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March 14, 2018

The Honorable Alex Azar  
Secretary  
Department of Health and Human Services  
200 Independence Avenue, S.W.  
Washington, D.C. 20201  
Via email: [secretary@hhs.gov](mailto:secretary@hhs.gov)

Dear Secretary Azar:

Knowledge Ecology International has identified a patent held by Pharmasset Inc. that fails to disclose relevant federal funding from the National Institutes of Health associated with the invention. A failure to disclose is a violation of federal law and regulations, as well as NIH guidelines and contractual agreements with the grant recipient.

### **Patent 7,964,580**

Specifically, U.S. Patent 7,964,580, filed on March 21, 2008 and granted June 21, 2011, identifies three inventors, all employed by Pharmasset at the time the patent was filed.

Patent number:	7,964,580
Date of patent grant:	June 21, 2011
Date of patent filing:	March 21, 2008
Patent title:	Nucleoside phosphoramidate prodrugs
Inventors:	Sofia; Michael Joseph (Doylestown, PA), Du; Jinfa (New Hope, PA), Wang; Peiyuan (Glen Rock, NJ)
Assignee:	Pharmasset, Inc. (Princeton, NJ)
Family ID:	39808855
Appl. No.:	12/053,015

## Research Grants from National Institute of Diabetes and Digestive and Kidney Diseases

Peiyuan Wang was hired by Pharmasset in 2000, directly after a postdoctoral research fellowship at the NIH. Jinfa Du joined Pharmasset in November 2001. Both Wang and Du received their PhDs from the University of Georgia. Michael Sofia joined Pharmasset in August 2005.

According to the National Institute of Health Reporter database, Jinfa Du was the principal investigator for four grants awarded to Pharmasset, titled *Dioxolane Nucleosides as Antiviral Agents* and *2'-and/or 4'-C-Modified Nucleosides as Anti-HCV Agents*.

Grant number	Titled	PI	Company	Grant budget start	Grant budget end	Agency
1 R43 AI056794 01	<a href="#">DIOXOLANE NUCLEOSIDES AS ANTIVIRAL AGENTS</a>	DU, JINF	PHARMASSET	15-Jul-2003	14-Jul-2004	NIAID
1 R01 DK066922 01	<a href="#">2'-AND/OR 4'-C-MODIFIED NUCLEOSIDES AS ANTI-HCV AGENTS</a>	DU, JINF	PHARMASSET	15-Sep-2004	31-Jul-2005	NIDDK
5 R01 DK066922 02	<a href="#">2'-AND/OR 4'-C-MODIFIED NUCLEOSIDES AS ANTI-HCV AGENTS</a>	DU, JINF	PHARMASSET	1-Aug-2005	31-Jul-2006	NIDDK
5 R01 DK066922 03	<a href="#">2'-AND/OR 4'-C-MODIFIED NUCLEOSIDES AS ANTI-HCV AGENTS</a>	DU, JINF	PHARMASSET	1-Aug-2006	31-Jul-2007	NIDDK

Of interest are the three grants with the same title: *2'-and/or 4'-C-Modified Nucleosides as Anti-HCV Agents*.

The grants describe the use of nucleosides to treat the viral hepatitis C infection (HCV). The abstract for grant 5R01DK066922-03 reads as follows:

DESCRIPTION (provided by applicant): Current therapies for chronic HCV infections are inadequate because of low response rates, toxic side effects, and unsustained viral load reductions. As with other chronic infections (HBV and HIV-1), long-term therapy with multiple drugs will most likely be required to successfully treat chronic HCV infections and significantly reduce or eliminate progressive hepatocellular damage and hepatocellular carcinoma. The only licensed therapy for chronic HCV is interferon (IFN)-alpha, either alone or in combination with ribavirin. Combination therapy with ribavirin and IFN-alpha for 6 to 12 months is currently the treatment of choice for HCV infection. The overall sustained response rate to treatment, defined as loss of HCV from serum 6 months after completion of treatment, is 40%. Thus, there is an urgent need for better agents to treat chronic HCV infections. We have designed a novel antiviral against HCV screening technology using the HCV replicon system. Using this approach we identified modified nucleoside analogues with potent and selective in vitro anti-HCV activity. In this grant proposal, **we plan to design and synthesize a total of one hundred and ninety novel 2'-C- and/or 4'-C-modified nucleosides, as well as 3'-deoxynucleosides as potential anti-HCV agents.** We will determine the anti-HCV activity of a series of newly designed compounds in vitro. In addition, in preparation for in vivo proof of principle studies, adequate safety and favorable pharmacokinetic (PK) profiles of candidate compounds will be determined in relevant animal models. Furthermore, potent HCV polymerase inhibitors will be used to select for drug-resistant viral mutants, and therefore, selection of HCV replicons with the proper mutations will be a relevant part of this proposal. [Emphasis added]

Among other things, the grant funded Pharmasset's, **"plan to design and synthesize a total of one hundred and ninety novel 2'-C- and/or 4'-C-modified nucleosides, as well as 3'-deoxynucleosides as potential anti-HCV agents."**

The patent provides several examples that appear to be the subject matter of the grants, including, to mention a few:

- EXAMPLE 4 Preparation of 2'-deoxy-2'-fluoro-2'-C-methyluridine
- EXAMPLE 5 Preparation of 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-phenyl methoxy-alanyl phosphate)
- EXAMPLE 6 Preparation of 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(phenyl methoxy-valyl phosphate)
- EXAMPLE 7 Preparation of 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-valyl phosphate)
- EXAMPLE 8 Preparation of 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-alanyl phosphate)
- EXAMPLE 9 Preparation of N.sup.4-(N,N-dimethylformamidinyl)-2'-deoxy-2'-fluoro-2'-C-methylcytidine
- EXAMPLE 10 Preparation of 2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-alanyl phosphate)

- EXAMPLE 11 Preparation of 2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-4-bromophenyl methoxy-valyl phosphate)
- EXAMPLE 12 Preparation of 2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-valyl phosphate)

KEI notes that patent 7,964,580 is the first patent listed in the FDA Orange Book for every single Gilead drug using sofosbuvir (SOF) as a treatment for HCV.

## **The Failure to Report Government Rights Violates Federal Law and Regulations, and May Result in the Government Receiving Title.**

The Bayh-Dole Act and federal regulations and guidelines obligate contractors to disclose government rights in subject inventions, including via: (1) a requirement to disclose within a reasonable time that federal funding contributed to a subject invention;<sup>1</sup> (2) NIH contractual requirements for disclosure;<sup>2</sup> and (3) required language to be inserted in patent applications and the patents, stating the role of federal funding and the government's rights.<sup>3</sup>

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.”<sup>4</sup>

## **Request for Investigation and Remedy for Non-disclosure**

KEI asks your office to conduct an investigation into the failure to disclose federal funding of this patent.

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<sup>1</sup> 35 U.S.C. § 202(c)(1)

<sup>2</sup> See 37 C.F.R. § 401.3(a), requiring that each federal funding agreement contain the “standard patent rights clause” found at 37 C.F.R. § 404.14(a); see also HHS Form 568, “Final Invention Statement and Certification (For Grant or Award), available at <https://grants.nih.gov/grants/hhs568.pdf>, requiring disclosure via iEdison; and National Institutes of Health, Reminder: All Subject Inventions Must Be Reported on the HHS 568 - Final Invention Statement and Certification (For Grant or Award) and in iEdison, NOT-OD-16-066 (Feb. 17, 2016), NIH Guide Notice, <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-066.html>.

<sup>3</sup> 35 U.S.C. § 202(c)(6); 37 C.F.R. § 1.77(b)(3); see also MPEP (9th ed. Rev. 07.2015, Nov. 2015), § 310 (recommending the insertion of a clause stating: “This invention was made with government support under (identify the contract) awarded by (identify the Federal agency). The government has certain rights in the invention.”).

<sup>4</sup> See *Campbell Plastics Engineering & Mfg., Inc. v. Brownlee*, 389 F.3d 1243 (Fed. Cir. 2004) (finding that federal government claim of title in invention was legitimate under federal acquisition regulations and supported by the policy considerations behind the Bayh Dole Act where disclosure submissions were “piecemeal” and violated the contractual agreement with the government); see also *Central Admixture Pharmacy Services, Inc. v. Advanced Cardiac Solutions, P.C.*, 482 F.3d 1347, 1352-53 (Fed. Cir. 2007) (“Critically, *Campbell Plastics* holds that a Bayh–Dole violation grants the government *discretionary* authority to take title. . . . When a violation occurs, the government can choose to take action; thus, title to the patent may be voidable.”).

If your office can confirm that there was a failure to disclose the relevant NIH grants in this patent, we then ask that the NIH take possession of the patent.

The patent in question may be worth billions of dollars. In addition to whatever liability for royalties Gilead could be responsible for stemming from its use of a government owned patented invention (if the government takes possession), there would be opportunities to use the Bayh-Dole royalty-free right to exercise considerable leverage over the prices of all SOF-based HCV treatments.

In considering the remedies, KEI notes that there have been several recent requests to use 28 USC § 1498 to obtain access to affordable generic versions of SOF-based HCV treatments for veterans,<sup>5</sup> for state-run HCV programs,<sup>6</sup> and more generally to extend treatment to more persons who are infected with HCV.<sup>7</sup> In the past, and as you know from your involvement in the 2001 ciprofloxacin case,<sup>8</sup> government agencies have been reluctant to use § 1498 for cases involving pharmaceutical drugs, out of concerns over the compensation required. However, when the government uses its royalty-free rights in connection with a § 1498 non-voluntary use of a patented invention, the risks of excessive compensation can be significantly reduced. Even if a § 1498 remedy is ultimately not used, the possibility of such an action will be considered more likely if the public has rights in this patent, and hence, a government agency will have more leverage to negotiate a better price — one that can expand treatment to all persons who are infected, as opposed to only those with the most serious immediate health consequences.

Indeed, taking action to remedy the non-disclosure of the patent creates all sorts of opportunities to advance the public's interests. For example, the federal government could condition Gilead's right to continue using the patent upon the provision of at-cost HCV medicines for veterans receiving care from the Department of Veterans Affairs, and thus remedy the situation where the high cost of sofosbuvir-based treatments has depleted the Department resources budgeted for health care for veterans.

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<sup>5</sup> May 12, 2015 [letter](#) from Senator Bernard Sanders to Secretary of the US Department of Veterans Affairs, Robert McDonald.

<sup>6</sup> Carolyn Y. Johnson, Louisiana considers radical step to counter high drug prices: Federal intervention, July 3, 2017

<sup>7</sup> See: James Love, *Nonvoluntary use of patents for drugs to treat the Hepatitis C Virus in the United States: Mechanisms available to the Federal Government, State Governments and Private Actors*, KEI Policy Brief 2014:1, July 18, 2014; Amy Kapczynski and Aaron Kesselheim, "Government Patent Use": A Legal Approach to Reducing Drug Spending," *Health Affairs*, Vol. 35, No. 5 (May 2016); [Letter of February 15, 2018](#) from Rep. Ro Khanna (D-CA-17), co-signed by Rep. Lloyd Doggett (D-TX-35), Rep. Mark Pocan (D-WI-2), Rep. Janice Schakowsky (D-IL-9), Rep. Chellie Pingree (D-ME-1), Rep. Peter Welch (D-VT-At large), Rep. Raúl Grijalva (D-AZ-3), Rep. Keith Ellison (D-MN-5), Rep. Gwen Moore (D-WI-4), Rep. Jamie Raskin (D-MD-8), Rep. Marcy Kaptur (D-OH-9), Rep. Rosa DeLauro (D-CT-3), Rep. Earl Blumenauer (D-OR-3), Rep. Steve Cohen (D-TN-9), Rep. Eleanor Holmes Norton (D-DC-At large), Rep. Elijah Cummings (D-MD-7), Rep. Judy Chu (D-CA-27), and Rep. Colleen Hanabusa (D-HI-1) to DHHS Secretary Alex Azar.

<sup>8</sup> Alex Azar II. CIPRO: Good Deal, Good Policy; Letters, *The American Lawyer*, April, 2002.

Thank you in advance for your attention to this matter. We request a meeting to discuss this matter further.

Kind regards,

Andrew S. Goldman, Counsel, Knowledge Ecology International

James Love, Director, Knowledge Ecology International

Priscille Ngana, Researcher, Knowledge Ecology International

Cc:

The Honorable Daniel R. Levinson, [Dan.Levinson@oig.hhs.gov](mailto:Dan.Levinson@oig.hhs.gov);

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Maura Calsyn and Thomas Huelskoetter, Center for American Progress

Robert Weissman, President, Public Citizen

Shaun O'Brien, AFL-CIO

Rebekah Gee, M.D., Secretary of the Louisiana Department of Health

Senator Amy Klobuchar (D-MN)

Senator Angus King (I-ME)

Senator Bernie Sanders (I-VT)

Senator Chuck Grassley (R-IA)

Senator Dick Durbin (D-IL)

Senator Elizabeth Warren (D-MA)

Senator John Thune (R-SD), Committee on Commerce, Science, and Transportation, Chair

Senator Lamar Alexander (R-TN), Committee on Health, Education, Labor & Pensions, Chair

Senator Richard Blumenthal (D-CT)

Senator Ron Wyden (D-OR)

Senator Sherrod Brown (D-OH)

Senator Susan Collins (R-ME), Special Committee on Aging, Chair

Representative Barbara Comstock (R-VA), Committee on Science, Space and Technology, Chair, Subcommittee on Research and Technology

Representative Elijah Cummings (D-MD)

Representative Gregg Harper (R-MS), Energy and Commerce Committee, Chair, Subcommittee on Oversight

Representative Jan Schakowsky (D-IL)

Representative Jim Jordan (R-OH), Oversight & Government Reform Committee, Chair, Subcommittee on Healthcare, Benefits, and Administrative Rules

Representative Lamar Smith (R-TX), Committee on Science, Space and Technology, Chair

Representative Lloyd Doggett (D-TX)

Representative Michael Burgess (R-TX), Energy and Commerce Committee, Chair, Subcommittee on Health

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