the molecule. T4-22:2-11, 131:12-132:7; JTX-0272.0001-2. His early experiments demonstrated that PD-1 was not, in fact, involved in programmed cell death. T4-17:7-14.

To learn more about PD-1's function, Dr. Honjo and Dr. Nagahiro Minato, a colleague studying tumor immunology, began experiments with PD-1 knockout mice. T4-14:1-18, 23:21-25, 29:3-7; T6-89:18-24; JTX-0354.0001. They discovered that mice without the gene encoding PD-1 showed symptoms typical of autoimmune disease, suggesting that PD-1 is involved in inhibiting the immune response. T4-26:11-16; T6-93:12-94:12; JTX-0354.0001. Dr. Honjo and Dr. Minato submitted these results for publication on April 12, 1999. T2-136:18-137:8; JTX-0354.0010. Their article was published in Immunity in August 1999 and described PD-1 as "a negative regulator of immune responses." JTX-0354.0001.

Once Dr. Honjo and Dr. Minato discovered that PD-1 inhibited the immune system through their knockout mouse experiments, they discussed the possibility that altering the PD-1 signal could have therapeutic applications for autoimmune diseases, infectious diseases, organ transplantation, and

cancer. T4-29:23-30:8; T6-129:19-25; Okazaki Depo. 50:25-51:13. They planned to conduct experiments involving tumors but did not do so at the time due to the limited manpower in their laboratories. T4-30:9-17; T6-98:22-99:8.

Based on its structure, Dr. Honjo knew PD-1 was in the same family of proteins as CTLA-4, another inhibitory receptor. T4-31:6-9. But he did not fully understand the molecular mechanism through which PD-1 had its inhibitory effect because he had not identified its ligand. T4-28:3-24, 32:16-25, 141:12-142:6; JTX-0354.0008. Multiple students in his laboratory tried and failed to find PD-1's ligand. T4-143:8-13.

In mid-1998, Dr. Honjo tasked a new graduate student, Dr. Yoshiko Iwai, with the ligand search. T4-38:8-24, 144:5-13; Iwai Depo. 12:2-25. At the May 21, 1999 meeting of Dr. Honjo's laboratory, Dr. Iwai reported her preliminary results. T4-42:23-43:3; JTX-0125.0021. She identified binding of various strengths with human and mouse PD-1 fusion protein in a number of mouse cells she had tested, including cells derived from mouse white blood cell tumor lines. T4-44:24-45:5, 147:8-149:4; Iwai Depo. 14:2-24; JTX-0125.0021. She also reported weak binding with PD-1 in one human B cell cancer line called Daudi. T4-47:17-48:1, 157:3-18; JTX-0125.0021.

Although these results showed binding with the PD-1 fusion protein, they did not identify what molecule the protein was



binding to. T4-146:10-147:7; Iwai Depo. 14:10-24, 15:5-12, 68:20-25, 70:9-17; Honjo Depo. 40:17-25. Dr. Iwai recognized that her experiment could have shown "false positives" because of the type of fusion protein she used. T4-48:2-19; JTX-0125.0022. About a month after disclosing her results, she reported at another laboratory meeting that PD-1's "[l]igand may express on B cell lines?!" JTX-0125.0024. She planned to conduct additional experiments using different fusion proteins to identify the ligand, but she had to take a leave of absence at the end of the summer due to illness. T4-49:2-8, 50:12-22, 51:11-18, 161:16-162:15; Iwai Depo. 13:13-14:5, 72:15-73:3, 82:7-19. The results of Dr. Iwai's experiments were never published. T4-51:1-9, 164:10-12.

**B. Dr. Honjo Asks for Help Identifying the Ligand for PD-1 and Begins to Collaborate with Dr. Wood in September 1998**

In September 1998, as Dr. Iwai was beginning her experiments to identify the ligand for PD-1, Dr. Honjo flew to Cambridge, Massachusetts for a meeting with representatives from Ono, a Japanese pharmaceutical company, and GI, a Cambridge biotechnology research and development company. T2-8:23-9:2, 20:3-6; T4-32:2-12; JTX-0432.0001. This meeting was part of a three-way research collaboration among GI, Dr. Honjo, and Ono that had been established in the mid-1990s. T2-18:6-19:7; JTX-0140; JTX-0142; Dkt. No. 314-1 ¶ 7 ("Stip."). This "signal

sequence trap" ("SST") collaboration involved using yeast-based traps to identify signaling proteins secreted by cells that could then be studied as potential targets for new drug candidates. T2-17:1-18:5; JTX-0140.0001-2. The ultimate goal of the collaboration was "the discovery, development and commercialization of novel pharmaceutical products." JTX-0142.0007. GI, Dr. Honjo, and Ono held core collaboration meetings biannually, which alternated between Cambridge and Japan. T2-19:13-21.

While in Cambridge, Dr. Honjo asked Dr. Steve Clark, the coordinator at GI for the SST collaboration, if he had any ideas for how to identify the PD-1 ligand. T4-32:7-19. Dr. Clark proposed using GI's newly acquired Biacore machine, which would allow for quick screening of many ligand candidates. T4-34:4-12, 35:9-11. Because Dr. Honjo did not have access to a Biacore machine at Kyoto University, he agreed. T4-35:7-8.

To facilitate this collaboration, Dr. Clark introduced Dr. Honjo to Dr. Clive Wood, the director of molecular immunology at GI, who also participated in the collaboration meeting that day. T2-13:13-15, 20:2-6; T4-36:18-22; JTX-0792.0004. Dr. Wood earned a PhD in biochemistry from Imperial College London. T2-8:2-6. He began working at GI in 1986 as a staff scientist. T2-8:19-22. In 1998, he was promoted to serve as the director of molecular immunology. JTX-0792.0004. He left

GI in the early 2000s and now works as a corporate senior vice president responsible for global research activities for Boehringer Ingelheim. T2-7:10-14; JTX-0792.0004.

Dr. Wood and Dr. Honjo had dinner the night of the September 1998 meeting and discussed Dr. Honjo's work on PD-1. T2-20:6-10; JTX-0432.0001. Dr. Honjo explained that he had discovered PD-1 and its inhibitory function but had not been able to find its ligand. T2-134:16-135:3. Dr. Wood agreed to collaborate with him to identify the ligand. T2-129:4-24.

On September 22, about a week after the meeting, Dr. Honjo sent Dr. Wood a letter with more details about their collaboration. JTX-0432.0001. Dr. Wood responded on September 28 confirming his interest. T2-22:6-14; JTX-0436.0001. He also told Dr. Honjo that he thought the PD-1 receptor could be a candidate for a collaboration GI was establishing with Cambridge Antibody Technology ("CAT") to develop antibodies as potential therapeutics. T2:22:21-23:6; JTX-0436.0001. The following day, Dr. Wood submitted a form to GI seeking approval for the PD-1 project and permission to exchange materials with Dr. Honjo. T2-23:14-24:6; JTX-0437.0001. Dr. Honjo sent PD-1 fusion proteins and cDNA developed in his laboratory to Dr. Wood to use in experiments to identify the ligand. T2-130:18-25; T4-36:23-37:2. Soon after their collaboration began, Dr. Honjo provided Dr. Wood with a confidential draft of his Immunity article that

described his PD-1 knockout mouse experiments. T2-135:12-136:22; T4-191:9-192:8. As part of these preliminary discussions, Dr. Wood and Dr. Honjo decided to add the PD-1 project to the existing SST collaboration, which GI, Dr. Honjo, and Ono formally agreed to in March 1999. T2-21:9-13, 26:21-27:10; Shibayama Depo. 82:16-19, 84:18-85:8; JTX-0450.0003; JTX-0471.0001.

When he started work on the project, Dr. Wood recognized that the PD-1 receptor looked like the CTLA-4 receptor found on T cells. T2-28:6-9. Accordingly, because B7-1 and B7-2 were ligands for CTLA-4, he hypothesized that the ligand for PD-1 would also be a member of the B7 family. T2-28:10-14, 29:11-12, 31:3-7, 69:8-16; JTX-0305.0002. And since the interaction between CTLA-4 and the B7 ligands inhibits T cells, he suspected that the interaction between PD-1 and its ligand would also be inhibitory. T2-29:12-14. However, his initial experiments failed to identify a B7 ligand that bound to PD-1. T2-35:14-17.

**C. Dr. Freeman Discovers the 292 Ligand in July 1998**

Dr. Gordon Freeman is a professor of medicine in the department of medical oncology at Dana-Farber and Harvard Medical School. T3:10:20-24, 11:18-22. Dana-Farber is a nonprofit cancer treatment and research center located in Boston, Massachusetts. Stip. ¶¶ 1, 26. Dr. Freeman earned a PhD from Harvard University in microbiology and molecular genetics

in 1979. T3-9:8-13. He then began a postdoctoral fellowship at Dana-Farber working on tumor immunology. T3-9:14-17, 11:23-12:3. He became an assistant professor in 1994. T3-12:12-15.

In July 1998, shortly before Dr. Honjo and Dr. Wood's meeting in Cambridge, Dr. Freeman began a search for novel B7 ligands. T3-22:14-23:1. Dr. Freeman's work had focused for almost fifteen years on B7 ligands, and he had discovered B7-2 and its role in immune regulation. T3-12:16-21, 17:21-18:11, 19:1-12, 20:22-21:1. Given the important interactions between the B7-1 and B7-2 ligands and the CD28 and CTLA-4 receptors, he suspected there might be similar ligands with immunological activity. T3-22:18-24. On July 27, 1998, Dr. Freeman ran a BLAST search with a sequence of 208 amino acids that forms part of binding portion of the B7-1 molecule. T3-25:25-26:18, 27:16-18, 150:13-21; JTX-0305.0002. The search produced a list of twelve ESTs that resembled the B7-1 sequence. T3-26:9-12, 151:11-14; JTX-0431.0001. Two of these twelve ESTs were part of the same sequence and came from a human ovarian tumor, which Dr. Freeman found interesting because the known B7 molecules were only expressed in immune cells, not in solid tumors. T3-28:9-24, 151:15-17; JTX-0431.0001. He decided to investigate this new sequence, which he called "292" after its label in the database. T3-28:24, 31:3-5. He generated the full human cDNA sequence for the 292 protein. T3-30:25-31:1. Through work on similar mouse

DNA sequences found in the BLAST database, he also identified the full-length sequence for mouse 292. T3-33:23-34:7.

In early 1999, Dr. Freeman investigated 292's expression and immunologic activity. T3-32:13-20. Although the ESTs came from a human ovarian tumor, his experiments showed that immune cells also express 292. T3-33:6-17. Given the similarities with B7-1 and B7-2, he thought 292 might affect the immune response. T3-33:18-22. When he exposed resting T cells to cells expressing the 292 protein, the T cells were mildly stimulated, suggesting that 292 does play a role in immune regulation. T3-35:6-23, 36:16-21.

Dana-Farber and GI had an existing oncology partnership, which included work on B7 ligands and related signaling molecules. T2-33:20-34:6; T3-21:6-19; Collins Depo. 17:3-6. Because of this existing collaboration and GI's expertise in making fusion proteins, Dr. Freeman thought GI could help with additional experiments on 292's biological function, including finding its receptor. T2-34:15-17; T3-38:4-13. In July 1999, he reached out to Dr. Mary Collins at GI and told her what he knew about 292. T2-34:12-15; T3-38:24-39:13; Collins Depo. 34:8-9; JTX-0480.0001. Dr. Collins agreed that GI could help, and Dr. Freeman sent GI the genetic materials encoding 292. T2-35:1-4; T3-39:14-18; JTX-0480.0001. Dr. Freeman and researchers at GI had a number of discussions over the next few months about

Dr. Freeman's experiments. T3-41:19-42:2. Because 292 appeared to be a B7 ligand, they thought its receptor would be similar to CD28 and CTLA-4 (though Dr. Freeman had already shown that 292 did not bind to either receptor). T3-42:3-15.

On August 23, 1999, shortly after reaching out to GI, Dr. Freeman filed a provisional patent application.<sup>5</sup> T3-39:22-24, 74:23-75:5; JTX-0043.0001. The application included his experimental results showing that 292 stimulated resting T cell activity. T3-75:22-78:21, 158:23-159:18; JTX-0043.0096, 108-109. Dr. Freeman hypothesized that 292, like B7-1 and B7-2, might have both inhibitory and stimulatory receptors. T3-154:6-17. Accordingly, the application listed embodiments in which anti-292 antibodies stimulate an immune response and others in which they inhibit an immune response. T3-154:6-156:24; JTX-0043.0008. The application identified the normal tissue cells on which Dr. Freeman had found 292 expression but did not mention that he discovered the molecule through ESTs from a human ovarian tumor. T3-157:17-158:22; JTX-0043.0095. The U.S. Patent and Trademark Office ("PTO") issued multiple patents to Dr. Freeman based on this application. T3-160:7-9. The claims of at least one patent were subsequently cancelled because, as discussed below,

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<sup>5</sup> The patent application refers to the molecule as "B7-4." JTX-0043.0002. B7-4 and 292 are the same molecule. T3-39:22-24.

Dr. Lieping Chen at the Mayo Clinic discovered the amino acid sequence for the same molecule before Dr. Freeman. T3-161:2-23. Dr. Freeman did not know about Dr. Chen's discovery, which was not published until December 1999, at the time he made his own independent discovery. T3-161:12-23.

A few days after this application, Dr. Freeman and Dr. Vicki Boussiotis, a member of his laboratory, began an experiment to test the effect of 292 on activated T cells, which express certain receptors that resting T cells do not. T3-37:5-24, 78:22-79:5, 79:16-80:18; JTX-0229.0323, 346; JTX-0778.0038. Unlike the prior experiment with resting T cells, this experiment showed an inhibitory effect on the immune response. T3-37:25-38:2, 79:6-11, 85:20-22, 86:7-24, 163:9-21; JTX-0778.0040; JTX-0801.0021. Dr. Freeman concluded that 292 primarily inhibits activated T cells. T3-180:8-25.

**D. Dr. Wood Connects the PD-1/PD-L1 Pathway in September 1999**

During the summer of 1999, while Dr. Wood was searching for the ligand for PD-1 for Dr. Honjo, he became involved in GI's work with Dr. Freeman to study 292. T3-44:21-25. Because he thought that the ligand for PD-1 would be a B7 ligand and he knew from Dr. Freeman that 292 was a B7 ligand, he tested whether PD-1 and 292 bound together. T2-35:5-22; Collins Depo.



34:10-18. Dr. Wood's initial experiment showed that they did.

T2-35:17-22; Collins Depo. 34:19-22.

Dr. Wood emailed Dr. Honjo about this preliminary result on September 7, 1999. JTX-0485.0001. He described his "significant progress" on the ligand search and his "encouraging" results.

T2-40:19-41:10; T4-53:14-54:7; JTX-0485.0001. To facilitate additional confirmatory experiments, he asked Dr. Honjo for more PD-1 fusion protein, which Dr. Honjo provided. T2-40:19-41:10; T4-55:21-57:5; JTX-0485.0001. Around the same time, Dr. Wood told Dr. Freeman he had identified a receptor for 292 that came from Dr. Honjo. T2-45:7-14; T3-45:1-13.

To ensure his initial experiment did not show a false positive, Dr. Wood ran confirmatory experiments. T2-36:6-24. Dr. Wood followed up with another email to Dr. Honjo on October 4 to report that these experiments confirmed that he had identified the ligand for PD-1. T2-42:22-43:22; T4-57:9-16; JTX-0489.0001. Dr. Wood also told Dr. Honjo that the ligand came from Dr. Freeman. T2-42:24-43:22; JTX-0489.0001. Dr. Wood proposed that the three men meet during the upcoming SST collaboration meeting. T2-42:22-43:22; JTX-0489.0001. Dr. Honjo responded with excitement at Dr. Wood's discovery and agreed to the upcoming meeting. T2-44:6-19; JTX-0492.0001.

After identifying 292, which the three scientists began to call "PD-L1,"<sup>6</sup> Dr. Wood ran experiments to test the immunological effect of PD-L1. T2-47:14-49:15; JTX-0501.0003. These experiments confirmed Dr. Wood's hypothesis that PD-L1 inhibits the immune response. T2-47:14-48:14; JTX-0501.0003. He conveyed these results via email to Dr. Honjo on October 12. T2-47:10-22; JTX-0501.0003. In his email, Dr. Wood also laid out an outline for a journal article he, Dr. Freeman, and Dr. Honjo could write about the discovery of PD-L1. T2-49:16-50:4; JTX-0501.0003. Finally, Dr. Wood asked Dr. Honjo to send him his anti-PD-1 antibodies so that he could test blocking of the PD-1/PD-L1 pathway. T2-147:4-25; JTX-0501.0003-4. In response, Dr. Honjo noted that he "appreciate[d] [Dr. Wood's] strong collaboration without which this work had not been accomplished so soon" and agreed to send Dr. Wood his antibodies. T2-55:9-16, 148:19-25; JTX-0501.0001, 7. Dr. Wood performed preliminary experiments that showed that the human and mouse antibodies bound strongly to human and mouse PD-1, respectively, and that the mouse antibody blocked the interaction between PD-1 and PD-L1. T2-61:10-63:5, 156:22-157:14; JTX-0086.0017.

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<sup>6</sup> From the record, it is unclear exactly when the trio began referring to "292" as "PD-L1." For ease of comprehension, the Court will call the molecule "292" when referring to events before Dr. Wood discovered that the molecule is a ligand for PD-1 and "PD-L1" when referring to events after this discovery.

Dr. Freeman emailed Dr. Honjo on October 22, three days before their scheduled meeting. T3-46:24-47:6; JTX-0505.0001. Dr. Freeman expressed his excitement about the possibility of a research collaboration on the PD-1/PD-L1 pathway. T3-47:7-17; JTX-0505.0001. Dr. Honjo responded that he was looking forward to their meeting. T3-48:3-12; JTX-0507.0001. These emails were the first communication between the two. T3-48:6-8.

### **III. October 25, 1999 Collaboration Meeting in Cambridge**

Dr. Freeman, Dr. Wood, and Dr. Honjo, along with representatives from Ono and GI, met as planned on October 25, 1999 during the prescheduled SST collaboration meeting in Cambridge, Massachusetts. T2-55:17-19, 56:2-13; T3-48:13-22; T4-58:3-5; JTX-0090.0001. Dr. Wood began the meeting by summarizing what he knew about PD-1 from Dr. Honjo's research. T2-156:8-21; T4-67:19-23; JTX-0086.0002. He then described how the similarities in the structure of PD-1 and CTLA-4 triggered his hypothesis that PD-1's ligand would be a B7 ligand. T2-57:2-23; Shibayama Depo. 106:19-107:12; JTX-0086.0003-4; JTX-0097.0003. He shared experimental results demonstrating that PD-L1 binds to PD-1 but not to CTLA-4. T2-57:2-23, 58:16-22; JTX-0086.0005-9; JTX-0097.0004. He ended with graphs showing his newest data on the inhibitory effect of PD-L1 and the successful blocking of the pathway with Dr. Honjo's antibodies. T2-59:12-63:5; T3-51:17-23, 53:7-55:6; JTX-0086.0013-17.

Dr. Freeman presented next. T2-64:11-13; T3-55:7-8; JTX-0090.0001. He shared that the 292 ESTs came from a human ovarian tumor. T2-64:4-10; T3-58:1-7; JTX-0095.0001; JTX-0456.0003. He explained that PD-L1 shares around 20% of its amino acid sequence, which he provided, with B7-1 and B7-2 but does not bind to either CD28 or CTLA-4. T3-59:22-61:21; JTX-0095.0003-6; JTX-0456.0003. Finally, he noted that 292 is expressed in certain types of cells, such as placenta, lung, and heart cells, but not in certain tumor cells. T4-66:10-67:7; JTX-0095.0009.

Dr. Honjo presented last of the three. T2-64:14-15; T3-61:22-62:1; JTX-0090.0001. He described his recently published data showing autoimmune-like symptoms in PD-1 knockout mice. T2-64:22-65:2; T3-62:2-8; T4-58:20-59:8; JTX-0091.0001. He presented unpublished knockout mouse data that also suggested PD-1 inhibits the immune response. T2-152:7-15; T4-59:13-60:15; JTX-0091.0012-14; JTX-0097.0004. He did not mention cancer during his presentation. T2-64:22-65:2; T3-63:7-9.

During the meeting and at dinner, Dr. Freeman, Dr. Wood, and Dr. Honjo agreed to continue to collaborate to study the PD-1/PD-L1 pathway.<sup>7</sup> T2-65:12-24; T3-65:12-19. They discussed

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<sup>7</sup> Dr. Wood remembers discussing the possibility of a second, stimulatory receptor for PD-L1 with Dr. Freeman and Dr. Honjo, T2-63:16-23, but it is not clear if he was referring to a conversation during the October 1999 meeting. In addition, Dr. Freeman remembers mentioning the possibility of treating cancer by manipulating the PD-1/PD-L1 pathway in a conversation

developing further tools to study the pathway, such as new fusion proteins and antibodies, and conducting additional experiments, including more knockout mouse studies. T3-63:10-18.

**IV. Developments Between the October 1999 and May 2000 Meetings**

**A. Dr. Freeman and Dr. Honjo Exchange Reagents, and Dr. Wood and Dr. Honjo Run Experiments Confirming the Inhibitory Effect of the PD-1/PD-L1 Pathway in November and December 1999**

Immediately after the October 25, 1999 meeting in Cambridge, Dr. Freeman and Dr. Honjo began the process of exchanging reagents. T3-67:1-16; JTX-0508.0001; JTX-0510.0001; JTX-0517.0001. They executed a Material Transfer Agreement in which Dr. Freeman agreed to send Dr. Honjo mouse and human PD-L1 cDNA and transfected cells for use solely in their "collaborative efforts." T3-68:7-70:2, 71:16-20; T4-82:18-84:5; Honjo Depo. 91:18-92:25; JTX-0159.0001. In a subsequent email to Dr. Freeman, Dr. Honjo expressed his pleasure that they had "reached at least a tentative agreement to push [their] collaboration as soon as possible." JTX-0517.0001. Dr. Freeman sent his own reagents to Dr. Honjo in November 1999. T3-71:21-72:3; Honjo Depo. 99:24-100:14; JTX-0522.0001; JTX-526.0001.

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with Dr. Honjo and representatives from GI at lunch. T3-63:19-64:9. Since no witness or document corroborated this testimony, the Court is not persuaded that Dr. Freeman is remembering the timing of this conversation accurately.

Dr. Honjo sent his PD-1 reagents to Dr. Freeman pursuant to a separate agreement. T3-70:3-14; JTX-0517.0001.

Meanwhile, Dr. Wood continued to run experiments exploring the function of the PD-1/PD-L1 pathway. JTX-0433.0026. On November 25, he reported to Dr. Honjo that he was getting "confusing" results with no "clearly reproducible effects." Id. A week later, the December issue of Nature Medicine was released. JTX-0433.0027. It included an article by Dr. Lieping Chen at the Mayo Clinic reporting the sequence for a molecule ("B7-H1") that was molecularly identical to PD-L1. T2-66:21-67:17; T4-75:10-25; JTX-0433.0027. In the article, Dr. Chen did not identify B7-H1's receptor, and he reported that B7-H1 has a stimulatory effect on the immune system. T2-66:21-67:17; T4-88:10-13; JTX-0433.0027. Dr. Wood emailed Dr. Honjo about the Chen article the day it came out. T2-66:21-25; JTX-0433.0027. He expressed surprise that Dr. Chen had found that B7-H1 has a stimulatory effect because the data he and Dr. Honjo had generated showed that PD-L1 is inhibitory. T2-67:4-9; JTX-0433.0027. Dr. Wood suggested that the existence of a second, stimulatory receptor could explain Dr. Chen's results and some data of his own showing stimulation. T2-67:14-17; T4-76:4-11; JTX-0433.0027.

Once he received Dr. Freeman's PD-L1 reagents, Dr. Honjo ran his own in vitro experiments on the function of the PD-1/PD-

L1 pathway. T4-77:1-9. These experiments showed that the pathway inhibited the immune response. Id. Unlike in Dr. Wood's experiments, Dr. Honjo used cells derived from a PD-1 knockout mouse as a control, which allowed him to attribute the inhibitory effect specifically to the PD-1/PD-L1 pathway. T4-77:3-12. He reported these results to Dr. Wood via email on December 6 and sent the underlying data on December 11. JTX-0433.0028; JTX-0535.0001-2. Dr. Wood responded with excitement at Dr. Honjo's "outstandingly good result." T4-79:13-80:8; JTX-0433.0029. He noted that he had just run some experiments that also showed inhibition, but he called Dr. Honjo's data "unquestionably the most convincing." JTX-0433.0029.

**B. Dr. Freeman and Dr. Wood File a Provisional Patent Application in November 1999**

On November 10, 1999, about two weeks after the meeting in Cambridge, Dr. Freeman and Dr. Wood filed a provisional patent application. T3-164:15-24; JTX-0045.0004. The application listed only the two as co-inventors. JTX-0045.0006. Dr. Freeman and Dr. Wood did not tell Dr. Honjo about this application at the meeting. T2-125:17-21; T3-166:7-11.

The application claimed methods of modulating the immune response via activating or blocking the PD-1/PD-L1 pathway. JTX-0045.117-119. It explained that the PD-1/PD-L1 interaction inhibits an immune response. T2-219:16-220:5; T3-205:16-206:4;

JTX-0045.0017. Because Dr. Freeman and Dr. Wood theorized that PD-L1, like B7-1 and B7-2, might have a second receptor, the application contained experimental results that show stimulation of T cells in the presence of PD-L1 and disclosed that PD-L1 could have both a stimulatory and inhibitory effect. T3-167:11-24, 169:15-170:9; JTX-0045.0114. The application included a claim in which PD-1 signaling is inhibited to upregulate the immune response to a tumor. JTX-0045.0118. It also listed an embodiment in which PD-L1 levels are increased in tumor cells to enhance the co-stimulatory interaction with PD-L1's second receptor to treat cancer. T3-168:4-169:3; JTX-0045.0084. Dr. Wood and Dr. Freeman submitted a corresponding international application in August 2000. JTX-0073.0001. The PTO issued three patents based on this application beginning in 2004. T3-199:16-200:5; JTX-0008; JTX-0011; JTX-0015.

**C. Dr. Freeman, Dr. Wood, and Dr. Honjo Draft a Journal Article on the PD-1/PD-L1 Pathway in March and April 2000**

Dr. Freeman, Dr. Wood, and Dr. Honjo agreed to write a journal article about the discovery of PD-L1. T4-97:13-98:1. Dr. Wood did the majority of the writing, though he solicited data and coordinated edits from Dr. Freeman and Dr. Honjo. T2-68:12-21; T3-92:22-93:1; T4-108:3-7. The article explained Dr. Honjo's discovery of PD-1, the need to find its ligand to further understand its function, Dr. Wood's hypothesis about the



similarities between PD-L1 and the known B7 ligands, Dr. Freeman's discovery of 292 via a BLAST search, and the results of experiments from Dr. Wood's and Dr. Honjo's laboratories showing that the PD-1/PD-L1 pathway inhibits the immune response. T2-69:8-22, 192:20-193:11; JTX-0305. All three scientists contributed data to the article. T3-94:25-96:9. The authors noted Dr. Chen's seemingly inconsistent results and explained their hypothesis that PD-L1 could have a second receptor. JTX-0305.0007.

Over two rounds of edits on March 19 and April 7, 2000, Dr. Freeman added the following two sentences to the last paragraph of the article: "PD-L1 is also expressed in some cancers, as three ESTs are from human ovarian tumors. This raises the possibility that some tumors may use PD-L1 to inhibit an antitumor immune response." T2-69:23-70:12; T3-91:18-92:14, 100:20-102:22; T4-99:17-100:5; JTX-0305.0007; JTX-0806.0014; JTX-0807.0014. Dr. Honjo did not receive a draft of the article containing Dr. Freeman's addition until April 8. T4-107:20-110:22; JTX-0420.0014; JTX-0568.0008, 11; JTX-0589.0014. The article was published in the Journal of Experimental Medicine on October 2, 2000. T2-68:4-11; JTX-0305.0001.

**D. Dr. Freeman Conducts Immunohistochemistry ("IHC") Experiments in the Winter of 2000**

In January 2000, Dr. Freeman began IHC experiments to determine which human tissues express PD-L1. T2-83:5-84:6; T3-112:11-13; T6-10:4-11. He conducted this work with Dr. David Dorfman, a pathologist at the Brigham and Women's Hospital, and Dr. Julia Brown, a new postdoctoral researcher in his own laboratory. T3-111:20-112:2; T6-8:8-10, 10:18-11:1. Dr. Freeman asked Dr. Dorfman to test both normal and tumor tissues, but he was particularly interested to know whether PD-L1 was expressed in tumors given the pathway's inhibitory function and his discovery of PD-L1 from ovarian tumor ESTs. T2-83:5-6; T3-112:3-10, 112:25-113:5; T6-11:2-7.

Dr. Dorfman shared preliminary results with Dr. Freeman in February and final results in March and April. T3-114:7-12; T6-12:10-12. He found that PD-L1 was highly expressed in placenta and endothelial cells in the heart and on various tumors, including squamous cell carcinoma of the tongue, breast lobular carcinoma, lung and colon adenocarcinoma, and anaplastic large cell lymphoma. T3-113:9-21, 114:13-119:25; JTX-0808-0813. Based on these results and other experiments Dr. Freeman and Dr. Brown conducted between December 1999 and August 2000 that showed PD-L1 expression on mouse and human tumor cells, Dr. Freeman hypothesized that some tumors use the PD-1/PD-L1 pathway to

inhibit an immune response. T3-108:5-110:1, 113:22-114:3; T6-11:21-12:24, 34:14-35:20; JTX-0332.0003. Dr. Freeman, Dr. Dorfman, and Dr. Brown did not publish the IHC results until 2003. T3-120:1-11; T6-13:3-12; JTX-0282.0008.

On March 14, 2000, Dr. Dorfman emailed Dr. Honjo explaining that he was working with Dr. Freeman to study staining of PD-L1 in both normal and cancerous human tissue. T5-10:4-22; JTX-0571.0001. He asked whether Dr. Honjo was interested in collaborating to study PD-1 expression in tumors. JTX-0571.0001. There is no evidence Dr. Honjo responded to Dr. Dorfman's email.

**E. Dr. Freeman Discovers PD-L2 in the Fall of 1999**

Soon after Dr. Wood discovered that 292 binds to PD-1, Dr. Freeman conducted a second BLAST search for molecules similar to 292. T3-102:24-103:15; T4-89:7-15; JTX-0332.0002. He identified another B7-like molecule that shares 38% of its amino acids with PD-L1. T2-75:10-15; T3-102:24-103:7; JTX-0332.0002. Dr. Freeman and Dr. Wood discovered that, like PD-L1, this molecule binds to PD-1 and its interaction with PD-1 inhibits the immune response. T2-75:10-15; T3-103:16-104:8. Between December 1999 and August 2000, Dr. Freeman ran a number of experiments showing that this ligand, which they called "PD-L2," was expressed on mouse tumor cells. T3-108:5-109:17; JTX-0332.0003.

On March 24, 2000, Dr. Freeman emailed Dr. Honjo to tell him about PD-L2. T3-104:25-105:13; JTX-0578.0001. A month and a half later, Dr. Freeman sent the PD-L2 cDNA and its sequence to Dr. Honjo. T3-106:3-22; Honjo Depo. 129:15-130:8; JTX-0599.0001. Dr. Honjo never himself conducted any experiments involving PD-L2. T2-75:16-19; T3-105:23-25; T4-117:22-23.

**F. Dr. Freeman, Dr. Wood, and Dr. Minato Independently Develop Antibodies Throughout 1999 and 2000**

Dr. Freeman, Dr. Wood, and Dr. Minato all separately worked to develop antibodies. Dr. Freeman began just before the October 1999 meeting, and he had a set of anti-PD-L1 antibody candidates by January 2000. T3-87:8-16; T6-9:7-10. Dr. Freeman and Dr. Brown tested how well these candidates bound to PD-L1 and blocked the PD-1/PD-L1 pathway to figure out which antibodies had the most promise for further research. T3-87:17-91:11; T6-9:11-23; JTX-0227.0525-526, 536. They had functional antibodies to use for in vitro experiments by February 2000. T6-9:24-10:3.

Dr. Wood developed anti-PD-1 and anti-PD-L1 antibodies through GI's collaboration with CAT. T2-78:8-18, 91:9-23. Through in vitro testing, they narrowed the pool of almost 150 antibody fragments to 26 unique PD-1 antibodies and 24 unique PD-L1 antibodies. T2-78:8-18, 91:9-94:3; JTX-0108.0026-32. Additional testing demonstrated that some of these antibodies

blocked the inhibitory PD-1/PD-L1 interaction and increased the proliferation of T cells. T2-94:6-97:25; JTX-0108.0046.

As soon as Dr. Honjo received Dr. Freeman's PD-L1 cDNA in late 1999, Dr. Minato started to make anti-PD-L1 antibodies. T6-100:6-17, 101:4-8. By April 2000, he created two mouse anti-PD-L1 antibodies. T6-102:13-22, 103:15-16, 136:25-137:6. He used these antibodies to test for expression of PD-L1 in normal and tumor cell lines in mice. T6-102:4-12, 105:3-9; JTX-0663.0001. The results, presented at his laboratory meeting on September 29, 2000, showed that PD-L1 was expressed on some of the tested cell lines. T6-102:1-3, 105:3-9, 138:12-139:4; JTX-0663.0001.

**G. Dr. Honjo and Dr. Wood's Meeting in March 2000**

On March 27, 2000, Dr. Honjo and Dr. Wood met again at the next SST collaboration meeting in Kyoto, Japan. T2-71:2-25; JTX-0101.0001. Dr. Freeman did not attend this meeting. T2-79:2-9. The attendees discussed the PD-1/PD-L1 collaboration for much of the meeting. Shibayama Depo. 141:21-142:15; JTX-0105.0003. Dr. Taku Okazaki, a graduate student in Dr. Honjo's laboratory, presented his work on PD-1 and autoimmune diseases. T4-94:21-95:24; JTX-0103.0015; JTX-0105.0003-4. Dr. Wood shared his and Dr. Freeman's discovery of PD-L2. T2-74:19-75:6. Dr. Wood also discussed the therapeutic possibilities of the PD-1/PD-L1 pathway, including using antagonistic anti-PD-1 antibodies to block the pathway and enhance the immune response. T2-75:20-

76:9; T4-96:13-21; JTX-0782.0019. He specifically described the possibility of using this technique to treat cancer. T2-76:10-12, 185:7-13, 186:25-187:6; JTX-0105.0004. As part of this discussion, he mentioned his collaboration with CAT to develop antibodies. T2-78:8-18; JTX-0105.0004. The participants in the meeting agreed that there were promising pharmaceutical applications for anti-PD-1 and anti-PD-L1 antibodies. Shibayama Depo. 142:17-22; JTX-0105.0003.

**H. Dr. Iwai Begins In Vivo Tumor Model Studies in March 2000**

Upon her return to Dr. Honjo's laboratory after her leave of absence in early 2000, Dr. Iwai resumed her work on PD-1. Iwai Depo. 83:05-20; JTX-0429.0027. By March 16, 2000, two days after Dr. Dorfman emailed Dr. Honjo about his work with Dr. Freeman, she began a series of experiments to study the effect of the PD-1/PD-L1 pathway on the immune response to tumors. T4-92:17-94:4; JTX-0573.0001, 3. She planned to introduce PD-L1 derived from Dr. Freeman's cDNA into mouse tumors to see whether PD-L1 had any effect on the tumor's growth. T4-90:14-91:1; T5-23:11-14; JTX-0125.0032. She presented her plan at the March 31, 2000 laboratory meeting. T4-90:7-17; JTX-0125.0032.

**V. May 13, 2000 Collaboration Meeting in Seattle**

Dr. Freeman, Dr. Wood, and Dr. Honjo all attended the American Association of Immunologists ("AAI") conference in Seattle, Washington in May 2000, so they decided to meet to update each other about their ongoing PD-L1/PD-L1 work. T2-84:12-18, 85:2-4; T3-106:3-16, 120:18-25, 121:19-122:6; Carreno Depo. 189:16-190:9. Dr. Freeman explained his IHC results showing expression of PD-L1 on a number of normal and tumor cells. T2-84:7-11, 19-23; T3-125:8-25; JTX-0815.0006. He also shared information about PD-L2. T3-123:17-22. Finally, he discussed his development of anti-PD-L1 antibodies and mentioned that he had seven that blocked the binding of PD-1 and PD-L1. T3-91:12-17, 124:21-125:3; JTX-0815.0004. The three scientists discussed the therapeutic possibilities of using antibodies to target the PD-1/PD-L1 pathway to treat cancer. T3-126:6-127:1.

**VI. Developments During the Summer of 2000**

In June 2000, Dr. Honjo found out about the provisional patent application Dr. Freeman and Dr. Wood filed in November 1999. T4-183:2-11, 183:22-184:9; JTX-0616.0001; JTX-0617.0001. Dr. Honjo wrote to both Dr. Wood and Dr. Clark at GI to explain that he should be a joint inventor on the application because he proposed the PD-L1 project based on his prior work on PD-1. T4-183:22-184:9, 190:17-191:2; JTX-0616.0001; JTX-0617.0001. In his email to Dr. Clark, he also noted that he was "very pleased with

[the] recent productive collaboration on PD-1 and PD-L1" and felt that it was "coming close to drug development." JTX-0617.0001. GI hired a lawyer to represent Dr. Honjo, and GI and Dr. Honjo began two years of discussions about his inventorship claim. T2-124:7-14; T4-123:16-24, 124:16-17, 188:4-8, 189:3-8, 190:2-16; JTX-0727.0001; JTX-0820.0001. As discussed below, GI ultimately decided not to add Dr. Honjo as a joint inventor on the patent application. Dr. Honjo never discussed this issue with Dr. Freeman. T4-188:9-15.

On August 23, Dr. Freeman emailed Dr. Honjo seeking feedback on an abstract about PD-L1 for the American Society of Hematology meeting in December. T3-127:23-128:6; T5-25:18-26:4; JTX-0647.0001. In the draft, Dr. Freeman wrote that "PD-L1 is also expressed on some tumors including many lung and breast malignancies and may have a role in attenuating immune attack against these tumors." T3-128:7-12; T5-26:9-24; JTX-0647.0001. Dr. Honjo approved the abstract. T3-128:21-129:2; JTX-0648.0001.

On September 1, Dr. Iwai reported results from her first tumor model experiment at a Honjo laboratory meeting. JTX-0626.0003. In this experiment, she injected PD-L1-expressing melanoma tumors into some mice and non-PD-L1-expressing melanoma tumors into others. Id. The PD-L1-expressing tumors grew faster than the non-PD-L1-expressing tumors. Id.



Dr. Freeman sent Dr. Honjo a draft of the article he and Dr. Wood were writing on PD-L2 on September 6. T3-107:14-19; JTX-0656.0001. This article, which included Dr. Honjo as a co-author, was published in March 2001 and discussed the possibility of targeting the PD-1/PD-L1 pathway as method of treating cancer. T3-110:2-23; JTX-0332.0001, 6. The article also included experimental data from Dr. Freeman's laboratory showing PD-L1 expression in a number of mouse tumor cell lines, including sarcoma, neuroma, and leukemia lines. T3-108:8-109:13, 135:11-18; JTX-0332.0003.

**VII. September 8, 2000 Collaboration Meeting in Cambridge**

On September 8, 2000, Dr. Freeman, Dr. Wood, and Dr. Honjo met again during the next SST collaboration meeting in Cambridge, Massachusetts. T2-85:5-15; T3-129:3-7; JTX-0108.0001-2; JTX-0111.0003. The main topic of the meeting was the PD-1/PD-L1 project. JTX-0111.0003. The meeting began with presentations from a number of GI scientists who worked with Dr. Wood. T3-130:7-12; JTX-0108.0002. They presented data showing that the PD-1/PD-L1 pathway inhibits both helper and killer T cells and that both PD-L1 and PD-L2 inhibit cytokine production. T2-86:23-87:25, 88:19-89:9; JTX-0108.0004, 7, 17. They also explained the results of an in vivo mouse study showing that the presence of antagonistic antibodies to block the inhibitory PD-1/PD-L1

interaction leads to the proliferation of T cells. T2-94:6-97:25; JTX-0108.0046

Dr. Freeman presented the same slides he used at the May 2000 meeting in Seattle. T3-129:13-130:6. He shared information on gene structures of PD-L1 and PD-L2. T2-98:17-20. He reported that he had found PD-L2 expression on dendritic cells, suggesting that it plays a role in immune inhibition. T2-98:21-99:9; JTX-0113.0001. Finally, he showed the IHC staining slides he received from Dr. Dorfman showing expression of PD-L1 on certain normal and tumor tissues. T2-99:10-20; T3-126:1-3, 132:23-133:15; T4-113:2-21; JTX-0100.0108-109; JTX-0113.0001. Dr. Freeman explained that he found PD-L1 expressed on all thymomas, some lung carcinomas, some tongue squamous cell carcinomas, and some T cell neoplasms, primarily anaplastic large cell lymphoma. T2-101:12-103:1; JTX-0100.0108-109; JTX-0113.0002.

Dr. Honjo was not scheduled to speak, but he shared an update after one of his graduate students gave a presentation. T2-103:5-11; JTX-0108.0002; JTX-0113.0002. As part of his update, Dr. Honjo presented the data from Dr. Iwai's tumor model experiment that she had generated a week earlier. T2-103:11-15, 104:6-23; T4-114:18-115:17; JTX-0116.0004.

**VIII. Dr. Honjo and Dr. Iwai Conduct In Vivo Mouse Tumor Model Experiments and the Collaboration Ends**

On September 26, 2000, Dr. Honjo emailed Dr. Freeman to ask for his human anti-PD-L1 monoclonal antibodies for use in his experiments. JTX-0661.0001. He added that, "Needless to say, we will do [the experiments] as collaboration." Id. As requested, Dr. Freeman sent Dr. Honjo some of his antibodies pursuant to a new Material Transfer Agreement. Honjo Depo. 181:23-183:11; JTX-0170.0001. Dr. Wood also provided Dr. Honjo with his own human anti-PD-L1 antibodies in October 2000. Honjo Depo. 445:15-446:4; JTX-0637.0013.

On October 27, 2000, Dr. Iwai reported the results of additional mouse tumor model experiments at another laboratory meeting in Japan. T4-115:18-116:20; JTX-0662.0003. The experiments confirmed the results she presented in September that PD-L1-expressing melanoma tumors grew faster in mice than non-PD-L1-expressing melanoma tumors. JTX-0662.0003. She also showed that PD-L1-expressing tumors grew less quickly in PD-1 knockout mice than in mice that expressed PD-1. T4-116:14-20; JTX-0662.0003. These results indicated to Dr. Iwai and Dr. Honjo that blocking PD-1 can suppress tumor growth. T4-116:21-24. Dr. Honjo, Dr. Minato, and Dr. Iwai began discussing using antibodies to block the PD-1/PD-L1 pathway as a method of treating cancer. T4-116:25-117:4, 118:13-18; T6-107:7-12; Honjo

Depo. 29:8-30:6; JTX-0662.0003. Defendants take the position that they conceived of the inventions in the Honjo patents at this point in October 2000.

Building off Dr. Iwai's results, Dr. Honjo and Dr. Minato conducted other experiments over the next two years to study the effect of the PD-1/PD-L1 pathway on tumors. Dr. Minato's laboratory examined the expression of PD-L1 on tumor and normal cells and how PD-L1 interacts with PD-1 on T cells. T6-110:13-15. Dr. Honjo's laboratory used knockout mice to investigate further how tumors grow in the presence or absence of PD-1 and PD-L1. T6-110:10-13; Iwai Depo. 92:24-94:3; JTX-0691.0001. Dr. Honjo also conducted experiments that showed less tumor growth after administration of anti-PD-1 antibodies. Iwai Depo. 144:24-145:12; JTX-0739.0005. The results of these experiments were not shared with Dr. Freeman and Dr. Wood.

Dr. Wood, Dr. Honjo, and others from Ono and GI discussed the PD-1/PD-L1 pathway one last time at an SST collaboration meeting on April 2, 2001. JTX-0118.0001. Dr. Beatriz Carreno from GI talked specifically about upregulating T cells to treat tumors. T2-110:2-11; JTX-0119.0001. Because there is no evidence of additional meetings, data sharing, or the like after this date, it appears the collaboration effectively ended.

**IX. Dr. Honjo and Ono File Patent Application in July 2002**

Meanwhile, attorneys for GI and Dr. Honjo were still discussing Dr. Honjo's inventorship claim for the November 1999 patent application. On April 12, 2002, Dr. Honjo sent a letter to Dr. Clark at GI expressing his belief that GI was not responding to his claim "faithfully." JTX-0820.0001. He told Dr. Clark that he felt "obliged to fight against [the] unfair and unfaithful attitude of the G.I. management." Id. Four days later, an attorney for GI wrote to Dr. Honjo's attorney explaining why GI would not list Dr. Honjo as a joint inventor. JTX-0727.0001. He stated that GI intended to allow the PTO examiner to make the final inventorship determination and encouraged Dr. Honjo to participate in the process. JTX-0727.0001-2.

In the wake of this angry exchange, Dr. Honjo and Ono filed their own Japanese patent application on July 3, 2002 claiming methods of treating cancer by blocking the PD-1/PD-L1 pathway. T4-119:5-13; JTX-0076.0001. The application contained the results of the experiments Dr. Honjo, Dr. Iwai, and Dr. Minato conducted beginning in 2000. T4-119:14-17. It named only the three as inventors, thereby excluding Dr. Freeman and Dr. Wood. T4-119:5-13; JTX-0076.0001. Dr. Honjo, Dr. Iwai, and Dr. Minato subsequently published the results of their in vivo tumor model

experiments on September 17, 2002 in PNAS. T4-119:18-24; JTX-0322.0001.

A year later, Dr. Honjo and Ono filed an international patent application claiming methods of treating cancer by administering antibodies to block the PD-1/PD-L1 pathway. JTX-0001.0002. In addition to Dr. Honjo, Dr. Minato, and Dr. Iwai, this application named Dr. Shiro Shibayama, an Ono scientist, as an inventor. T4-120:25-121:2; JTX-0001.0002. Dr. Shibayama attended collaboration meetings in 1999 and 2000. JTX-0090.0001; JTX-0108.0002. He also conducted one in vitro experiment in February 2003, the results of which were included in the patent application. T4-121:3-8; T5-17:23-18:13; Shibayama Depo. 13:7-18, 30:25-31:2, 46:22-47:3; JTX-0001.0019.

The PTO issued six patents from 2009 to 2016: Patent No. 7,595,048 on September 29, 2009 ("the '048 Patent"); Patent No. 8,168,179 on May 1, 2012 ("the '179 Patent"); Patent No. 8,728,474 on May 20, 2014 ("the '474 Patent"); Patent No. 9,067,999 on June 30, 2015 ("the '999 Patent"); Patent No. 9,073,994 on July 7, 2015 ("the '994 Patent"); and Patent No. 9,402,899 on August 2, 2016 ("the '899 Patent"). JTX-0001.0002; JTX-0002.0002; JTX-0003.0002; JTX-0004.0002; JTX-0005.0002; JTX-

0006.0001. The six Honjo patents list Dr. Honjo, Dr. Minato, Dr. Iwai, and Dr. Shibayama as inventors.<sup>8</sup> Id.

**X. BMS Develops Nivolumab with Exclusive License to the Honjo Patents**

In the mid-2000s, Medarex, an American biotechnology company, negotiated with Ono to secure an exclusive license to the Honjo patents. T6-43:12-15, 44:21-45:1. Medarex began clinical trials on nivolumab, an anti-PD-1 monoclonal antibody, as a treatment for cancer in 2006. T6-40:25-41:6, 43:6-15, 47:10-15. On July 22, 2009, BMS acquired Medarex along with its drug pipeline and exclusive license to the Honjo patents. T6-40:2-5, 44:8-13, 68:21-24. At the time of the acquisition, nivolumab was in the first of three phases of clinical trials. T6-46:8-47:9.

Since the acquisition, BMS has run approximately 150 clinic trials for nivolumab, including some at Dana-Farber. T6-48:11-49:2. BMS is still conducting trials for new indications and began new trials after this lawsuit was initiated. T6-49:21-50:10, 72:19-73:12. Beginning in 2008, Medarex and BMS published studies with the results of the trials. T6-54:2-60:4; JTX-0281; JTX-0825-826. BMS spent around \$3 billion in research and development for nivolumab between 2011 and 2018. T6-51:7-17.

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<sup>8</sup> Dr. Wood and GI filed a patent application in 2003 claiming the specific anti-PD-1 antibodies they had developed. T2-203:18-217:2; JTX-0061.0002, 41.

Nivolumab was first approved in Japan in July 2014 and then in the United States that December. T6-49:3-12. The U.S. Food and Drug Administration initially approved it for late-stage pretreated patients with melanoma and has now extended its approval for fifteen indications covering more than nine different cancers. T6-49:13-20. BMS launched nivolumab commercially in January 2015 under the name "Opdivo." T6-40:17-21, 71:13-17. BMS earned revenues on sales of nivolumab of \$4.9 billion and \$6.7 billion in 2017 and 2018, respectively. T6-52:6-8, 72:2-4.

Despite BMS's exclusive rights to the Honjo patents, other pharmaceutical companies have developed their own anti-PD-1 and anti-PD-L1 antibodies, including Merck, Regeneron, Novartis, Tesaro, Roche Genentech, and AstraZeneca. T6-60:24-61:5, 62:17-22. BMS filed patent infringement lawsuits against these companies but has not sought to take their products off the market. T6-61:20-63:10.

#### **XI. Dana-Farber Initiates This Lawsuit**

Dr. Freeman learned about the '048 Patent in 2010. T3-195:17-23. He did not realize the patent used his discoveries until sometime between 2012 and 2014. T3-197:5-19. He did not sue then because he did not know an inventor could bring a lawsuit to be added to a patent. T3-198:11-14. Dr. Wood did not focus on the Honjo patents until Dana-Farber filed its lawsuit,



although he admitted he might have known about them earlier. T2-127:12-24. Neither Dr. Freeman nor Dr. Wood talked to Dr. Honjo about inventorship of the Honjo patents. T2-126:17-127:2; T3-197:20-25. Dana-Farber became aware of the '048 and '179 Patents in September 2014 after the initiation of patent infringement litigation between BMS and Merck. Hodges Depo. 54:13-55:04, 58:5-17. Dana-Farber learned about the other Honjo patents shortly after they issued between 2014 and 2016. Hodges Depo. 55:18-23, 60:2-14, 62:12-17.

In March 2015, in connection with his consulting work, Dr. Freeman told Novartis, a Swiss pharmaceutical company, about his collaboration with Dr. Honjo and Dr. Wood on the PD-1/PD-L1 pathway. T3-201:7-202:19; Hodges Depo. 99:6-13, 101:1-10. Novartis was interested in Dr. Freeman's collaboration and his potential inventorship claim because it was developing anti-PD-1 antibodies and anticipated being sued by BMS for patent infringement. Hodges Depo. 120:2-13, 122:20-123:15. Novartis thought that if it entered into an agreement to license whatever rights Dana-Farber might have to the Honjo patents and then brought suit with Dana-Farber to correct inventorship, it could participate in any settlement BMS might strike with the other companies developing antibodies targeting the PD-1/PD-L1 pathway. Id. Realizing that Dr. Freeman might have a claim to be added as an inventor on the Honjo patents, Novartis began to

gather more information from him about the collaboration. Hodges Depo. 90:6-21; JTX-0829.0001.

On June 6, 2015, Novartis and Dr. Freeman reached out to Dana-Farber to discuss his inventorship claim. Hodges Depo. 97:18-98:3, 99:14-21, 100:6-11. Until these discussions began, Dana-Farber did not know the extent of Dr. Freeman's collaboration with Dr. Honjo. Hodges Depo. 113:12-114:2. Dana-Farber, Novartis, and Dr. Freeman discussed bringing an inventorship claim. Hodges Depo. 145:11-146:6. Ultimately, Dana-Farber decided to proceed without an agreement with Novartis because of its policy of not granting exclusive licenses, which Novartis was seeking if Dr. Freeman were added to the patents. Hodges Depo. 119:11-22, 145:11-146:6. Dana-Farber filed this lawsuit on its own on September 25, 2015.

### **XII. Dr. Honjo Wins the Nobel Prize**

In 2018, Dr. Honjo was awarded the Nobel Prize in Physiology or Medicine for his work on treating cancer via suppression of negative immune regulation. T4-13:1-11. During his Nobel lecture in Sweden, he presented a slideshow listing "[m]ajor outside collaborators" with whom he had worked. JTX-0828.0002. Under "Cancer immunotherapy by PD-1 blockade," Dr. Honjo listed four names. Id. Three were colleagues at Kyoto University, including Dr. Minato. Id. The fourth was Dr. Freeman. Id.

**EXPERT OPINIONS**

Both sides offered an expert to give an opinion on whether the contributions Dr. Freeman and Dr. Wood allegedly made to conception of the Honjo patents were significant.

**I. Dana-Farber's Expert: Dr. Kenneth Murphy**

Dr. Kenneth Murphy, Dana-Farber's expert, is a professor of pathology and immunology at Washington University in St. Louis. T5-29:14-22. He received a medical degree and PhD in neuroscience from Johns Hopkins University and completed an anatomic pathology residency at Washington University in St. Louis. T5-30:1-10. For the past ten years, his research has focused on the biology, function, and development of dendritic cells, including the use of dendritic cells in antitumor immune responses. T5-30:14-31:6. He is the first author of a leading immunology textbook. T5-31:15-32:3.

In determining whether Dr. Freeman's and Dr. Wood's contributions were significant, he applied a "deletion test" that asked whether the invention would have been possible if Dr. Freeman and/or Dr. Wood had not made a given contribution. T5-51:15-22. This test, essentially but-for causation, does not accurately reflect the joint inventorship standard, which will be discussed below. See Yeda Research & Dev. Co. v. Imclone Sys., Inc., 443 F. Supp. 2d 570, 621 (S.D.N.Y. 2006). Nevertheless, I credit much of Dr. Murphy's opinion as to the

scientific significance of Dr. Freeman's and Dr. Wood's contributions.

Dr. Murphy opined that Dr. Freeman and Dr. Wood are joint inventors of all six patents because they made eight significant contributions (which the parties refer to as "pillars") to conception of the patents. T5-34:20-35:7, 38:3-5. First, Dr. Murphy explained that Dr. Freeman discovered and characterized 292 through a BLAST search and in vitro experiments. T5-38:5-6, 41:15-18, 48:16-49:5. This contribution was significant because PD-L1, as 292 is now known, is an essential element of all of the claims that involve the administration of an anti-PD-L1 antibody or administration of an anti-PD-1 antibody to a tumor that expresses PD-L1. T5-39:16-40:16. Dr. Freeman's discovery of 292 through ovarian tumor ESTs also piqued his interest in 292 and its relationship to cancer because other B7 ligands are only found on immune cells. T5-42:25-43:22.

Second, Dr. Freeman and Dr. Wood jointly discovered that PD-L1 is a ligand for PD-1. T5-38:7-8. This discovery was significant because the Honjo patents rely on blocking the interaction between PD-1 and its ligand. T5-54:4-15. Developing a successful method of blocking the PD-1/PD-L1 interaction requires knowledge of the structure of PD-L1. T5-61:18-24.

Third, Dr. Murphy opined that Dr. Freeman and Dr. Wood discovered that the binding of PD-1 by PD-L1 inhibits T cell activation through in vitro experiments they shared with Dr. Honjo at the October 1999 meeting. T5-38:9-10, 79:2-10. Knowing that the PD-1/PD-L1 pathway is inhibitory was essential to understanding that antibodies that block the pathway could stimulate an immune response to treat cancer. T5-78:10-79:1.

Fourth, in his view, Dr. Freeman contributed the idea of treating cancer by blocking the PD-1/PD-L1 pathway through his edits to one of the articles he co-authored with Dr. Wood and Dr. Honjo. T5-38:11-13, 80:24-81:16. Before his suggestion, Dr. Honjo's work on PD-1 was focused on autoimmunity. T5-82:13-83:3. This idea was highly significant because the patents claim variants of the method Dr. Freeman proposed. T5-81:17-24.

Fifth, Dr. Murphy explained that Dr. Freeman provided PD-L1 reagents that Dr. Iwai used in her in vivo mouse tumor model experiments. T5-38:14-17. Without these reagents, Dr. Iwai would not have been able to conduct these critical experiments. T5-83:4-84:2.

Sixth, through his IHC work with Dr. Dorfman, Dr. Freeman discovered that human PD-L1 is expressed by a variety of different primary human solid tumors. T5-38:18-20, 92:17-93:18. Dr. Iwai's experiments demonstrated that mice tumors expressing PD-L1 inhibited an antitumor immune response, but these results

only suggest a method of treating cancer in humans if human tumors also express PD-L1. T5-89:19-90:7. The expression of PD-L1 is also an essential element of claims that recite a method treating tumors that express or overexpress PD-L1. T5-90:13-22. And certain dependent claims refer specifically to the types of tumors that Dr. Freeman discovered express PD-L1 in his IHC experiments. T5-98:12-99:9.

Seventh, Dr. Freeman and Dr. Wood discovered and characterized PD-L2 as a second ligand for PD-1. T5-38:21-22. Many of the claims in the Honjo patents refer to tumors that express PD-L2, and Dr. Honjo and the other named inventors did no experimental work themselves on PD-L2. T5-100:21-101:16.

Eighth and finally, Dr. Murphy opined that Dr. Freeman and Dr. Wood developed human antibodies that blocked the interaction between PD-1 and PD-L1. T5-38:23-25. Since some antibodies fail to block the receptor-ligand interaction they are meant to target, it was significant to Dr. Honjo's conception of the inventions to know that antibodies can in fact block the PD-1/PD-L1 pathway. T5-101:17-103:6.

## **II. Defendants' Expert: Dr. Mark Greene**

Dr. Mark Greene, Defendants' expert, is a professor of medical science at the University of Pennsylvania. T6-157:22-25. His research focuses on tumor immunology and receptor biology. T6-158:12-15. He received a medical degree and PhD in tumor

immunology from the University of Manitoba and practices as an internist specializing in oncology. T6-158:20-160:5.

Like Samson, Dr. Greene tries to pull down all the pillars supporting the claim of joint inventorship. He emphasized the importance of conducting in vivo experiments to understand the impact of a receptor-ligand interaction because in vitro experiments do not reflect the full complexity of all of the interactions in a living organism. T6-164:11-165:9, 166:18-167:3. Given the large number of receptor-ligand interactions that regulate the immune system, he stressed that a scientist must study the structure and function of a specific interaction to know if it is a useful target for medical treatment. T6-175:16-25. Accordingly, he opined that none of Dr. Freeman's and Dr. Wood's eight purported contributions to conception of the inventions in the Honjo patents was significant, either alone or in combination, because Dr. Freeman and Dr. Wood lacked a fundamental understanding of the function of the PD-1/PD-L1 pathway in the immune system. T6-185:21-186:4; T7-43:2-12.

As to the three first alleged contributions, Dr. Greene explained that when Dr. Freeman discovered 292, he did not know its function. T6-194:21-195:1. Because many cells make short DNA fragments that are not ultimately expressed as proteins, the fact that the 292 ESTs came from ovarian tumors could not tell Dr. Freeman that 292 has a functional effect in cancer. T6-

195:2-24. Dr. Freeman's subsequent discovery that 292 did not bind to CD28 or CTLA-4 contributed little to his understanding of 292's function because of the myriad of other receptors to which 292 could bind. T6-197:15-198:4. Dr. Wood's initial experiments showing binding of 292 to PD-1 demonstrated a weak interaction and did not reveal anything about the pathway's function. T6-200:5-201:14. Dr. Greene explained that Dr. Freeman and Dr. Wood's inclusion of an example in their November 1999 provisional patent application showing stimulation from PD-L1 underscores that they did not truly understand PD-L1's inhibitory effect. T6-202:4-203:18. Dr. Wood also expressed confusion about Dr. Chen's published results showing stimulation. T7-6:5-8:13. Instead, Dr. Honjo was the one who definitively showed that the interaction between PD-1 and PD-L1 is inhibitory through his controlled experiment in December 1999. T7-8:14-9:23, 13:2-23.

For the fourth pillar, Dr. Greene explained that Dr. Freeman's suggestion of treating cancer by blocking the PD-1/PD-L1 pathway at the October 1999 meeting was pure speculation without evidence to support that it would work. T7-19:7-19. Dr. Freeman's addition of two sentences to one of the papers the three scientists co-authored about the possibility that tumors use PD-L1 to inhibit an antitumor immune response was also purely speculative. T7-22:1-11. In addition, Dr. Honjo and



Dr. Iwai started to work on in vivo tumor model experiments before receiving a draft of the article with Dr. Freeman's addition. T7-22:12-23:17. Dr. Freeman's provision of reagents to Dr. Honjo (the fifth alleged contribution) was not significant because he merely provided material to use in an experiment without explaining its function. T7-27:14-21.

Dr. Greene downplayed the sixth purported contribution, Dr. Freeman's IHC results showing expression of PD-L1 on human tumors, because an IHC experiment does not indicate anything about the functional role of the molecule. T7-32:1-33:12. In fact, the results would have discouraged a scientist from targeting the PD-1/PD-L1 pathway to treat cancer because they showed expression of PD-L1 on normal cells as well. T7-33:13-19. Dr. Freeman and Dr. Wood's discovery and characterization of PD-L2 (the seventh alleged contribution) was not significant because another scientist had already discovered PD-L2's sequence and the Honjo patents claim use of only anti-PD-1 and anti-PD-L1 antibodies. T7-34:24-35:9, 40:6-8.

As to the eighth contribution, Dr. Freeman and Dr. Wood did not make a significant contribution through their development of blocking antibodies, as use of antibodies to block receptor-ligand interactions was state of the art at the time and Dr. Honjo had already developed his own anti-PD-1 antibodies. T7-40:14-41:23.

CONCLUSIONS OF LAW

**I. Joint Inventorship**

**A. Legal Standard**

"[W]henver . . . through error an inventor is not named in an issued patent, the [PTO] may, on application of all parties and assignees, with proof of the facts and such other requirements as may be imposed, issue a certificate correcting such error." 35 U.S.C. § 256(a). A putative joint inventor "who was not listed as an inventor on the patent may bring a cause of action to correct inventorship in a district court." Vapor Point LLC v. Moorhead, 832 F.3d 1343, 1348 (Fed. Cir. 2016) (per curiam) (quoting Eli Lilly & Co. v. Aradigm Corp., 376 F.3d 1352, 1356 n.1 (Fed. Cir. 2004)). A court "may order correction of the patent on notice and hearing of all parties concerned." 35 U.S.C. § 256(b).

35 U.S.C. § 116(a) establishes 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.

This standard "is one of the muddiest concepts in the muddy metaphysics of patent law." In re VerHoef, 888 F.3d 1362, 1365

(Fed. Cir. 2018) (quoting Mueller Brass Co. v. Reading Indus., Inc., 352 F. Supp. 1357, 1372 (E.D. Pa. 1972)).

An individual qualifies as "a joint inventor only if he contributes to the conception of the claimed invention." Eli Lilly, 376 F.3d at 1359. Conception "requires a 'definite and permanent idea of an operative invention, including every feature of the subject matter sought to be patented.'" In re VerHoef, 888 F.3d at 1366 (quoting Sewall v. Walters, 21 F.3d 411, 415 (Fed. Cir. 1994)). "An idea is definite and permanent when the inventor has a specific, settled idea, a particular solution to the problem at hand, not just a general goal or research plan." Id. (quoting Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223, 1228 (Fed. Cir. 1994)).

Conception is complete when "only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation." Bd. of Educ. ex rel. Bd. of Trs. of Fla. State Univ. v. Am. Bioscience, Inc., 333 F.3d 1330, 1338 (Fed. Cir. 2003) (quoting Ethicon, Inc. v. U.S. Surgical Corp., 135 F.3d 1456, 1460 (Fed. Cir. 1998)). As such, a "bare idea" or "general hope" of an invention is not enough for conception. Burroughs Wellcome, 40 F.3d at 1229-30. But an inventor "need not know that his invention will work for conception to be complete," as long as he has a "complete mental picture of the invention." Id. at 1228. "A conception is not complete if the

subsequent course of experimentation, especially experimental failures, reveals uncertainty that so undermines the specificity of the inventor's idea that it is not yet a definite and permanent reflection of the complete invention as it will be used in practice." Id. at 1229.

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, 376 F.3d at 1358 (quoting Fina Oil & Chem Co. v. Ewen, 123 F.3d 1466, 1473 (Fed. Cir. 1997)). In particular, a putative joint inventor "need not demonstrate that he made a contribution equal in importance to the contribution made by the listed inventors." Id. Instead, courts ask whether the contribution is "not insignificant in quality, when . . . measured against the dimension of the full invention." In re VerHoef, 888 F.3d at 1366 (quoting Pannu v. Iolab Corp., 155 F.3d 1344, 1351 (Fed. Cir. 1998)). An individual who proposes the idea for what becomes "an essential feature of the claimed invention" has made a sufficient contribution and qualifies as a joint inventor. Id. On the other hand, simply explaining well-known concepts or the state of the art does not make one a joint inventor of another's invention, see id., nor does suggesting "an idea of a result to be accomplished, rather than means of accomplishing it," Nartron Corp. v. Schukra U.S.A., Inc., 558 F.3d 1352, 1359 (Fed. Cir. 2009) (quoting Garrett Corp. v.

United States, 422 F.3d 874, 881 (Cl. Ct. 1970)). A joint inventor's contribution can be purely experimental. See Fina Oil, 123 F.3d at 1473.

Collaboration is a key requirement for joint inventorship. See Falana v. Kent State Univ., 669 F.3d 1349, 1357 (Fed. Cir. 2012) ("A joint invention is the product of a collaboration between two or more persons working together to solve the problem addressed." (quoting Burroughs Wellcome, 40 F.3d at 1227)). Joint inventorship arises only "when collaboration or concerted effort occurs -- that is, when the inventors have some open line of communication during or in temporal proximity to their inventive efforts." Eli Lilly, 376 F.3d at 1359. Put differently, a putative "joint inventor seeking to be listed on a patent must demonstrate that his labors were conjoined with the efforts of the named inventors." Id.; see also Vanderbilt Univ. v. ICOS Corp., 601 F.3d 1297, 1303 (Fed. Cir. 2010) ("The interplay between conception and collaboration requires that each co-inventor engage with the other co-inventors to contribute to a joint conception."). "Individuals cannot be joint inventors if they are completely ignorant of what each other has done until . . . after their individual independent efforts" or are "totally independent of each other." Kimberly-Clark Corp. v. Proctor & Gamble Distrib. Co., 973 F.2d 911, 917 (Fed. Cir. 1992). On the other hand, joint inventors need "not

physically work on the invention together or at the same time.”  
Falana, 669 F.3d at 1357.

Inventorship is determined on a claim-by-claim basis, and a putative co-inventor need only show that he contributed to the conception of one claim. See Vapor Point, 832 F.3d at 1348-49. A joint inventorship analysis proceeds in two steps. First, a court must construe the claims “to determine the subject matter encompassed thereby.” Gemstar-TV Guide Int’l, Inc. v. Int’l Trade Comm’n, 383 F.3d 1352, 1381-82 (Fed. Cir. 2004). Second, a court must compare “the alleged contributions of each asserted co-inventor with the subject matter of the correctly construed claim to determine whether the correct inventors were named.” Id. at 1382. “The determination of whether a person is a joint inventor is fact specific, and no bright-line standard will suffice in every case.” Fina Oil, 123 F.3d at 1473.

“Because the issuance of a patent creates a presumption that the named inventors are the true and only inventors, the burden of showing . . . nonjoinder of inventors is a heavy one and must be proved by clear and convincing evidence.” Falana, 669 F.3d at 1356 (quoting Bd. of Educ., 333 F.3d at 1337). Evidence meets the clear and convincing standard if it “place[s] in the ultimate factfinder an abiding conviction that the truth of its factual contentions are highly probable.” Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1359 n.5 (Fed. Cir. 2007)

(alteration in original) (quoting Colorado v. New Mexico, 467 U.S. 310, 316 (1984)).

**B. Claim Construction**

The first step in a joint inventorship analysis is to construe the scope of the claims at issue. See Gemstar-TV Guide, 383 F.3d at 1381-82. "Only by doing so is it possible to compare the contributions of the claimed co-inventor with the subject matter of the properly construed claim to determine whether the correct inventors were named." Finkelstein v. Mardkha, 495 F. Supp. 2d 329, 338 (S.D.N.Y. 2007). However, a court need not hold a claim construction hearing if the parties do not request one. See Eli Lilly, 376 F.3d at 1360. In the absence of such a request, "the claims are given their ordinary and customary meaning as they would have been understood by a person of ordinary skill in the art at the time of the invention." Scott v. Zimmer, Inc., 889 F. Supp. 2d 657, 663 n.2 (D. Del. 2012); see also Stryker Corp. v. Zimmer, Inc., 837 F.3d 1268, 1272 (Fed. Cir. 2016) ("In construing a claim term, we look at the term's plain and ordinary meaning as understood by a person of ordinary skill in the art."). Neither party requested a claim construction hearing, and both parties concede that the claims should be given their plain and ordinary meaning.

### C. Corroboration

As a threshold issue, Defendants assert that Dana-Farber has failed to present sufficient corroboration of its joint inventorship claim. To meet the clear and convincing evidence standard, putative joint inventors must provide some corroborating evidence instead of relying solely on their own testimony. Symantec Corp. v. Comput. Assocs. Int'l, Inc., 522 F.3d 1279, 1295 (Fed. Cir. 2008). This requirement for corroboration "addresses the concern that a party claiming inventorship might be tempted to describe his actions in an unjustifiably self-serving manner in order to obtain a patent." Chen v. Bouchard, 347 F.3d 1299, 1309 (Fed. Cir. 2003). As such, the corroboration requirement only applies to a putative joint inventor's testimony; documentary evidence does not need corroboration before a court may consider it. Price v. Symsek, 988 F.2d 1187, 1195 (Fed. Cir. 1993).

Courts use a "rule of reason" analysis to determine if a putative joint inventor has sufficiently corroborated his testimony. Symantec Corp., 522 F.3d at 1295. This analysis requires considering "all pertinent evidence" to judge "the credibility of the inventor's story." Id. (quoting Gemstar-TV Guide, 383 F.3d at 1382). "There is no particular formula that an inventor must follow in providing corroboration of his testimony." Chen, 347 F.3d at 1309. "[R]ecords made



contemporaneously with the inventive process” are the most reliable corroborating evidence, but courts also consider “[c]ircumstantial evidence of an independent nature” and “oral testimony from someone other than the alleged inventor.” Linear Tech. Corp. v. Impala Linear Corp., 379 F.3d 1311, 1327 (Fed. Cir. 2004). Oral testimony of one putative joint inventor is not enough on its own to corroborate the oral testimony of another. See TransWeb, LLC v. 3M Innovative Props. Co., 812 F.3d 1295, 1302 (Fed. Cir. 2016) (“We have generally been most skeptical of oral testimony that is supported only by testimonial evidence of other interested persons.” (emphasis added)). But such testimony can help to corroborate along with other evidence.<sup>9</sup> Adenta GmbH v. OrthoArm, Inc., 501 F.3d 1364, 1372-73 (Fed. Cir. 2007) (upholding a district court’s conclusion that there was sufficient corroboration where the plaintiff provided oral testimony from both interested and disinterested witnesses and documentary evidence).

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<sup>9</sup> Citing the Federal Circuit’s decision in Medichem, S.A. v. Rolabo, S.L., Defendants claim that the “testimony of one co-inventor cannot be used to help corroborate the testimony of another” at all. 437 F.3d 1157, 1171 (Fed. Cir. 2006). The Federal Circuit has not repeated this statement from Medichem in a published opinion, and this proposition of law appears to be an overbroad reading of the case the Federal Circuit cited. See Lacks Indus., Inc. v. McKechnie Vehicle Components USA, Inc., 322 F.3d 1335, 1350 (Fed. Cir. 2003) (refusing to accept the oral testimony of interested witnesses as sufficient corroboration on its own in the absence of corroborating documents).

Dana-Farber has presented sufficient independent corroborating evidence to satisfy the rule of reason analysis. The record includes agendas from all but one of the three scientists' collaboration meetings, slides from the meetings, numerous emails and letters exchanged by the three scientists in 1999 and 2000, and published journal articles. These documents explain Dr. Freeman's and Dr. Wood's hypotheses, experimental results, and conclusions and are alone sufficient to constitute corroborating evidence. See Allergan, Inc. v. Apotex Inc., 754 F.3d 952, 968 (Fed. Cir. 2014) (noting that corroborating evidence may be "found through multiple written documents").

In addition to the plethora of documents, Dana-Farber provided corroboration from a number of witnesses. Dr. Brown corroborated Dr. Freeman's testimony about his antibody and IHC work. Dr. Carreno, a former GI scientist, confirmed that the trio met in May 2000 in Seattle. Dr. Collins at GI testified that Dr. Freeman reached out about finding 292's receptor and that Dr. Wood discovered that 292 is a ligand for PD-1.

Especially significantly, Dr. Honjo, who was present for the trial, confirmed most of the events to which Dr. Freeman and Dr. Wood testified. The "cohesive web of allegedly corroborative evidence" leaves no doubt that Dr. Freeman and Dr. Wood testified truthfully about the experiments they conducted, the communications they exchanged, and the substance of the meetings

they attended. Hahn v. Wong, 892 F.2d 1028, 1033 (Fed. Cir. 1989) (quotation omitted); see also NFC Tech., LLC v. Matal, 871 F.3d 1367, 1372 (Fed. Cir. 2017) (“At bottom, the goal of the analysis is to determine whether the inventor’s story is credible.” (quotation omitted)).

Faced with this flood of corroborating evidence, Defendants do not contest Dana-Farber’s satisfaction of the rule of reason analysis. Instead, they argue the Court cannot consider certain insufficiently corroborated facts. They challenge the contents of Dr. Freeman’s presentations at the October 1999 and May 2000 meetings because only Dr. Wood and Dr. Freeman testified about what he said and his slides are unidentified and undated. And they contend that an unwitnessed laboratory notebook is insufficient to corroborate Dr. Freeman’s testimony about the results of his September 1999 experiments that showed the inhibitory effect of 292.

This argument misconstrues the corroboration requirement. The Federal Circuit has “repeatedly rejected an element-wise attack on corroboration of oral testimony.” TransWeb, 812 F.3d at 1302. A putative joint inventor need not corroborate every detail of his testimony. See, e.g., Ohio Willow Wood Co. v. Alps S., LLC, 735 F.3d 1333, 1348 (Fed. Cir. 2013); Cooper v. Goldfarb, 154 F.3d 1321, 1330 (Fed. Cir. 1998); Ethicon, 135 F.3d at 1464. In fact, such a requirement would be “the

antithesis of the rule of reason." Cooper, 154 F.3d at 1331 (quoting Knorr v. Pearson, 671 F.2d 1368, 1374 (C.C.P.A. 1982)). The rule of reason is instead a "flexible . . . demand for independent evidence that, as a whole, makes credible the testimony of the purported" joint inventor. TransWeb, 812 F.3d at 1302 (quoting Fleming v. Escort Inc., 774 F.3d 1371, 1377 (Fed. Cir. 2014)).

Defendants cite to the Federal Circuit's recent decision in Aparator Miitors ApS v. Kamstrup A/S, 887 F.3d 1293 (Fed. Cir. 2018), to support their argument that the Court must ignore specific facts that are insufficiently corroborated. The case is easily distinguishable. In Aparator, the Federal Circuit found that the appellant had failed to antedate a prior art reference because it did not present independent corroborating evidence of its inventor's testimony concerning his conception of the invention. Id. at 1296. The copies of two emails to which the inventor testified that he had attached documents with drawings demonstrating the invention did not actually show that any documents were attached. Id. The inventor testified that the date listed on another document was not the date he created it, but he had no independent evidence of this. Id. And while an unwitnessed laboratory notebook has some corroborative value, it could not on its own corroborate the inventor's testimony of conception. Id. at 1297.

Unlike the appellant in Apator, Dana-Farber has presented hundreds of documents, as well as testimony from a number of independent witnesses, that corroborate the vast majority of Dr. Freeman and Dr. Wood's narrative. Dana-Farber also offered independent corroborating evidence for the testimony Defendants challenge. Dr. Shibayama from Ono was present at the first collaboration meeting in October 1999. His notes from the meeting contain information from Dr. Freeman's slides, specifically that 292 shares around 20% of its amino acids with B7-1 and B7-2, Dr. Freeman discovered 292 from a human ovary tumor EST, and he had membrane and secreted versions of 292. JTX-0095.0003, 5; JTX-0097.0003-4; JTX-0768.0082. While Dr. Shibayama's notes do not attribute this information to Dr. Freeman, they provide some corroboration of what Dr. Freeman presented at the meeting. Numerous emails demonstrate that Dr. Honjo intended to meet with Dr. Freeman and Dr. Wood at the AAI meeting in Seattle in May 2000. The metadata showing that Dr. Freeman last edited his slides the day before the meeting corroborates his testimony that he finished the slides a few hours before getting on the airplane to go to Seattle. JTX-0815.0011.<sup>10</sup> And the relevant pages of the unwitnessed laboratory

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<sup>10</sup> Defendants raised an objection to the introduction of the metadata before Dr. Freeman's testimony. However, they agreed that they would not object if Dana-Farber could establish the authenticity of the slides during Dr. Freeman's direct

notes list dates in late August and early September 1999, as Dr. Freeman testified. JTX-0229.0323; JTX-0778.0038. While "an unwitnessed laboratory notebook, alone, cannot corroborate an inventor's testimony of conception," it may serve as an "aid in corroborating witness testimony alongside other, more persuasive, evidence." Apator Mitors, 887 F.3d at 1297. For the foregoing reasons, I find Dr. Freeman's and Dr. Wood's testimony sufficiently corroborated and therefore credible.

**D. The Collaboration of Dr. Freeman, Dr. Wood, and Dr. Honjo**

To show that Dr. Freeman and Dr. Wood are joint inventors of the Honjo patents, Dana-Farber must demonstrate that they collaborated with Dr. Honjo to develop the methods claimed in the patents. See Falana, 669 F.3d at 1357 ("A joint invention is the product of a collaboration between two or more persons working together to solve the problem addressed." (quoting Burroughs Wellcome, 40 F.3d at 1227)). There is no question that the three collaborated. The trio met for the first time in October 1999 to discuss the PD-1/PD-L1 pathway. After this meeting, Dr. Freeman and Dr. Wood exchanged reagents with Dr. Honjo, and Dr. Wood and Dr. Honjo formally added the PD-1/PD-L1 pathway to the SST collaboration. The three continued to

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testimony, and they did not preserve their objection when the slides were entered into evidence. T3-124:15.

exchange confidential data for over a year. Dr. Honjo and Dr. Wood met four more times over the next eighteen months, twice with Dr. Freeman present. The three co-authored multiple journal articles on the PD-1/PD-L1 pathway. Despite the fact that they did not physically work on the invention together, Dr. Freeman, Dr. Wood, and Dr. Honjo plainly had an "open line of communication . . . in temporal proximity to their inventive efforts." Eli Lilly, 376 F.3d at 1359; see also CODA Dev. S.R.O. v. Goodyear Tire & Rubber Co., 916 F.3d 1350, 1359-60 (Fed. Cir. 2019) (holding that allegations that the plaintiff and defendant companies had two meetings and signed a nondisclosure agreement to cooperate in developing a specific technology were sufficient to allege collaboration).

Defendants point to Dr. Freeman and Dr. Wood's November 1999 patent application, their work without Dr. Honjo, and Dr. Wood and Dr. Honjo's March 2000 meeting in Japan without Dr. Freeman to argue that the three scientists were not fully collaborating. There is no requirement, however, that joint inventors take every step in the collaboration together. See Falana, 669 F.3d at 1357. That two of the three interacted without the third at times does not cast doubt on their tripartite collaboration. In their post-trial brief, Defendants pivot, arguing for the first time (and only after they settled with Pfizer) that Dr. Wood and Dr. Honjo collaborated without

Dr. Freeman. Dkt. No. 380 at 12. Yet Dr. Honjo's recognition of Dr. Freeman as a collaborator in his Nobel Prize speech, together with the extensive evidence at trial, leaves no doubt that Dr. Freeman was a part of the collaboration.

Defendants also contend that the collaboration was limited to identifying the ligand for PD-1 and its function. Dr. Honjo testified to this effect at trial. Compare T4-185:19-23 ("[T]he whole focus of the collaboration was to find the ligand"), with T4-186:16-21 (explaining that he agreed to collaborate further with Dr. Freeman and Dr. Wood after discovering PD-L1 because "[w]e have to identify the function"). His testimony about the purpose of the collaboration was underinclusive. By the October 1999 meeting in Cambridge, Dr. Wood had identified Dr. Freeman's 292 molecule as the ligand for PD-1, as well as its inhibitory function, and conveyed this to Dr. Honjo. If the whole purpose of the collaboration were to identify the ligand and its function, there would have been no reason to add the PD-1/PD-L1 pathway to the SST collaboration (which was specifically aimed at pharmaceutical development), continue to exchange confidential experimental data, co-author multiple journal articles, and meet four more times over the next eighteen months. Dr. Honjo himself told Dr. Clark of GI in a June 2000 email that he was "very pleased with [the] recent productive collaboration on PD-1 and PD-L1" and felt that the



"collaboration [was] coming close to drug development." JTX-0617.0001.

The trio were also talking about the role of the PD-1/PD-L1 pathway in the treatment of diseases, including cancer, throughout their collaboration. At the March 2000 meeting in Kyoto, Dr. Wood and Dr. Honjo discussed therapeutic applications for anti-PD-1 and anti-PD-L1 antibodies, including treating cancer. They discussed this again with Dr. Freeman at the May 2000 meeting in Seattle. Dr. Freeman included the possibility that tumors use PD-L1 to inhibit an antitumor immune response in two journal articles he wrote with Dr. Wood and Dr. Honjo throughout 2000 and an abstract he sent to Dr. Honjo in August 2000. At the September 2000 meeting in Cambridge, Dr. Honjo discussed preliminary results from Dr. Iwai's mouse tumor model study. I find that one purpose of the collaboration among the three scientists was to harness the PD-1/PD-L1 pathway to treat cancer.

Defendants' reliance on Rubin v. General Hospital Corp., No. 09-10040-DJC, 2011 WL 1625024 (D. Mass. Apr. 28, 2011), to cast doubt on the collaboration is misplaced. In Rubin, the putative joint inventors and named inventors never had any direct communication. Id. at \*2, \*6. To show collaboration, the putative joint inventors relied on their awareness of the named inventors' research and their claim that one of the named

inventors read their journal abstract. Id. at \*6. In finding this evidence insufficient for collaboration, the court noted that the putative joint inventors filed their own provisional patent application after the alleged collaboration without including the named inventors. Id. at \*7. From this, the court gleaned that the putative joint inventors did not consider themselves to be collaborating with the named inventors. Id. In this case, Dr. Freeman, Dr. Wood, and Dr. Honjo had multiple collaboration meetings, exchanged confidential data and reagents, and co-authored multiple journal articles. While the exclusion of Dr. Honjo from Dr. Freeman and Dr. Wood's provisional patent application is troubling, it came only two weeks after their first tripartite collaboration meeting, and the collaboration continued robustly well after this time.

When Dr. Honjo initially asked Dr. Wood to help find the ligand for PD-1 in September 1998, he did not know this partnership would expand into a tripartite collaboration with Dr. Freeman to develop therapeutic applications for the PD-1/PD-L1. Regardless, as Dr. Honjo admitted in his contemporaneous email to Dr. Clark quoted above, this is what happened. Dana-Farber has shown by clear and convincing evidence that Dr. Freeman, Dr. Wood, and Dr. Honjo collaborated to discover and characterize the PD-1/PD-L1 pathway and to develop therapeutic applications based on blocking this inhibitory

interaction with antibodies and enhancing the immune response for treatment of cancer and other diseases.

**E. Conception of the Honjo Patents**

Because "one does not qualify as a joint inventor by merely assisting the actual inventor after conception of the claimed invention," Ethicon, 135 F.3d at 1460, contributions Dr. Freeman and Dr. Wood made before the date of conception are determinative of the joint inventorship analysis, see, e.g., Gen. Elec. Co. v. Wilkins, 750 F.3d 1324, 1332 (Fed. Cir. 2014) (finding no joint inventorship where the named inventors "had already conceived of their [invention] before corresponding with" the putative co-inventor). Defendants propose a conception date of October 27, 2000, after Dr. Iwai presented the results of her in vivo mouse tumor model experiments. Dana-Farber does not contest this date. Before this date, Dr. Honjo, Dr. Minato, Dr. Iwai, Dr. Freeman, and Dr. Wood all had the idea and hope that the PD-1/PD-L1 pathway might have some role in tumor immunology. Dr. Iwai's in vivo experiments demonstrated that tumors expressing PD-L1 grew more quickly in normal mice than in PD-1 knockout mice. With these results, Dr. Honjo had a "definite and permanent idea" that the PD-1/PD-L1 pathway played a role in inhibiting the immune response to tumors and permitted tumors to grow. In re VerHoef, 888 F.3d at 1366 (quoting Sewall, 21 F.3d at 415). This understanding also gave him the "definite

and permanent idea" that blocking the PD-1/PD-L1 pathway using antibodies could treat cancer.<sup>11</sup>

Based on this conception date, Defendants emphasize that Dr. Freeman and Dr. Wood cannot be joint inventors of the Honjo patents because they did not contribute to Dr. Iwai's in vivo mouse experiments that triggered conception. In Vanderbilt University v. ICOS Corp., however, the Federal Circuit expressly rejected the argument that all contributors had to "have their own contemporaneous picture of the final claimed invention in order to qualify as joint inventors." 601 F.3d at 1303. Instead, the law requires only that "a group of co-inventors . . . collaborate and work together to collectively have a definite and permanent idea of the complete invention." Id. at 1308. This holding fits with the joint inventorship statute's recognition that two or more people may be joint inventors even if they did not work "at the same time." 35 U.S.C. § 116(a). In addition, the statute codified the holding of Monsanto Co. v. Kamp, 269 F. Supp. 818 (D.D.C. 1967), including the principle that "[i]t is

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<sup>11</sup> I am not convinced Dr. Honjo conceived of all of the claims of all six patents by this date. Some dependent claims list types of tumors for which there is no evidence Dr. Honjo had any data or had ever specifically considered before this date. The parties have not presented sufficient evidence of the events after October 2000 to determine when Dr. Honjo conceived of all the claims. Because Dr. Freeman and Dr. Wood are joint inventors of all six patents based on their contributions before October 27, 2000, I need not decide the dates of conception of these dependent claims.

not necessary that the entire inventive concept should occur to each of the joint inventors." Kimberly-Clark, 973 F.2d at 916 (quoting Monsanto, 269 F. Supp. at 824).

Before Vanderbilt University, the Federal Circuit was less clear on whether joint inventors must achieve contemporaneous conception of the entire invention. See, e.g., Ethicon, 135 F.3d at 1460 ("One who simply provides the inventor with well-known principles or explains the state of the art without ever having 'a firm and definite idea' of the claimed combination as a whole does not qualify as a joint inventor."); Burroughs Wellcome, 40 F.3d at 1229 ("[E]ach inventor must contribute to the joint arrival at a definite and permanent idea of the invention as it will be used in practice."). The Federal Circuit's direct holding on point in Vanderbilt University is controlling. While an invention is not complete until one of the joint inventors reaches conception, Burroughs Wellcome, 40 F.3d at 1227-28, a co-inventor need only make a not insignificant contribution to conception, see Fina Oil, 123 F.3d at 1474 (rejecting the notion that, "because the first person did not conceive or reduce to practice the entire claimed invention, he or she did not at least contribute in some significant way to the ultimate conception").

Accordingly, while the fact that Dr. Freeman and Dr. Wood were not present during Dr. Iwai's in vivo mouse tumor model

experiments is relevant to determining how significant their contributions were to conception, it is not dispositive. See Rhone-Poulenc Agro, S.A. v. Monsanto Co., 445 F. Supp. 2d 531, 549 (M.D.N.C. 2006) (finding co-inventorship even though the putative co-inventors were not informed of the final experiments that led to conception). Instead, Dr. Freeman and Dr. Wood are joint inventors if they made a significant contribution to reaching conception. See Falana, 669 F.3d at 1359 (holding that an individual was a joint inventor of a patent claiming a type of compound because he contributed the method used to make the compounds, even though he left the research team before the team created the novel compounds).

**F. Dr. Freeman's and Dr. Wood's Contributions to Conception**

1. *Dr. Freeman and Dr. Wood's Discovery of PD-L1 and Blocking Antibodies and Dr. Wood's Discovery of the Inhibitory Effect of the PD-1/PD-L1 Pathway*

Dr. Freeman and Dr. Wood's first contribution was their joint discovery and characterization of PD-L1. Dr. Freeman's BLAST search in July 1998 uncovered 292 as a B7 ligand. Although the 292 ESTs Dr. Freeman identified came from a public database, the fact that 292 was a B7-like molecule was not known. He subsequently showed that 292 was immunologically active but, unlike B7-1 and B7-2, did not bind to CD28 or CTLA-4. He provided the 292 molecule to GI to help identify its receptor.

Meanwhile, once Dr. Honjo asked for Dr. Wood's assistance in identifying the ligand for PD-1, Dr. Wood hypothesized that the ligand would be a B7-like molecule because of PD-1's role in regulating the immune system and its similarity to CTLA-4. By testing a group of B7 ligands Dr. Freeman had sent to GI, he was able to identify 292 as PD-L1, a ligand for PD-1, which he communicated to Dr. Honjo in October 1999. Dr. Freeman then disclosed PD-L1's amino acid sequence to Dr. Honjo.

Defendants point out that Dr. Chen at the Mayo Clinic discovered that 292 was a B7 ligand before Dr. Freeman. Dr. Chen published his discovery in December 1999, however, after Dr. Freeman independently identified 292 in July 1998, shared his molecule with GI in July 1999, and discussed his knowledge about 292 at the first collaboration meeting with Dr. Honjo in October 1999. "Generally speaking, scientific articles become part of the prior art on the date of their publication." Univ. of Utah v. Max-Planck-Gesellschaft Zur Förderung Der Wissenschaften e.V., 134 F. Supp. 3d 576, 585 (D. Mass. 2015). Dr. Chen's earlier discovery therefore was not a "well-known concept[] and/or the current state of the art" at the time of Dr. Freeman's contribution. Pannu, 155 F.3d at 1351.

That Dr. Iwai might have identified the ligand after returning from her leave of absence is also irrelevant. Defendants cite no case that permits speculation as to whether

the named inventors would have eventually reached the same result without a putative joint inventor's contribution. The fact remains that it was Dr. Freeman and Dr. Wood, not Dr. Iwai, who discovered PD-L1 and provided it to Dr. Honjo. In addition, since Dr. Iwai and other graduate students in Dr. Honjo's laboratory tried and failed to identify the ligand, the discovery of 292 required more than "the basic exercise of ordinary skill in the art."<sup>12</sup> Nartron Corp., 558 F.3d at 1357.

Dr. Wood's second contribution was his discovery that the interaction between PD-1 and PD-L1 inhibits the immune response. After discovering PD-L1, Dr. Wood conducted in vitro experiments to study its function, which demonstrated that the pathway is inhibitory. Dr. Wood shared these results with Dr. Freeman and Dr. Honjo at the October 1999 meeting. Dr. Honjo had not knowingly conducted any experiments that involved PD-L1 before this meeting.

Dr. Greene criticized Dr. Wood's experiments because Dr. Wood did not use a non-PD-1 control, whereas Dr. Honjo subsequently showed inhibition in a more robust experiment utilizing cells from a PD-1 knockout mouse. T7-8:14-9:23, 13:2-

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<sup>12</sup> The parties and their experts spar over whether Dr. Iwai's experiments before her leave of absence showed binding with PD-L1 or another molecule. T5-69:3-78:9; T6-176:11-180:12. In the end, it does not matter whether the interactions Dr. Iwai observed were false positives for evaluating this contribution because, as Defendants concede, she never identified PD-L1.



14:8. Dr. Honjo's more definitive experiment does not diminish Dr. Wood's contribution. Scientific collaborations frequently involve one researcher building on the work of another to advance the understanding of both. Failing to credit Dr. Wood's in vitro experiments would disincentivize scientists from participating in this type of innovative research collaboration. See Univ. of Utah, 134 F. Supp. 3d at 588-89.

Defendants contend that Dr. Wood could not have contributed an understanding of PD-L1's function at the October 1999 meeting because he was confused as to whether PD-L1 is an inhibitory or stimulatory ligand. To demonstrate his confusion, they point to his November 1999 provisional patent application with Dr. Freeman and his email exchange in late November and early December 1999 with Dr. Honjo. This evidence shows only that Dr. Wood believed PD-L1 could have a second, stimulatory receptor. Although this hypothesis turned out to be incorrect, it was reasonable given that B7-1 and B7-2 have separate inhibitory and stimulatory receptors. Even Dr. Honjo propounded this theory in journal articles as late as 2003. JTX-0305.0007; JTX-0356.0002; JTX-0819.0008. In any event, Dr. Wood's slides demonstrate that he told Dr. Honjo during the October 1999 meeting that the interaction between PD-1 and PD-L1 is inhibitory.

Defendants also argue that Dr. Honjo already knew PD-1 is an inhibitory receptor before Dr. Wood's experiments with PD-L1. See Maxtech Consumer Prods., Ltd. v. Robert Bosch Tool Corp., 255 F. Supp. 3d 833, 848 (N.D. Ill. 2017) (finding no joint inventorship where the alleged contribution "added nothing to an idea the named inventors already had"); Univ. of Utah, 134 F. Supp. 3d at 588 (same where the putative joint inventor shared information the named inventor had previously received). As Dr. Greene pointed out, the receptor, not the ligand, determines the function of a signaling pathway. T6-193:1-4.

But the proof is in the pudding. Dr. Honjo reached out to Dr. Wood to find PD-L1 because he did not fully understand the biological mechanism of the PD-1 signaling pathway. While Dr. Honjo knew that activation of PD-1 has an inhibitory effect, he did not know that PD-L1 triggers this effect when it binds to PD-1 or how strong the inhibitory signal is. Furthermore, Dr. Murphy explained that not all antibodies that bind to the receptor or ligand block the signal. T5-57:19-58:2. Dr. Greene did not contest that Dr. Honjo needed to understand the receptor-ligand interaction to develop antibodies to block the pathway as a method of treating cancer. T7-115:14-24. Dr. Honjo's efforts to identify the ligand for PD-1, including assigning multiple graduate students to the project and then seeking GI's assistance, belie the notion that he already knew

what he needed about PD-1 before collaborating with Dr. Freeman and Dr. Wood.

Dana-Farber argues that Dr. Freeman also deserves credit for confirming that the PD-1/PD-L1 pathway is inhibitory. Dr. Freeman did conduct an experiment with 292 in late August/early September 1999 that showed inhibition. But the record is devoid of evidence that he shared these results with Dr. Honjo. See Eli Lilly, 376 F.3d at 1364 (setting aside a jury verdict where there was insufficient evidence to show that the putative joint inventor communicated his purported contribution to the named inventors).

Third, Dr. Freeman and Dr. Wood discovered that anti-PD-1 and anti-PD-L1 antibodies can block the pathway's inhibitory signal. Dr. Wood conducted an experiment using one of Dr. Honjo's anti-PD-1 antibodies that showed blockage of the PD-1/PD-L1 pathway, and both Dr. Freeman and Dr. Wood developed their own anti-PD-L1 blocking antibodies. They communicated these results to Dr. Honjo at multiple collaboration meetings before the date of conception.

Defendants contend that any immunologist at the time would have known that antibodies are a therapeutic tool to block a signaling pathway. Dr. Murphy responded that not all antibodies that bind to the receptor or ligand block the signal. While the sharing of the antibodies is strong proof of collaboration, the

particular antibodies Dr. Freeman and Dr. Wood developed are not significant, inventive contributions, as the Honjo patents do not claim antibodies. See Caterpillar Inc. v. Sturman Indus., Inc., 387 F.3d 1358, 1378 (Fed. Cir. 2004) (declining to find the contribution of two specific types of steel to be inventive contributions where the limitation in the patent referred to a broader category of materials). But their discovery that anti-PD-1 and anti-PD-L1 antibodies can block the pathway is not an insignificant contribution to the invention.

As a coda, the Court rejects Defendants' claim that Dr. Honjo could use Dr. Freeman's and Dr. Wood's discovery and characterization of PD-L1 and the PD-1/PD-L1 pathway (as well as the other contributions described below) without including them as joint inventors because Dr. Freeman and Dr. Wood published their discoveries in 2000 before Dr. Honjo filed his patent application. Throughout the collaboration, Dr. Freeman and Dr. Wood exchanged confidential, unpublished experimental results with Dr. Honjo. The Federal Circuit has never "barred co-inventorship, as a matter of law, just because the contribution later appeared in the public domain, where the ideas contributed were not contemporaneously available to an ordinary skilled artisan and were otherwise significant in producing the inventive conception at the time it was

completed." CardiAQ Valve Techs., Inc. v. Neovasc Inc., 708 F. App'x 654, 660 (Fed. Cir. 2017).

This Court's decision in University of Utah v. Max-Planck-Gesellschaft Zur Förderung Der Wissenschaften e.V. is not to the contrary. In University of Utah, a university alleged that one of its professors was a joint inventor of patents relating to RNA interference based on a confidential manuscript of hers a named inventor read a few weeks before publication and a conversation she had with him at a scientific conference. 134 F. Supp. 3d at 581-82, 585, 588. This Court held that the professor was not a joint inventor because she did not collaborate with the named inventors. Id. at 585. As to the manuscript, the Court noted that, although the named inventor received a confidential copy with the professor's alleged contribution, he would have received the same information as prior art when it was published three weeks later. Id. at 586-87. Here, there is no doubt Dr. Freeman, Dr. Wood, and Dr. Honjo collaborated sufficiently to qualify as joint inventors as early as October 1999, almost three years before Dr. Honjo filed his first patent application and a year before the conception date. Dr. Freeman and Dr. Wood shared their confidential experimental results on PD-L1 with Dr. Honjo a year before publishing them.

2. *Dr. Freeman's Discovery of the Expression of PD-L1 on Certain Tumors*

Dr. Freeman also contributed his discovery that PD-L1 is expressed on certain tumors. The 292 ESTs he identified via his BLAST search came from a human ovarian tumor, which he told Dr. Honjo at the October 1999 meeting. As both experts explained, the possible expression of a B7 ligand on a tumor cell was notable because other B7 ligands are only expressed on immune cells. T5-42:25-43:22; T7-61:19-62:8. Dr. Freeman used the source of the 292 ESTs as a starting point for further investigation. With Dr. Dorfman's help, he conducted IHC experiments in early 2000 to examine PD-L1 expression on solid human tumor tissues. The IHC work showed that PD-L1 is highly expressed on different types of human tumors.

Together, these observations led Dr. Freeman to add a sentence to the draft of the article he co-authored with Dr. Wood and Dr. Honjo about the possibility that tumors use PD-L1 to inhibit an antitumor immune response. Dr. Honjo saw this addition in early April 2000 when he received the new draft. Dr. Freeman communicated his IHC results to Dr. Honjo at the May 2000 meeting in Seattle and then again at the September 2000 meeting in Cambridge. He also shared data from his laboratory showing PD-L1 expression in certain mouse tumor cell lines by

September 6, 2000, when he sent Dr. Honjo a draft of their article on PD-L2.

Defendants argue that Dr. Honjo already knew that human tumors express PD-L1 from Dr. Iwai's experiments in the summer of 1999. Her experiments attempting to identify PD-L1 did show weak binding between her PD-1 fusion protein and Daudi cells from a human blood cell cancer line. She recognized, however, that her experiments might have shown false positives because of the type of fusion protein she used, and she expressed uncertainty about her results. JTX-0125.0022, 24. After Dr. Iwai's results, Dr. Honjo continued to emphasize the connection between PD-1 and autoimmune disease (not cancer), including in his October 1999 presentation. Dr. Freeman's IHC results provided much stronger evidence of PD-L1 expression on a range of solid human tumors than Dr. Iwai's results did. And while Dr. Minato also investigated PD-L1 expression on various cell lines, he only tested mouse cells before the date of conception and did not use solid tumors.

Dr. Freeman gets credit for this significant contribution despite the fact that Dr. Dorfman assisted him with the IHC experiments. See Fina Oil, 123 F.3d at 1473 (noting that a "person does not lose his or her status as a joint inventor just because he or she used the services, ideas, and aid of others in the process of perfecting the invention"). While Dr. Dorfman

chose the tissues to study, administered the antibodies, and prepared the staining, he did so at Dr. Freeman's direction. Dr. Freeman and Dr. Dorfman collaborated to investigate PD-L1 expression, but there is no evidence Dr. Dorfman was part of the collaboration with Dr. Wood and Dr. Honjo. It was Dr. Freeman, not Dr. Dorfman, who communicated the results to Dr. Honjo.

Dr. Greene downplayed this contribution by noting that Dr. Freeman's IHC work did not tie PD-L1 to cancer specifically but instead showed PD-L1 expression on both tumor and normal tissues. T6-195:2-24; T7-33:13-19. Defendants also contend a reasonable scientist would not conclude from Dr. Freeman's discovery of the 292 ESTs on ovarian tumor cells that PD-L1 is functionally related to cancer. However, Dr. Freeman made this connection, and he was right. He also shared it with Dr. Wood and Dr. Honjo. Given that other B7 ligands are not found on tumor cells, I credit Dr. Freeman's testimony that the expression of PD-L1 on tumor cells was an important finding.

3. *Dr. Freeman and Dr. Wood's Discovery and Characterization of PD-L2*

Dr. Freeman and Dr. Wood also contributed knowledge of the existence, structure, and function of PD-L2. Dr. Freeman discovered PD-L2 via a BLAST search for molecules similar to PD-L1. Dr. Freeman and Dr. Wood together generated the full-length sequence for the molecule, showed that it binds to PD-1 and



inhibits the immune response, and found that it is expressed on certain mouse tumor cells. Dr. Freeman told Dr. Honjo about their discovery via email on March 24, 2000, and Dr. Wood and Dr. Freeman provided more details about PD-L2 to Dr. Honjo at the March, May, and September 2000 meetings. Dr. Honjo never attempted to identify a second ligand for PD-1 or conduct any experiments involving PD-L2. Everything he knew about PD-L2 came from Dr. Freeman and Dr. Wood.

Defendants point out that Dr. Freeman discovered PD-L2 in a publicly available database and that another scientist had already disclosed PD-L2's sequence. T7-35:3-9. Before Dr. Freeman and Dr. Wood identified the molecule as a ligand for PD-1, however, its receptor and biological function were unknown. T5-131:12-133:3.

#### 4. *Method of Treating Cancer*

Dana-Farber claims Dr. Freeman contributed the idea of blocking the PD-1/PD-L1 pathway as a method of treating cancer. It is clear Dr. Honjo and his colleagues were focused on the relationship between PD-1 and autoimmune disease, not cancer, before the collaboration with Dr. Freeman and Dr. Wood began. All three scientists were thinking about the relationship between the PD-1/PD-L1 pathway and cancer in the winter and spring of 2000: Dr. Freeman began his IHC experiments in January and included two sentences about the pathway and cancer in their

draft article in March; Dr. Wood mentioned using antibodies to block the pathway to stimulate an immune response to treat cancer at the SST collaboration meeting in March; and Dr. Iwai (working with Dr. Honjo) began her in vivo mouse tumor model experiments in March. As noted above, this simultaneous focus on the PD-1/PD-L1 pathway and cancer and the numerous communications the scientists exchanged on this topic are clear and convincing evidence that they collectively conceived of harnessing the pathway as a method of treating cancer.

The parties battle over who had the first idea of blocking the pathway as a method of treating cancer. All three scientists began to consider this idea seriously in early 2000. However, Dana-Farber has not produced clear and convincing evidence that Dr. Freeman or Dr. Wood came up with this idea first and communicated it to Dr. Honjo before Dr. Honjo had the idea himself. The first time Dr. Freeman directly communicated his idea of a connection between the pathway and cancer to Dr. Honjo was in the edits he made to their draft journal article in March, but there is no evidence Dr. Honjo saw these edits before April. Dr. Wood first communicated his idea to Dr. Honjo at the end of March 2000 at their SST collaboration meeting in Kyoto. Meanwhile, in Japan, Dr. Iwai was planning her in vivo mouse tumor experiments, indicating that she and Dr. Honjo were

already focused on the connection between the pathway and cancer.

The fact that the Court cannot attribute this contribution to Dr. Freeman or Dr. Wood individually by clear and convincing evidence does not doom their joint inventorship claim. The trio's simultaneous focus on blocking the pathway to treat cancer in early 2000 shows that they were all working toward a shared goal. Even if it is not clear who was the first to contribute the idea of blocking the pathway to treat cancer, Dr. Freeman and Dr. Wood made the contributions described above as part of a collaboration aimed at developing a treatment for cancer, and they all understood and communicated with excitement the connection between their discoveries relating to the pathway and cancer. Ultimately, conception of the inventions in the Honjo patents was the result of the collaboration of all three scientists.

5. *Dr. Freeman's and Dr. Wood's Provision of Reagents*

Dr. Freeman and Dr. Wood also provided PD-L1 fusion protein and anti-PD-L1 antibody reagents that Dr. Honjo and Dr. Iwai used in their experiments. Providing reagents that named inventors use to develop their invention is not a meaningful contribution to conception. See BJ Servs. Co. v. Halliburton Energy Servs., Inc., 338 F.3d 1368, 1373-74 (Fed. Cir. 2003).

Although provision of the PD-L1 fusion protein hastened Dr. Honjo's conception of the method of treating cancer, joint inventorship law requires more than showing that the putative joint inventor made it easier for the named inventor to conceive of the claim or that the named inventor would not have achieved conception but for the contribution. See Yeda, 443 F. Supp. 2d at 621; Eli Lilly & Co. v. Crabtree, 485 F. Supp. 2d 982, 1000 (S.D. Ind. 2006). Dr. Freeman's and Dr. Wood's inventive contributions were not the provision of reagents but instead discovery of those reagents' existence, structure, and function.

**G. Significance of Dr. Freeman's and Dr. Wood's Contributions to the Claims in the Honjo Patents**

The Court must determine whether these contributions relating to the PD-1/PD-L1 pathway and PD-L2 were significant to conception in light of the dimension of the full inventions in the six Honjo patents. See In re VerHoef, 888 F.3d at 1366. The patents all claim methods of treating cancer by administering anti-PD-1 or anti-PD-L1 antibodies. Defendants argue only briefly and without analysis that the significance of Dr. Freeman's and Dr. Wood's contributions varies among the patents. They point out more directly that Dr. Freeman and Dr. Wood each made different contributions to conception of the patents. While that is true, I find that Dr. Freeman and Dr. Wood worked together on important contributions, namely the

discovery of PD-L1, characterization of the PD-1/PD-L1 pathway, and discovery that antibodies block the inhibitory effect of the pathway and stimulate the immune system.<sup>13</sup> This contribution was significant to conception of the inventions in all six Honjo patents. Nevertheless, I discuss each patent because the joint inventorship analysis asks about contributions to the invention specifically claimed in a patent.

1. *Use of Anti-PD-1 or Anti-PD-L1 Antibodies to Treat Cancer*

Dr. Freeman and Dr. Wood are clearly joint inventors of the '899 Patent. Claim 1 recites a "method of treating a tumor in a human patient in need thereof comprising administering to the human an effective amount of an anti-PD-L1 monoclonal antibody that inhibits an interaction between PD-1 and PD-L1, wherein the anti-PD-L1 monoclonal antibody treats the tumor in the patient." JTX-0006.0040. The '899 Patent contains three other independent claims (claims 19, 36, and 52) that also involve decreasing, suppressing, and treating tumors by blocking the interaction between PD-1 and PD-L1 with an anti-PD-L1 monoclonal antibody. JTX-0006.0040-41.

Both Dr. Freeman and Dr. Wood made not insignificant contributions to conception of this method. Dr. Freeman and

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<sup>13</sup> Both Dr. Freeman and Dr. Wood made this final contribution, but they did their antibody work separately.

Dr. Wood jointly discovered the molecular structure for PD-L1. This discovery was essential for conception of a method of using an anti-PD-L1 antibody to block the PD-1/PD-L1 pathway, which the '899 Patent specifically claims. Dr. Wood also provided Dr. Honjo with the first experimental data confirming that PD-L1 inhibits the immune response. Without this knowledge, there would be no reason to use an antagonistic antibody to treat cancer. These contributions provided fundamental building blocks for Dr. Iwai's tumor model experiments on the effect of the PD-1/PD-L1 pathway on tumor growth. And Dr. Honjo learned from both Dr. Freeman and Dr. Wood that antibodies could block the interaction between PD-1 and PD-L1, which is the method of treating cancer claimed in the '899 Patent.

Dr. Freeman's discovery that PD-L1 is highly expressed on human tumor cells was also a significant contribution because the method claimed in the '899 Patent is premised on the tumor's expression of PD-L1. As Dr. Murphy explained, the results of Dr. Iwai's tumor model experiments only triggered conception because Dr. Honjo knew from Dr. Freeman's work that, like the transfected tumors in Dr. Iwai's experiments, human tumors express PD-L1. T5-89:19-90:7. The fact that Dr. Iwai planned her mouse tumor model experiments in March before Dr. Freeman communicated his IHC results concerning human tumors to Dr. Honjo in May does not undermine the significance of this

contribution to conception. While an anti-PD-1 or anti-PD-L1 antibody may enhance an immune response against a tumor by blocking inhibitory signaling triggered by PD-L1 on a nontumor cell, conception of the invention was inextricably linked to the expression of PD-L1 on human tumors. Even Dr. Greene admitted that Dr. Honjo and Dr. Iwai would not have designed their in vivo experiments the way they did if they did not know that human tumors express PD-L1. T7-90:25-91:8. Dr. Freeman was the first to make that discovery.

In Defendants' version of the events at issue, Dr. Freeman and Dr. Wood provided Dr. Honjo with knowledge of PD-L1's existence but had no understanding of its functional use. Defendants analogize this case to BJ Services Co. v. Halliburton Energy Services, Inc., in which the Federal Circuit held that the inventor of a polymer listed in a dependent claim was not a joint inventor of a patent claiming a method of fracturing a subterranean formation because he "had no knowledge of the method [or] how the polymer would be used." 338 F.3d at 1373. Dr. Freeman's and Dr. Wood's contributions went well beyond the mere provision of a molecule. When Dr. Freeman sent GI his 292 molecule, he did not know it was a ligand for PD-1 or that it inhibits the immune response. But, as Dr. Murphy explained, his theory that 292 was a B7 ligand was key to Dr. Wood's ability to connect PD-1 and 292 as a receptor-ligand pair. T5-50:23-51:14.

So was Dr. Wood's hypothesis that PD-1's ligand would be a B7-like molecule. Id. In addition, Dr. Wood contributed experimental data showing the PD-1/PD-L1 pathway is inhibitory, and Dr. Freeman provided knowledge of PD-L1 expression in human tumors. These contributions enhanced Dr. Honjo's understanding of PD-1 and its biological function.

For similar reasons, I reject Dr. Greene's opinion that that these contributions were insignificant to conception. Because Dr. Greene explained the insignificance of each contribution individually, he overlooked the way in which Dr. Freeman's and Dr. Wood's multiple hypotheses and experiments together were significant. For example, he opined that Dr. Wood's experiments showing binding between 292 and PD-1 were insignificant because they did not reveal anything about 292's function. T6-200:5-201:14. But Dr. Wood conducted additional experiments that demonstrated that 292, or PD-L1, inhibits the immune response. When examined together, Dr. Freeman's and Dr. Wood's contributions relating to PD-L1's structure and function show an understanding of the PD-1/PD-L1 pathway on which Dr. Honjo relied in his ensuing research.

Dr. Greene also emphasized that Dr. Freeman's and Dr. Wood's contributions were not significant because they did not participate in Dr. Iwai's in vivo experiments and thus never had a full understanding of the effect of the PD-1/PD-L1 pathway



on the antitumor immune response. T6-164:11-165:9, 166:18-167:3. As noted above, the law does not exclude Dr. Freeman and Dr. Wood from joint inventorship simply because they were not present for and did not participate in the final step that triggered conception. This absence also does not render their contributions scientifically insignificant. As Dr. Greene admitted, scientists often use in vitro experiments to develop hypotheses for future research. T7-77:21-78:14. He conceded that Dr. Freeman and Dr. Wood could be joint inventors based on their in vitro experiments as long as they understood the PD-1/PD-L1 pathway. T7-49:17-50:1. Dr. Freeman and Dr. Wood did understand the pathway and communicated their discoveries to Dr. Honjo. Dr. Freeman and Dr. Wood's joint discovery of PD-L1 and blocking antibodies, Dr. Wood's discovery that its interaction with PD-1 is inhibitory, and Dr. Freeman's discovery of PD-L1 expression on human tumors were fundamental and essential building blocks for conception of the method of treating cancer claimed in the patent. As a result of these contributions, Dr. Freeman and Dr. Wood are joint inventors of the '899 Patent.

The other five Honjo patents claim a method of treating cancer via administration of an anti-PD-1<sup>14</sup> or anti-PD-L1

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<sup>14</sup> Claim 1 of the '048 Patent recites a "method for treatment of cancer, wherein a pharmaceutically effective amount of completely human anti-PD-1 antibody is parenterally administered

antibody.<sup>15</sup> Dr. Honjo's conception of using either type of antibody to cure cancer required knowledge of PD-L1's molecular structure and inhibitory function. As Dr. Murphy opined, both types of antibodies work by blocking the PD-1/PD-L1 pathway. T5-55:16-56:5. Although Dr. Honjo had anti-PD-1 antibodies before the collaboration began, he conducted no experiments before conception to test whether his anti-PD-1 antibodies affected tumor growth. Dr. Freeman's and Dr. Wood's contributions of PD-L1's structure and function and the knowledge that antibodies

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to a subject with cancer in which PD-L1 or PD-L2 is over-expressed, postoperatively." JTX-0001.0032.

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." JTX-0003.0033.

Claim 1 of the '999 Patent recites a "method of treating a lung cancer comprising administering a composition comprising a human or humanized anti-PD-1 monoclonal antibody to a human with the lung cancer, wherein the administration of the composition treats the lung cancer in the human." JTX-0004.0038.

Claim 1 of the '994 Patent recites a "method of treating a metastatic melanoma comprising intravenously administering an effective amount of a composition comprising a human or humanized anti-PD-1 monoclonal antibody and a solubilizer in a solution to a human with the metastatic melanoma, wherein the administration of the composition treats the metastatic melanoma in the human." JTX-0005.0038.

<sup>15</sup> Claim 1 of the '179 Patent recites a "method of treating a PD-L1-expressing tumor, comprising administering a pharmaceutically effective amount of an anti-PD-L1 antibody to a patient in need thereof, in combination with a pharmaceutically effective amount of one or more chemotherapy drugs, [with specific options for the type of chemotherapy drugs]." JTX-0002.0033.

can block the PD-1/PD-L1 interaction were significant and render them joint inventors of the other five Honjo patents as well.

2. *Expression or Over-Expression of PD-L1 or PD-L2*

Dr. Freeman and Dr. Wood made additional not insignificant contributions to conception of the patents' claims. The independent claims of the '048 and '179 Patents limit the method of treating cancer to tumors that express or over-express PD-L1 or PD-L2.<sup>16</sup> A tumor "over-expresses" PD-L1 if it expresses more PD-L1 than the healthy tissue from which the tumor is derived. T5-90:23-91:19. Dr. Honjo could not conceive of a method of treating a tumor expressing or over-expressing PD-L1 or PD-L2 without knowing of the existence and function of PD-L1 or PD-L2. Dr. Honjo learned about PD-L1's molecular structure and

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<sup>16</sup> In addition to Claim 1 of the '179 Patent, see supra footnote 15, the independent claims of the '048 Patent are as follows:

1. A method for treatment of cancer, wherein a pharmaceutically effective amount of completely human anti-PD-1 antibody is parenterally administered to a subject with cancer in which PD-L1 or PD-L2 is over-expressed, postoperatively. . . .

3. A method for enhancing cytotoxic T cell activity toward PD-L1 or PD-L2 over-expressing cancer cells, which comprises administering a pharmaceutically effective amount of a completely human anti-PD-1 antibody to a subject with cancer in which PD-L1 or PD-L2 is over-expressed, wherein the effective dose of the completely human anti-PD-1 antibody is administered parenterally and postoperatively.

JTX-0001.0032.

inhibitory function from Dr. Freeman and Dr. Wood at the October 1999 meeting. Throughout 2000, Dr. Freeman and Dr. Wood also told Dr. Honjo about PD-L2, which he did not study himself at all before the date of conception of the patents. Without learning from Dr. Freeman and Dr. Wood about PD-L2, Dr. Honjo would not have conceived of using anti-PD-1 antibodies to block PD-1's interaction with PD-L2. Finally, Dr. Honjo learned from Dr. Freeman that many human tumors express high levels of PD-L1, which is the premise of this limitation.

In the '994 and '999 Patents, only dependent claims include the limitation that the tumor expresses PD-L1 or PD-L2.<sup>17</sup> The parties dispute whether a contribution to a limitation in a dependent claim renders the contributor a joint inventor of the whole patent. The Federal Circuit has explained that an individual "does not necessarily attain the status of co-inventor by providing the sole feature of a dependent claim." Nartron Corp., 558 F.3d at 1358. Instead, a court must consider

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<sup>17</sup> The '994 Patent contains ten dependent claims that add a limitation requiring that the melanoma tumor express PD-L1 or PD-L2 (claims 14-18, 20-24) and six more that require that the PD-L1 or PD-L2 expression be identified by immunohistochemistry (claims 25-30). JTX-0005.0038.

The '999 Patent contains seven dependent claims that add a limitation requiring that the lung cancer tumor express PD-L1 or PD-L2 (claims 19-25) and five more that require that the PD-L1 or PD-L2 expression be identified by immunohistochemistry (claims 26-30). JTX-0004.0038.

the additional limitations of a dependent claim in the context of the independent claim on which it depends. See id.; see also Yeda, 443 F. Supp. 2d at 618 (noting that the two dependent claims were "to be construed in light of their dependence on" two independent claims and evaluating a putative co-inventor's contributions "with an eye toward the independent claims"). The focus is whether the contribution is "not insignificant in quality, when . . . measured against the dimension of the full invention."<sup>18</sup> In re VerHoef, 888 F.3d at 1366 (quoting Pannu, 155 F.3d at 1351).

Sixteen of the twenty-nine dependent claims in the '994 Patent and twelve of the twenty-nine dependent claims in the '999 Patent contain the additional limitation that the tumor expresses PD-L1 or PD-L2 (and in some claims that this expression is identified via immunohistochemistry). JTX-0004.0038; JTX-0005.0038. Given Dr. Freeman's and Dr. Wood's other contributions, they did not just "provid[e] the sole

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<sup>18</sup> Citing Ethicon, 135 F.3d at 1464, Dana-Farber contends that a significant contribution to any element of any claim is sufficient for joint inventorship. As noted, the Federal Circuit clarified in Nartron Corp. that contributing the sole limitation in a dependent claim is not necessarily sufficient for joint inventorship. 558 F.3d at 1358. Because Dr. Freeman and Dr. Wood made contributions to multiple elements of the claims in the Honjo patents that are significant in light of the full invention, the Court need not decide under what circumstances a contribution to a single element of a claim would render an individual a joint inventor.

feature of a dependent claim." Nartron Corp., 558 F.3d at 1358. Their contributions relating to PD-L1 and PD-L2 are significant in light of the full invention.

3. *PD-L1 Expression by Specific Tumors*

The '179, '474, and '899 Patents include dependent claims that limit the method of treating cancer to the following types of tumors: carcinoma, squamous carcinoma, adenocarcinoma, sarcoma, leukemia, neuroma, melanoma, and lymphoma.<sup>19</sup> Between the IHC results he presented at the May and September 2000 meetings and the draft article he sent to Dr. Honjo two days before the September 2000 meeting, Dr. Freeman shared data with Dr. Honjo showing that all but one of these types of tumors express PD-L1. JTX-0332.0003; JTX-0808-0813. The one exception is melanoma, the tumor type Dr. Iwai used in her in vivo mouse experiments. Defendants argue that Dana-Farber is engaging in "hindsight

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<sup>19</sup> Claim 2 of the '179 Patent recites the "method of claim 1, wherein the PD-L1-expressing tumor is one or more selected from the group consisting of carcinoma, squamous carcinoma, adenocarcinoma, sarcomata, luekosis, neuroma, melanoma, and lymphoma." JTX-0002.0033.

Claim 3 of the '474 Patent recites the "method of claim 2, wherein the tumor is one or more selected from the group consisting of a carcinoma, squamous carcinoma, adenocarcinoma, sarcoma, leukemia, neuroma, melanoma, and lymphoma." JTX-0003.0033.

Claims 6, 23, 38, and 57 of the '899 Patent recite the claimed methods of treating cancer "wherein the tumor is one or more selected from a carcinoma, a squamous carcinoma, an adenocarcinoma, a sarcoma, a leukemia, a neuroma, a melanoma, and a lymphoma." JTX-0006.0040-41.

matching" by using Dr. Freeman's data as evidence of his contribution to these dependent claims. However, Defendants have presented no evidence that Dr. Honjo learned that these types of tumors express PD-L1 from any source other than Dr. Freeman, and the matching of the types of tumors is striking. While this dependent claim limitation does not by itself render Dr. Freeman a joint inventor of the patent, it adds another inventive contribution to Dr. Honjo's conception of the claims.

Finally, the Court notes that Dr. Freeman's contribution of his IHC data was even more significant for conception of the '999 Patent. Dr. Freeman told Dr. Honjo in May 2000 that his IHC results showed high levels of PD-L1 expression in a type of lung cancer. The '999 Patent claims the treatment of lung cancer through an anti-PD-1 antibody. JTX-0004.0038. There is no evidence Dr. Honjo ever conducted any independent experiments relating to the PD-1/PD-L1 pathway in lung cancer, let alone before the date of conception.

#### **H. Conclusion**

Dr. Honjo's discovery of PD-1, his initial research on its inhibitory function, and the experiments he oversaw in his laboratory with PD-1 knockout mice were vital for developing the definite and permanent idea of the methods of treating cancer claimed in the Honjo patents. Dr. Honjo has made Nobel Prize-winning contributions to the field of cancer immunology.

However, the fact that Dr. Honjo did substantial work to develop this method does not preclude the naming of Dr. Freeman and Dr. Wood as joint inventors for their significant individual and joint contributions. Dr. Freeman and Dr. Wood made significant contributions to conception of the inventions claimed in the Honjo patents through their discovery of PD-L1 and PD-L2, their discoveries of blocking antibodies, Dr. Wood's discovery of the inhibitory interaction between PD-1 and PD-L1, and Dr. Freeman's discovery of the expression of PD-L1 on tumor cells. Accordingly, Dana-Farber has proven by clear and convincing evidence that Dr. Freeman and Dr. Wood are joint inventors of the six Honjo patents.

## II. Laches

Defendants raise a weak laches defense to all of Dana-Farber's claims for correction of inventorship.<sup>20</sup> They contend Dana-Farber's delay in waiting to bring this lawsuit until 2015 was unreasonable because Dr. Freeman was aware of the Honjo patents as early as 2009 or 2010. They claim both evidentiary prejudice from lost documents and faded memories of the twenty-year-old events at issue and economic prejudice from BMS's

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<sup>20</sup> Because Defendants discuss their laches argument for only one page of their proposed findings of fact and conclusions of law and not at all in their post-trial brief, they have waived it. Given that the laches defense is easily rejected, the Court nevertheless addresses the argument on the merits.



significant investment into developing and commercializing nivolumab in reliance on its exclusive license to the Honjo patents.

**A. Legal Standard**

"Laches is an equitable defense that may bar an inventorship claim." Serdarevic v. Advanced Med. Optics, Inc., 532 F.3d 1352, 1358 (Fed. Cir. 2008). "To prevail on a defense of laches, a defendant must establish that (1) the plaintiff's delay in filing a suit was unreasonable and inexcusable; and (2) the defendant suffered material prejudice attributable to the delay." Lismont v. Alexander Binzel Corp., 813 F.3d 998, 1002 (Fed. Cir. 2016) (quotations omitted). A court conducting a laches analysis must "look at all of the particular facts and circumstances . . . and weigh the equities of the parties." A.C. Aukerman Co. v. R.L. Chaides Constr. Co., 960 F.2d 1020, 1032 (Fed. Cir. 1992) (en banc), abrogated on other grounds by SCA Hygiene Prods. Aktiebolag v. First Quality Baby Prods., LLC, 137 S. Ct. 954 (2017).

Delay is measured "from the time a purportedly omitted inventor knew or should have known of the issuance of the relevant patent." Lismont, 813 F.3d at 1002. "The length of time which may be deemed unreasonable has no fixed boundaries but rather depends on the circumstances." Vita-Mix Corp. v. Basic Holding, Inc., 581 F.3d 1317, 1333 (Fed. Cir. 2009) (quoting

Aukerman, 960 F.2d at 1032). When the plaintiff raises claims concerning multiple patents, a court must consider the delay separately for each patent. See Stark v. Advanced Magnetics, Inc., 29 F.3d 1570, 1576 (Fed. Cir. 1994) (noting "the general rule that each patent is a separate chose in action" and stating that "the laches period does not accrue until each patent issues, even if the patents are interrelated").

Material prejudice can be "either economic or evidentiary." Serdarevic, 532 F.3d at 1360 (quoting Aukerman, 960 F.2d at 1033). "Economic prejudice may arise where a defendant and possibly others will suffer the loss of monetary investments or incur damages which likely would have been prevented by earlier suit." Id. (quoting Aukerman, 960 F.2d at 1033). Merely showing increased investment and expense during the period of the delay is insufficient to show economic prejudice, as the "change in the economic position . . . must be as a result of the delay." Gasser Chair Co. v. Infanti Chair Mfg. Corp., 60 F.3d 770, 775 (Fed. Cir. 1995). A defendant thus cannot rely solely on "a business decision to capitalize on a market opportunity." Hemstreet v. Comput. Entry Sys. Corp., 972 F.2d 1290, 1294 (Fed. Cir. 1992).

Evidentiary prejudice occurs if the defendant cannot "present a full and fair defense on the merits due to the loss of records, the death of a witness, or the unreliability of

memories of long past events." Serdarevic, 532 F.3d at 1360 (quoting Aukerman, 960 F.2d at 1033). To demonstrate evidentiary prejudice, the defendant must point to specific evidence that was lost. Meyers v. Asics Corp., 974 F.2d 1304, 1308 (Fed. Cir. 1992). "Conclusory statements that there are missing witnesses, that witnesses' memories have lessened, and that there is missing documentary evidence, are not sufficient." Id.

Courts apply "a rebuttable presumption of laches . . . whenever more than six years passes from the time a purportedly omitted inventor knew or should have known of the issuance of the relevant patent" to when he initiates litigation. Lismont, 813 F.3d at 1002. "A § 256 claim for correction of inventorship does not accrue until the patent issues," however, even if "the omitted inventor knew or should have known of the omitted inventorship while the patent application was pending before the PTO." Hor v. Chu, 699 F.3d 1331, 1335-37 (Fed. Cir. 2012).

## **B. Analysis**

The presumption of laches does not apply to any of Dana-Farber's correction of inventorship claims. The first of the Honjo patents, the '048 Patent, issued on September 29, 2009. Dana-Farber filed its complaint on September 25, 2015, just shy of six years after issuance of the '048 Patent. Defendants suggest that Dr. Freeman and Dana-Farber should have been aware of the Honjo patents before the '048 Patent issued from the

clinical trial data on nivolumab, which Medarex first published in 2008, but a correction of inventorship claim does not accrue until the patent is issued. See id. Since a presumption of laches does not apply to any of Dana-Farber's claims, Defendants bear the burden to demonstrate both unreasonable delay and material prejudice.<sup>21</sup>

Defendants argue that Dana-Farber unreasonably delayed in bringing its claims because Dr. Freeman learned of the '048 Patent in 2010. Each of Dana-Farber's correction of inventorship claims accrued when the relevant patent issued. Thus, the starting point for measuring Dana-Farber's delay for each claim is not when it became aware of the first patent, though its knowledge of the first patent may be relevant in determining the reasonableness of delay. Instead, I must evaluate Dana-Farber's delay patent-by-patent starting with the date each patent issued. See Lismont, 813 F.3d at 1002; Stark, 29 F.3d at 1576.

Defendants provide no evidence that the delay of sixteen months between issuance of the '474 Patent in May 2014 and the filing of this lawsuit in September 2015 was unreasonable, let

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<sup>21</sup> Pfizer, Wyeth, and GI did not move to intervene until September 22, 2017, more than six years after the '048 Patent issued in September 2009. Dana-Farber's complaint sought to add Dr. Wood to the '048 Patent, however, which put Defendants on notice of Dr. Wood's claim. Accordingly, no presumption of laches applies to the claim that Dr. Wood is a joint inventor of the '048 Patent.

alone the delay of three months in bringing the claims relating to the '999 and '994 Patents issued in June and July 2015, respectively. The eight days between issuance of the '899 Patent on August 2, 2016 and Dana-Farber's motion to amend its complaint was also not unreasonable. However, the delay of almost six years and over three years in bringing suit over inventorship of the '048 and '179 Patents, respectively, might be a different story.

Even if these delays were unreasonable, Defendants cannot show material prejudice. For evidentiary prejudice, Defendants fail to explain what specific documents they lost or what events their witnesses were unable to recount. See Meyers, 974 F.2d at 1308. They mention missing documents memorializing Dr. Honjo and Dr. Minato's pre-1999 discussions of PD-1 and cancer and Dr. Freeman's inability to remember all of his meetings with Dr. Wood, but they do not explain why such evidence would change the outcome of the case. Defendants also have not shown that they would not have suffered these evidentiary issues had Dana-Farber brought suit promptly after the '048 and '179 Patents issued.

For economic prejudice, Defendants argue that BMS has made financial investments of over \$3 billion in developing and commercializing nivolumab in reliance on its exclusive license to the Honjo patents. This theory of economic prejudice does not

pass the blush test. As Dr. Namouni, BMS's head of oncology development, testified at trial, having an exclusive license to a patent is only one of a number of factors BMS considers before investing in a product. He stated that BMS would have invested in nivolumab regardless of whether it had an exclusive license to the Honjo patents. See Gasser Chair Co., 60 F.3d at 775 (stating that the defendant "must prove that the change in economic position would not have occurred had the [plaintiff] sued earlier"). In fact, BMS began clinical trials for new indications for nivolumab after Dana-Farber filed suit. See Yeda, 443 F. Supp. 2d at 630 (declining to consider any investment made by the defendant after they became aware of the inventorship dispute in the laches analysis). BMS's "business decision to capitalize on a market opportunity" cannot support a claim of economic prejudice. Hemstreet, 972 F.2d at 1294. Additionally, BMS has already earned billions of dollars in profits from nivolumab. BMS has not suffered economic prejudice when it has profited so immensely from its product.

**ORDER**

The Court enters judgment in favor of Dana-Farber. Dana-Farber shall submit a form of judgment within ten days ordering correction of the patents.

SO ORDERED.

/s/ PATTI B. SARIS  
Hon. Patti B. Saris  
Chief United States District Judge