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Michelle Bulls
Director
Office of Policy for Extramural
Research Administration (OPERA)
National Institutes of Health
Via Email: michelle.bulls@nih.gov

RE: Failure to disclose government funding associated with cancer immunotherapy patents that name Gordon Freeman as inventor and are assigned to the Dana-Farber Cancer Institute

Dear Ms. Bulls:

Knowledge Ecology International (KEI) requests that the National Institutes of Health (NIH) investigate the apparent **failure to disclose federal support** on six patents recently corrected to name Dr. Gordon Freeman as one of the co-inventors and recently co-assigned to the Dana-Farber Cancer Institute. These six patents claim methods of cancer immunotherapy premised on blocking the inhibitory interaction of the PD-1/PD-L1 pathway, and have generated over a billion dollars in licensing revenue. The patents are co-assigned to the manufacturer of *Opdivo* (nivolumab) and have been asserted in patent infringement lawsuits against *Keytruda* (pembrolizumab) and other cancer immunotherapies that target the PD-1/PD-L1 pathway.

These patents, collectively referred to here as “the Honjo patents”, are the following:

1. Patent No. 7,595,048 (“the ’048 patent”);
2. Patent No. 8,168,179 (“the ’179 patent”);
3. Patent No. 8,728,474 (“the ’474 patent”);
4. Patent No. 9,067,999 (“the ’999 patent”);
5. Patent No. 9,073,994 (“the ’994 patent”);
6. Patent No. 9,402,899 (“the ’899 patent”).

These patents initially named Drs. Tasuku Honjo, Nagahiro Minato, Yoshiko Iwai, and Shiro Shibayama as co-inventors. They were initially assigned to Ono Pharmaceutical and Dr. Honjo.

A judgement entered by the United States District Court, District of Massachusetts, on June 12, 2019, ordered the Director of the United States Patent and Trademark Office "to add Dr. Gordon Freeman and Dr. Clive Wood as inventor" of the Honjo patents, and "to issue a Certificate of Correction accordingly." The corresponding certificates of correction adding Dr. Gordon Freeman and Dr. Clive Wood as co-inventors were issued on July 30, 2019 and August 20, 2019. Dr. Gordon Freeman assigned these patents to the Dana-Farber Cancer Institute on August 6, 2019.

Dr. Freeman benefited from several government grants that supported the research leading to his PD-L1 discoveries. One part of the persuasive evidence of failure to disclose in this case stems from the fact that two key papers on the PD-1/PD-L1 pathway co-authored by Dr. Freeman and Dr. Honjo, along with others, acknowledged National Institutes of Health (NIH) grants. These papers were among the facts considered by the District Court to conclude that Dr. Freeman made significant contributions to the conception of the inventions in the Honjo patents. Since these papers acknowledged NIH grants to Dr. Freeman, the Honjo patents that now name Dr. Freeman as co-inventor should have also disclosed the NIH funding supporting the research, pursuant to the Bayh-Dole Act, 35 U.S.C. §§ 200 *et seq.*

Dr. Freeman funded his PD-L1 research with government grants

Dr. Gordon Freeman is a professor of medicine in the Department of Medical Oncology at the Dana-Farber Cancer Institute and Harvard Medical School. He received a PhD from Harvard University in microbiology and molecular genetics in 1979 and joined the Dana-Farber Cancer Institute first as a postdoctoral fellow. Dr. Freeman has been working at Dana-Farber continuously for 40 years. In 2014 he received (jointly with Drs. Tasuku Honjo, Lieping Chen, and Arlene Sharpe) the William B. Coley Award for identifying the PD-1/PD-L1 ligand pathway.

In July 1998, Dr. Freeman began a search for novel B7 ligands.[1] Using the Basic Local Alignment Search Tool (BLAST) administered by the National Center for Biotechnology Information (NCBI) he found 12 molecules similar to B7-1, a previously known B7 ligand. One of these molecules was identified as AA292201. Dr. Freeman generated the full-length sequence of the AA292201 molecule, and conducted experiments to investigate its expression and immunologic activity. He confirmed that the AA292201 molecule is an immunologically active

[1] The B7 family of immune-regulatory ligands consists of structurally related ligands which bind to receptors on lymphocytes that regulate immune responses. Activation of T and B lymphocytes is initiated by engagement of cell-surface, antigen-specific T-cell receptors or B-cell receptors, but additional signals delivered simultaneously by B7 ligands determine the ultimate immune response. Interaction of B7-family members with costimulatory receptors augments immune responses, and interaction with coinhibitory receptors attenuates immune responses. See: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1175965/

member of the B7 family. Accordingly, Dr. Freeman named the AA292201 molecule “B7-4”. The B7-4 molecule is now commonly referred to as the Programmed Death-Ligand 1 (PD-L1).

On August 23, 1999, Dr. Freeman and three other colleagues at Dana-Farber filed U.S. provisional application 60/150,390, directed to the sequence and the protein of the then-called B7-4 molecule. On November 10, 1999, Dr. Freeman and Dr. Clive Wood from the Genetics Institute, Inc, filed U.S. provisional application 60/164,897, directed to methods of modulating the immune response via activating or blocking the PD-1/PD-L1 pathway. *Table 1* lists six U.S. patents issued thereof that claimed the priority benefits of US provisional applications 60/150,390 and 60/164,897, collectively referred to here as “the Freeman PD-L1 patents.”

U.S. provisional applications 60/150,390 and 60/164,897, as well as the six patents issued thereof, all disclosed NIH grants pursuant to the Bayh-Dole Act, 35 U.S.C. §§ 200 *et seq.*

Table 1. U.S. patents claiming the priority benefits of 60/150,390 and 60/164,897

ID	Date Filed	Date Issued	Grants Disclosed
6,936,704	08/23/2000	08/30/2005	AI039671, AI044690, CA084500*, AI041584 from the NIH
6,808,710	08/23/2000	10/26/2004	AI039671, AI044690, CA084500*, AI041584 from the NIH
7,038,013	11/02/2001	05/02/2006	AI039671, AI044690, CA084500*, AI041584 from the NIH
7,101,550	02/06/2002	09/05/2006	AI039671, AI044690, CA084500*, AI041584 from the NIH
7,635,757	01/26/2006	12/22/2009	AI039671, AI044690, CA084500*, AI041584 from the NIH
7,638,492	08/31/2006	12/29/2009	AI039671, AI044690, CA084500*, AI041584 from the NIH

*Not disclosed in the provisional application, but disclosed in the non-provisional applications

The NIH grant AI041584 funded 13 projects between 1998 and 2000, totaling $3,470,187 in cost. The description of all of these projects mention research related to ligands in the B7 family. NIH grant core number AI039671 funded 11 projects between 1998 and 2002, totaling $4,660,978 in cost. Several projects funded with this core grant investigated the B7 ligand family. For example, according to its description the objective of project 5P01AI039671-04 was “to determine whether B7-1 and B7-2 costimulatory molecules provide the second signal which can induce either the afferent or efferent phases of autoreactive T cell activation leading to pathologic autoimmune disease.” Although neither the AI041584 nor the AI039671 grants list Dr. Freeman as principal investigator on their Project RePORTER entries, they list colleagues at Dana-Farber. For example, several of these projects list Dr. Arlene Sharpe as principal investigator. Dr. Sharpe has co-authored multiple papers with Dr. Freeman and is a co-recipient of the William B. Coley Award. Moreover, the fact that these grants are disclosed in the Freeman PD-L1 patents is a clear indication that they funded the research that led Dr. Freeman to his PD-L1 discoveries.

The NIH grant CA084500 does list Dr. Freeman as a principal investigator. This grant funded three projects between 2000 and 2002, totaling $669,664. All three projects in this core grant describe research related to the B7 ligand family, and in particular anti-tumor immunity.

In late 1999 Dr. Freeman, Dr. Tasuku Honjo, and other scientists started drafting a paper to report their findings related to the PD-1/PD-L1 pathway, based in part on the PD-L1 discoveries of Dr. Freeman.[2] This paper was published on October 2, 2000, in the Journal of Experimental Medicine, and reported that "engagement of PD-1 by PD-L1 leads to the inhibition of TCR-mediated lymphocyte proliferation and cytokine secretion."[3] In May 2000, Dr. Freeman and Dr. Honjo began collaborating on another paper, which related to the expression of PD-L1 on a variety of tissues and tumor cells.[4] That paper was published March 2001 in Nature Immunology.[5] Dr. Freeman, Dr. Honjo and others suggested there that "blocking the PD-1 pathway may enhance anti-tumor immunity," and that the pathway "may be an attractive therapeutic target."

Both of these papers acknowledged benefiting from three NIH grants to Dr. Freeman, citing NIH grant numbers AI039671, AI041584 and CA084500. These grants were also disclosed in the Freeman PD-L1 patents. The acknowledgements in these papers read as follows, respectively:

> "This work was supported by a Center of Excellence grant from the Ministry of Education, Science, Sports, and Culture of Japan, and by National Institutes of Health grants AI39671, AI41584, and CA84500 (to G.J. Freeman)."
>
> "Supported by a Wellcome Trust Travel Fellowship (to Y. L.) and National Institutes of Health grants AI38310, AI40614 (to A. H. S.) and AI39671, AI41584 and CA84500 (to G. J F.)."

We note again that neither the AI041584 nor the AI039671 grants list Dr. Freeman as principal investigator on their Project RePORTER entries. However, the acknowledgements in both of these papers clearly reflect that Dr. Freeman funded his PD-L1 ligand research based on these NIH grants. Grant number CA084500 does list Dr. Freeman as a principal investigator.

Dr. Freeman's NIH-funded research led to the conception of the Honjo patents

[2] Dana-Farber v. Ono Pharmaceutical et al., at 32-33
[3] *Engagement of the Pd-1 Immunoinhibitory Receptor by a Novel B7 Family Member Leads to Negative Regulation of Lymphocyte Activation*. J Exp Med 2 October 2000; 192 (7): 1027–1034. doi: https://doi.org/10.1084/jem.192.7.1027
[4] Dana-Farber v. Ono Pharmaceutical et al., at 41
[5] *PD-L2 is a second ligand for PD-1 and inhibits T cell activation*. Nat Immunol 2, 261–268 (2001) doi:10.1038/85330

Dr. Tasuku Honjo is a professor at the medical school at Kyoto University. Dr. Honjo discovered a new receptor expressed on certain mouse immune cells in the early 1990s. He named the molecule “PD-1” because he believed the receptor was involved in programmed cell death. Dr. Honjo isolated the human DNA sequence for the gene that encodes PD-1 and developed antibodies against mouse and human PD-1. Dr. Honjo knew PD-1 was in the same family of other proteins with inhibitory activity, but he “did not fully understand the molecular mechanism through which PD-1 had its inhibitory effect because he had not identified its ligand.”[6]

In September 1998, Dr. Honjo began collaborating with Dr. Clive Wood in his search for the PD-1 ligand. At the time Dr. Wood was Director of Molecular Immunology at the Genetics Institute, Inc, a company based in Cambridge, MA. During the summer of 1999, at a time when he was still searching for the PD-1 ligand for Dr. Honjo, Dr. Wood became involved in Dr. Freeman’s work relating to the B7-4 ligand.[7] Dr. Freeman had shared information about his B7-4 findings with the Genetics Institute through a partnership they had with Dana-Farber.[8] Dr. Wood tested whether PD-1 and B7-4 bound together, and his experiments showed that they did. B7-4 started to be more commonly referred to as PD-L1, as it was identified as the PD-1 ligand.

In the following months Drs. Honjo, Wood, and Freeman began collaborating to study the PD-1/PD-L1 pathway. Their collaboration produced the two papers acknowledging NIH grants, one of which suggested that “blocking the PD-1 pathway may enhance anti-tumor immunity.”[9]

On July 3, 2002, Ono Pharmaceutical filed Japanese patent application 2002-194491 naming Dr. Honjo as co-inventor. Ono then filed Japanese patent application 2003-029846 on February 6, 2003, also naming Dr. Honjo co-inventor. Six U.S. patents issued thereof claimed the priority benefits of these applications: the ’048, ’179, ’474, ’999, ’994 and ’899 patents, collectively referred to here as the Honjo patents. These patents are directed to methods of cancer immunotherapy premised on blocking the inhibitory interaction of the PD-1/PD-L1 pathway. The Honjo patents were originally assigned to Ono Pharmaceutical and Dr. Honjo. None of the Honjo patents disclose federal funding pursuant to the Bayh-Dole Act, 35 U.S.C. §§ 200 *et seq.*

Dr. Freeman was not originally named on the Honjo patents. On September 25, 2015, the Dana-Farber Cancer Institute filed a complaint before the United States District Court, District of Massachusetts, to correct inventorship of these patents under 35 U.S.C. § 256, by adding Dr. Freeman and Dr. Wood as co-inventors.[10] After a bench trial Judge Patti B. Saris found on May 17, 2019, that “Dana-Farber has presented clear and convincing evidence that Dr. Freeman and Dr. Wood are joint inventors of the six Honjo patents.”[11] A judgement entered by the Court on

[6] *Dana-Farber v. Ono Pharmaceutical et al., at 16.*
[7] *Dana-Farber v. Ono Pharmaceutical et al., at 24*
[8] *Dana-Farber v. Ono Pharmaceutical et al., at 22.*
[9] Nat Immunol 2, 261–268 (2001) doi:10.1038/85330
[10] The original complaint cites five of the six PD-1/PD-L1 patents. The amended complaint includes a sixth.
[11] Dana-Farber v. Ono Pharmaceutical et al., at 5.

June 12, 2019, ordered the Director of the United States Patent and Trademark Office "to add Dr. Gordon Freeman and Dr. Clive Wood as inventor" of the Honjo patents, and "to issue a Certificate of Correction accordingly." The certificates of correction adding Drs. Gordon Freeman and Clive Wood as co-inventors of the Honjo patents were issued on July 30, 2019 and August 20, 2019. Dr. Freeman assigned these patents to the Dana-Farber Cancer Institute on August 6, 2019.

Judge Patti B. Saris' decision to order the correction of the Honjo patents relied on evidence showing the PD-L1 work conducted by Dr. Freeman between 1998 and 2001, and his collaborations with Dr. Honjo during that period. Among the facts considered as evidence of these contributions were the two papers relating to the PD-1/PD-L1 pathway co-authored by Dr. Freeman and Dr. Honjo,[12] one of which suggested that "blocking the PD-1 pathway may enhance anti-tumor immunity," and that the pathway "may be an attractive therapeutic target."

As explained above, Dr. Freeman contributions to the research reported in these papers were funded with NIH grants AI039671, AI041584 and CA084500. This provides convincing evidence of the fact that the Honjo patents that were recently corrected to name Dr. Freeman as an inventor should have disclosed the grants he received to support that research.

The Honjo patents have generated over a billion dollars in licensing revenue

Bristol-Myers Squibb, the manufacturer of the anti-PD-1 cancer immunotherapy approved by the FDA on December 22, 2014 under the brand name Opdivo, has an exclusive license in certain territories to the Honjo patents. On September 4, 2014, Ono Pharmaceutical and Bristol-Myers Squibb filed a lawsuit against Merck alleging patent infringement through the manufacture of Keytruda, an anti-PD-1 cancer immunotherapy that competes with Opdivo. The patent asserted by Ono and Bristol-Myers Squibb against Merck in this lawsuit was the '474 patent. In 2015, Ono and Bristol-Myers Squibb filed an additional infringement lawsuit against Merck based on alleged infringement of the '994 patent and the '999 patent through the manufacture of Keytruda.

On January 1, 2017, Ono Pharmaceutical and Bristol-Myers Squibb reached a lucrative agreement with Merck to settle their ongoing patent litigation. Under the terms of the settlement, Merck obtained a license to the patents in exchange for an upfront payment of $625 million plus an ongoing royalty of 6.5% on worldwide sales of Merck's PD-1 drug Keytruda. This settlement involved patents that now name Dr. Freeman as co-inventor and should have disclosed the grants he received from the NIH pursuant to the Bayh-Dole Act, 35 U.S.C. §§ 200 *et seq.*

Ono Pharmaceutical and Bristol-Myers Squibb have filed additional patent infringement lawsuits against Genentech for the manufacture of Tecentriq, an anti-PD-L1 antibody approved by the FDA in 2016; Pfizer for the manufacture of Bavencio, an anti-PD-L1 antibody approved in 2017;

[12] Dana-Farber v. Ono Pharmaceutical et al., at 66

and AstraZeneca for the manufacture of Imfinzi, an anti-PD-L1 antibody approved in 2017. The patent asserted in these infringement lawsuits was the ‘899 patent.

On June 21, 2019, following the judgement entered by the District Court ordering to name Dr. Freeman as a co-inventor of the Honjo patents, the Dana-Farber Cancer Institute filed a complaint requesting the court to “[o]rder BMS or Ono to disgorge some or all of the settlement proceeds, licensing fees, royalties and other benefits that BMS and Ono and their agents, beneficiaries, assignees, licensees, and successors have derived as a result of any and all litigation, agreements, and/or representations they undertook, entered into, or otherwise made concerning the Patents.” According to their complaint, Dana-Farber estimates that Ono and Bristol-Myers Squibb have generated “more than $1.6 billion in licensing revenue” related to the Honjo patents. Based on publicly available information, this litigation is still ongoing.

Bayh-Dole Disclosure Requirements

The Bayh-Dole Act and federal regulations and guidelines make clear several obligations for contractors in the disclosure of government rights in subject inventions, including: (1) a requirement to disclose that federal funding contributed to an invention; (2) NIH contractual requirements for disclosure; and (3) required language to be inserted in patent applications and patents, stating the role of federal funding and the government’s rights.

Under 35 U.S.C. § 202(c)(1), any contractor that receives funding from the federal government is required to “disclose each subject invention to the Federal agency within a reasonable time after it becomes known to contractor personnel responsible for the administration of patent matters.”

Under 37 C.F.R. § 401.3(a), each federal funding agreement shall contain the “standard patent rights clause” found at 37 C.F.R. § 401.14, barring specific circumstances and exceptions. Subsection (c)(1) of the patent rights clause outlines the disclosure requirements.

37 C.F.R. § 401.14(c)(1)

(c) Invention Disclosure, Election of Title and Filing of Patent Application by Contractor

(1) The contractor will disclose each subject invention to the Federal Agency within two months after the inventor discloses it in writing to contractor personnel responsible for patent matters. The disclosure to the agency shall be in the form of a written report and shall identify the contract under which the invention was made and the inventor(s). It shall be sufficiently complete in technical detail to convey a clear understanding to the extent known at the time of the disclosure, of the nature, purpose, operation, and the physical, chemical, biological or electrical characteristics of the invention. The disclosure shall also identify any publication, on sale or public use of the invention and whether a manuscript describing the invention has been submitted for publication and, if so, whether it has been accepted for publication at the

time of disclosure. In addition, after disclosure to the agency, the Contractor will promptly notify the agency of the acceptance of any manuscript describing the invention for publication or of any on sale or public use planned by the contractor.

According to 37 C.F.R. § 401.14(f)(4) and NIH Guidelines for Grants and Contracts, grant recipients must include the following language in their patent applications and patents:

> "This invention was made with Government support under (grant/contract number) awarded by the (Federal agency). The Government has certain rights in the invention."

Finally, under 35 U.S.C. § 202(c)(6) and 37 C.F.R. § 1.77(b)(3), contractors are required to state within the patent application or patent that the federal government contributed funding to support the discovery of the invention and that the government retains certain rights.

35 U.S.C. § 202(c)(6)

(c) Each funding agreement with a small business firm or nonprofit organization shall contain appropriate provisions to effectuate the following:

(6) An obligation on the part of the contractor, in the event a United States patent application is filed by or on its behalf or by any assignee of the contractor, to include within the specification of such application and any patent issuing thereon, a statement specifying that the invention was made with Government support and that the Government has certain rights in the invention.

Remedies

KEI urges the NIH to promptly investigate the apparent non-disclosure and take all appropriate remedial action, including taking title to the patents. Failure to disclose subject inventions pursuant to 35 U.S.C. § 202(c)(1) permits the federal government to "receive title to any subject invention not disclosed to it within such time[.]"

If the NIH never revokes a patent or imposes any meaningful sanctions, universities and other contractors will continue to underreport federal funding. A certificate of correction on the patent does not send a strong enough signal regarding the public's right to know its rights in patented inventions.

The disclosure requirements were designed to protect the government's rights in federally-sponsored technology such as biomedical inventions. We are asking the NIH to ensure that when taxpayer investments are relevant to an invention, the government is diligent in

ensuring that the public's rights are acknowledged and secured. In order to protect the public's rights, we ask that the government take possession of patents when grant recipients do not make timely disclosures, as is required by law, and as appears to be the case here.

Finally, KEI requests information from the NIH about its efforts to enforce the obligations to disclose federal funding in patented biomedical inventions. Specifically:

1. How many times has the NIH asked an inventor to correct a non-disclosure of NIH funding in an invention since January 1, 2015?
2. Has the NIH ever taken title to a patent on the grounds that the inventor failed to disclose the NIH funding of the invention?
3. Can you share a list of the several requests that KEI has filed since January 1, 2015 to address this issue for specific inventions? And, can you provide information on what the NIH has done to address each of the previous complaints we have filed?

We look forward to your response addressing the failure to disclose in the Honjo patents as well as the questions listed above. Thank you for your attention to this important issue.

Sincerely,

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