



1621 Connecticut Ave NW Suite 500  
Washington, D.C. 20009  
+1 (202) 332-2670  
<http://keionline.org>

October 16, 2017

The Honorable Eric D. Hargan  
Acting Secretary  
Department of Health and Human Services  
200 Independence Avenue, S.W.  
Washington, D.C. 20201  
Via: [eric.hargan@hhs.gov](mailto:eric.hargan@hhs.gov)

Re: The failure of the University of Pennsylvania to disclose the NIH interest in five CAR T patents

Dear Secretary Hargan:

This letter requests that you investigate substantial evidence that the Trustees of the University of Pennsylvania ("UPenn") failed to satisfy disclosure requirements under the Bayh-Dole Act, 35 U.S.C. §§ 200 *et seq.*, and federal regulations, 37 C.F.R. §§ 401.3(a) & 401.14, with regard to federally-funded subject inventions related to chimeric antigen receptor T cell ("CAR T") therapy in human cancers such as hematologic malignancies, embodied in the following U.S. Patent Nos.:

8,916,381 (the "381 patent")  
8,975,071 (the "071 patent")  
9,102,760 (the "760 patent")  
9,101,584 (the "584 patent")  
9,102,761 (the "761 patent")

We have a high degree of confidence that these five patents (collectively, the "2014 patents") are subject inventions under the Bayh-Dole Act, in that they were "conceived or first actually reduced to practice in the performance of work under a funding agreement." 35 U.S.C. § 201(e).

In spite of the significant federal funding supporting the chimeric antigen receptor research at UPenn, none of the 2014 patents list government rights in the invention, nor the role of National Institutes of Health (NIH) grants in the development of the CAR T technology.

*The 13 patents sharing the same 5 inventors*

Table 1 provides information on 13 granted patents that mention “chimeric antigen receptor”, are assigned to the Trustees of the University of Pennsylvania, and which have the same 5 inventors — all current or former employees of the University of Pennsylvania.

For these 13 patents, there are 5 and only 5 inventors mentioned on the patent.

- The four patents filed from June 2012 to December 2013 disclosed several NIH grants and federal government rights in the patent.
- The five patents filed from August to December 2014 disclosed no federal funding.
- The four patents filed from December 2015 to January 2016 also disclosed NIH grants and federal government rights in the patents.

The five patents of interest are those filed between August and December 2014 which share the exact same inventors and the exact same earliest priority date. We believe these 5 patents failed to disclose federal rights in the patents.

**Table 1: UPenn CAR Patents with the Five Main Inventors**

Patent Number	NIH Grants	Date filed	Earliest priority date	Carl H June	Michael D Kalos	Bruce L Levine	Michael C Milone	David L Porter
9,499,629	K24CA11787901, R01CA120409, 1R01CA105216, R01AI057838 and R011113482**	2012-06-14	2010-12-09	Y	Y	Y	Y	Y
8,906,682	K24CA11787901, R01CA120409, 1R01CA105216, R01AI057838 and R011113482**	2013-07-10	2010-12-09	Y	Y	Y	Y	Y
8,911,993	K24CA11787901, R01CA120409, 1R01CA105216, R01AI057838 and R011113482	2013-07-10	2010-12-09	Y	Y	Y	Y	Y

9,328,156	K24CA11787901, R01CA120409, 1R01CA105216, R01AI057838 and R011113482**	2013-12-16	2010-12-09	Y	Y	Y	Y	Y
8,916,381	None reported	2014-08-22	2010-12-09	Y	Y	Y	Y	Y
8,975,071	None reported	2014-08-22	2010-12-09	Y	Y	Y	Y	Y
9,102,760	None reported	2014-12-11	2010-12-09	Y	Y	Y	Y	Y
9,101,584	None reported	2014-12-12	2010-12-09	Y	Y	Y	Y	Y
9,102,761	None reported	2014-12-12	2010-12-09	Y	Y	Y	Y	Y
9,481,728	K24CA11787901, R01CA120409, 1R01CA105216, R01AI057838 and R011113482**	2015-12-30	2010-12-09	Y	Y	Y	Y	Y
9,464,140	K24CA11787901, R01CA120409, 1R01CA105216, R01AI057838 and R011113482**	2016-01-14	2010-12-09	Y	Y	Y	Y	Y
9,540,445	K24CA11787901, R01CA120409, 1R01CA105216, R01AI057838 and R011113482**	2016-01-14	2010-12-09	Y	Y	Y	Y	Y
9,518,123	K24CA11787901, R01CA120409, 1R01CA105216, R01AI057838 and R011113482**	2016-01-15	2010-12-09	Y	Y	Y	Y	Y

There is one additional relevant patent that has three of the same five inventors, was filed January 15, 2016, and that disclosed funding from six NIH grants.

**Table 2: The CAR Patent with 3 of the 5 Inventors**

Patent Number	NIH Grants	Date filed	Earliest priority date	Carl H June	Michael D Kalos	Bruce L Levine	Michael C Milone	David L Porter
9,572,836	K24CA11787901, 1R01CA120409, 1R01CA105216, R01AI057838, R011113482** and 1PN2EY016586	2016-01-15	2012-07-13	Y	Y	Y		

We believe that the 2014 patents, which share the exact same inventors and the exact same earliest priority date, have failed to disclose NIH funding and acknowledge U.S. governmental rights in the patents.

Furthermore, we submit evidence, presented below, that the NIH itself has identified at least three NIH grants as related to each of the five 2014 patents.

### *Why disclosure is important*

CAR T technology is a critical development for immunotherapy that relies on the patient's own cells for the treatment of cancer. This type of treatment holds great promise, with multiple companies including, but not limited to, Novartis, Juno, and Gilead focused on bringing products to market.

There is a concern is that CAR T patents will be used to block innovation by competitors. The relationship between Novartis and UPenn suggests commercial interests will play an important role in enforcing any granted patents. The past litigation involving UPenn, Juno, St Jude's Hospital and others is an early indication there are overlapping claims on CAR T patents and the potential for future litigation. In the past, aggressive litigation by Novartis over Chiron patents on the hepatitis C virus delayed introduction of new drugs by several years. After the announcement that Gilead would acquire Kite Pharma, Gilead indicated to KEI that it expects considerable litigation over CAR T patent claims, in part due to overlapping claims.

The pricing of CAR T treatments will be high when monopolies persist. Novartis's opening price of \$475,000 per treatment for Kymriah<sup>1</sup> is an early indication that CAR T prices will be aggressive, placing burdens on Medicare, Medicaid and other federal programs, as well as the private sector payers.

When the federal government has rights in patents under the Bayh-Dole Act, there are opportunities to force less restrictive licensing, as was done on the WARF patents on stem cells and the patents on vaccine manufacturing technologies using reverse genetics.

The Bayh-Dole Act also requires federally-funded inventions to be made "available to the public on reasonable terms."

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<sup>1</sup> Gina Kolata, "New Gene-Therapy Treatments Will Carry Whopping Price Tags," *New York Times*, September 11, 2017. Available at <https://www.nytimes.com/2017/09/11/health/cost-gene-therapy-drugs.html>

## I. The Bayh-Dole Act Requires Disclosure of Government Rights in Subject Inventions

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 the patents, stating the role of federal funding and the government's rights.

First, contractors are required to disclose subject inventions discovered with federal funding in a timely manner and with sufficient detail to describe the invention.

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.”

The statute defines a “subject invention” at 35 U.S.C. § 201(e) as “any invention of the contractor conceived or first actually reduced to practice in the performance of work under a funding agreement,” and defines a contractor at 35 U.S.C. § 201(c) as “any person, small business firm, or nonprofit organization that is party to a funding agreement.”

“Funding agreement” is defined at 35 U.S.C. § 201(b) to mean “any contract, grant, or cooperative agreement entered into between any Federal agency, other than the Tennessee Valley Authority, and any contractor for the performance of experimental, developmental, or research work funded in whole or in part by the Federal Government.”

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(a), barring specific circumstances and exceptions.<sup>2</sup> Subsection (c)(1) of the patent rights clause outlines the disclosure requirements, including a two month time limit on the disclosure of patents and a requirement that the disclosure have sufficient detail:<sup>3</sup>

### **37 C.F.R. § 401.14(a)(c)(1)**

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

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<sup>2</sup> The exceptions do not contain reference to the disclosure requirements.

<sup>3</sup> Italics in original.

(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*.

...

(4) Requests for extension of the time for disclosure, election, and filing under subparagraphs (1), (2), and (3) may, at the discretion of the *agency*, be granted.

Second, in implementing this regulation, the NIH requires contractors to disclose subject inventions via iEdison, an online electronic system for reporting inventions and patents discovered under federal grants, and via HHS Form 568, entitled, "Final Invention Statement and Certification (For Grant or Award)," available at: <https://grants.nih.gov/grants/hhs568.pdf>.

The NIH specifies the required information on an FAQ related to the use of iEdison, and also notes that contractors should disclose the subject invention even if they have, in the past, failed to report the invention within the two month period:<sup>4</sup>

## **iEdison & Intellectual Property FAQs and Resources**

### **5. What information is required to report a subject invention?**

The invention disclosure must include the following information:

- Either the EIR Number, Invention Docket Number, or both.
- Invention Title
- Names of all of the inventors and the institutions with which they are associated
- Invention Report Date

<sup>4</sup> Available at: [https://era.nih.gov/iedison/iedison\\_faqs.cfm#VIII5](https://era.nih.gov/iedison/iedison_faqs.cfm#VIII5) (accessed Oct. 10, 2017).

-Description of the Invention that must meet the standards set forth per 37 CFR Sec. 401.14 (a)(c)(1):

**“. . . 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.”37 C.F.R. 401.14(a)(c)(1)”**

-Primary Funding Agency

-All funding agreement numbers and names of the funding agencies

- 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

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**9. If I upload a patent application, can that patent application satisfy the Invention Disclosure Report requirement?**

Yes, so long as the EIR Number or Invention Docket Number is included on the submission, the patent record containing the patent/patent application number has been reported in iEdison, and you upload proof that the patent application was filed with the USPTO, e.g., a USPTO submission receipt.

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**10. What should a grantee/contractor do if a subject invention hasn't been reported to the awarding agency within the required 2 month period?**

Always report the invention, even if it is late. The invention report date should be the date the inventor notified the awardee institution of the subject invention. Provide an explanation in the "Explanatory Notes" section of the invention record.

On February 17, 2016, the NIH issued a notice entitled “Reminder: All Subject Inventions Must Be Reported on the HHS 568 - Final Invention Statement and Certification (For Grant or Award) and in iEdison.” The notice explained that failure to disclose the subject invention via both iEdison and Form 568 could result in the loss of rights in the invention.<sup>5</sup> As explained below in section V on remedies, this notice is consistent with precedent related to failure to disclose.

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 that the federal government contributed funding to support the discovery of the invention and that the government retains certain rights:

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<sup>5</sup> 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>.

**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.

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**35 C.F.R. § 1.77(b)(3)**

(b) The specification should include the following sections in order:

...

(3) Statement regarding federally sponsored research or development.

The Manual of Patent Examining Procedure contains the following recommended language:

“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>6</sup>

## **II. UPenn Failed to Disclose the 2014 Patents as Subject Inventions Under the Bayh-Dole Act**

*UPenn received substantial federal funding from the NIH for the development of CAR T technology*

Seven grants from the NIH between the years of 1995 and 2017 helped push UPenn to the forefront of research institutions working on the development of CAR T technology.

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<sup>6</sup> MPEP (9th ed. Rev. 07.2015, Nov. 2015), § 310.



**Table 3a: NIH Grants to UPenn Relating to CAR T Technology**

NIH Grant	Grant Period	Grant Title	Patents	Grant Recipient	Grant Amount
1R01CA105216	2004	CULTURE SYSTEMS TO PROPOGATE [sic] HUMAN T CELL SUBSETS	12	JUNE, CARL H.	\$286,100
1R01CA120409	2006	IMMUNOTHERAPY OF MESOTHELIN EXPRESSING TUMORS WITH LENTIVIRAL ENGINEERED T CELLS	2	JUNE, CARL H.	\$278,675
R01CA120409	2006-2016	IMMUNOTHERAPY WITH CAR T CELLS/ IMMUNOTHERAPY OF MESOTHELIN EXPRESSING TUMORS WITH LENTIVIRAL ENGINEERED T CELLS	10	JUNE, CARL H.	\$2,676,065
K24CA11787901	2006	MID-CAREER INVESTIGATOR AWARD IN ALLOGENEIC ADOPTIVE IMMUNOTHERAPY	9	PORTER, DAVID	\$155,592
R01CA172921	2013-2017	USE OF GENETICALLY ENGINEERED T CELLS TARGETING TUMOR STROMA TO TREAT LUNG CANCER	1	ALBELDA, STEVEN MARK	\$1,177,634
R01AI057838	2004-2008	REGULATION OF HUMAN T CELL ACTIVATION BY THE CD28 FAMILY	12	RILEY, JAMES L	\$1,731,361
P01CA66726	1995-2016	IMMUNO/IMMUNO-GENE THERAPIES FOR THORACIC MALIGNANCIES, GENE THERAPY FOR MALIGNANT MESOTHELIOMA	1	ALBELDA, STEVEN MARK et al.	\$22,203,754

In addition, the University of Pennsylvania was co-recipient of one grant with the Wistar Institute:

**Table 3b: NIH Grants to UPenn as Co-Recipient Relating to CAR T Technology**

NIH Grant	Grant Period	Grant Title	Patents	Grant Recipient	Grant Amount
CA141144	2010-2014	FIBROBLAST ACTIVATION PROTEIN IN THE TUMOR MICROENVIRONMENT IN LUNG CANCER	1	PURE', ELLEN	\$1,573,613

*UPenn is the currently the assignee of twenty-nine patents relating to CAR technology*

As of the date of this letter, the Trustees of the University of Pennsylvania is the assignee of twenty-nine US patents that include the term "chimeric antigen receptors." The filing dates for the patents are from February 4, 2011 to January 15, 2016. The patents were granted from December 23, 2014 to October 10, 2017.

*Thirteen of the twenty-nine patents share the same five inventors, including the 2014 patents*

As described at the outset, thirteen of the twenty-nine patents list the same five inventors: Carl H June, Michael D Kalos, Bruce L Levine, Michael C Milone, and David L Porter. A fourteenth patent omits Milone and Porter as inventors, while June, Kalos and Levine remain listed.

As shown in Table 1, of these particular patents with the same five inventors, only the 2014 patents fail to disclose the NIH grants that supported the invention.

Note that of the thirteen patents with the five main inventors, all except the 2014 patents refer to the same grants: K24CA11787901, R01CA120409, 1R01CA105216, R01AI057838 and R011113482\*\*. The fourteenth patent (with three of the five inventors) discloses these same grants in addition to NIH grant 1PN2EY016586.

All thirteen of the patents with these five main inventors have patents with the same earliest priority date of December 09, 2010. The 2014 patents in particular were filed on August 22 and December 12 of 2014.

*The inventors of the 2014 patents*

#### **Carl H. June, M.D.**

Carl H. June is the Richard W. Vague Professor in Immunotherapy, Director of the Center for Cellular Immunotherapies, and Director of the Parker Institute for Cancer Immunotherapy at the University of Pennsylvania's Perelman School of Medicine. He is the director of Translational Research at the Abramson Cancer Center as well as as an investigator of the Abramson Family Cancer Research Institute. His lab researches and develops CARs and the means to deliver them into human T cells.<sup>7</sup> Dr. June has been examining T cell systems and CAR therapies for several decades, and has published extensively on the topics. In July 2014, his lab's CAR T approach to cancer immunotherapy received US FDA Breakthrough Therapy designation, the first academic research center to received such a recognition. In 2017 Dr. June received the

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<sup>7</sup> <http://www.med.upenn.edu/apps/faculty/index.php/g275/p2328>

David A. Karnofsky Memorial Award for his role in developing engineered T cells in targeted cancer therapy. Dr. June became tenured faculty at UPenn in 1999.<sup>8</sup>

### **Michael D. Kalos, PhD**

Michael D. Kalos is the Chief Scientific Officer in Cancer Immunobiology at Eli Lilly and Company, but was a faculty member at the University of Pennsylvania from 2008 to 2013, where he established the Translational and Correlative Studies Laboratory within the Perelman School of Medicine.<sup>9</sup>

### **Michael Milone**

Michael Milone is an Associate Professor of Pathology and Laboratory Medicine at the Hospital of the University of Pennsylvania and Perelman School of Medicine.<sup>10</sup> Milone's LinkedIn entry notes that as a postdoctoral fellow working with Dr. Carl June, Milone "designed CTL019 (TN: Kymriah, INN: tisagenlecleucel), a CD19-specific T cell immunotherapy, and conducted the IND-enabling, pre-clinical studies of this novel genetically-engineered cell therapy required for the initial Phase I clinical trial."<sup>11</sup> His current research includes, "developing chimeric antigen receptors (CARs) for adoptive immunotherapy of cancer with enhanced function and improved safety, developing and applying synthetic immunoreceptors to the treatment of immune-mediated disease, and exploring the role of co-stimulatory signals in directing T cell metabolism and the way this metabolism affects T cell function within tumors."<sup>12</sup> Dr. Milone has been with the University since 1999.<sup>13</sup>

### **Bruce Levine**

Dr. Bruce Levine is a Barbara and Edward Netter Professor in Cancer Gene Therapy, and is the Founding Director of the Clinical Cell and Vaccine Production Facility (CVPF) in the Department of Pathology and Laboratory Medicine and the Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, and has been with the University since 1999.<sup>14</sup> Dr. Levine lists "good manufacturing practices" as an area of expertise in his biography on the UPenn website.<sup>15</sup>

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<sup>8</sup> <http://www.aacr.org/Funding/Pages/su2c-cri-committee-detail.aspx?ItemID=2#.Wd0TLUuGPq6>

<sup>9</sup> <https://www.linkedin.com/in/michael-kalos-81366b9>

<sup>10</sup> <http://pathology.med.upenn.edu/department/people/439/michael-c-milone>

<sup>11</sup> <https://www.linkedin.com/in/michael-milone-5a251736/>

<sup>12</sup> <http://pathology.med.upenn.edu/department/people/439/michael-c-milone>

<sup>13</sup> <https://www.linkedin.com/in/michael-milone-5a251736/>

<sup>14</sup> <https://www.linkedin.com/in/bruce-levine-9976859/>

<sup>15</sup> <http://pathology.med.upenn.edu/department/people/291/bruce-l-levine>

## David L. Porter

David L. Porter is the Jodi Fisher Horowitz Professor in Leukemia Care Excellence, and Director of Blood and Marrow Transplantation at the Hospital of the University of Pennsylvania.<sup>16</sup> He was with the University at least as early as 2002 when working in the division of Hematology-Oncology.<sup>17</sup> Dr. Porter, as well as Dr. Milone, are also the two clinical collaborators in the Nanomedicine Center for Mechanobiology Directing the Immune Response, which receives funding from the NIH Common Fund.<sup>18</sup>

*The NIH RePORTER website shows that the 2014 Patents share an identical “Core NIH Project Number” for NIH grant number R01CA105216*

The NIH RePORTER website is a tool that “allows users to search a repository of NIH funded research projects”.<sup>19</sup> NIH grant number R01CA105216, entitled “Culture Systems to propagate [sic] Human T cell Subsets” and given to Dr. Carl H. June at the University of Pennsylvania, is connected to 12 patents (see Figure 1). This project was awarded a total of \$1,460,542 from 2004 to 2008 to study antigen presenting cells and T cell subsets for cancer and HIV immunotherapy.

The findings from this project were published in 31 articles found in academic peer-reviewed journals. These findings are related to and support claims from patents listed in Table 2, including 8916381, 8975071, 9102760, 9101584 and 9102761. For example, Dr. June’s lab reported on better ways to culture and grow CAR T cells, and, characterized CARs constructed with multiple intracellular co-stimulatory domains such as CD28 or 4-1BB with CD3zeta.<sup>20</sup> These signaling domains are claimed as key parts of the CAR construction in the 2014 patents.

Methods and compositions in the 2014 patents clearly stem from project R01CA105216 and other NIH funded research conducted in Dr. June’s laboratory. Though the NIH reports these patents to be connected to R01CA105216, there is a failure to mention the government interests within the patents.

### **Figure 1: Screenshot of NIH-RePORTER Results (taken October 10, 2017) of Patents Connected to Grant Number R01CA105216.**

<sup>16</sup> <https://www.med.upenn.edu/apps/faculty/index.php/g348/p4492>

<sup>17</sup> [https://www.researchgate.net/publication/10953797\\_Umbilical\\_cord\\_blood\\_transplantation\\_Where\\_do\\_we\\_stand](https://www.researchgate.net/publication/10953797_Umbilical_cord_blood_transplantation_Where_do_we_stand)

<sup>18</sup> <https://commonfund.nih.gov/nanomedicine/devcenters/mechanicalbiology>

<sup>19</sup> <https://projectreporter.nih.gov/reporter.cfm>

<sup>20</sup> Frigault MJ *et al.* Identification of chimeric antigen receptors that mediate constitutive or inducible proliferation of T cells. *Cancer Immunol Res.* Apr 2015  
(<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4390458/#SD1>)

U.S. Department of Health & Human Services

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Core NIH Project Number	Patent Number	Patent Title	Patent Owner	Primary Agency
R01CA105216	7754482	<a href="#">Artificial antigen presenting cells and uses therefor</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01CA105216	8722400	<a href="#">Artificial antigen presenting cells and uses therefor</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01CA105216	9102761	<a href="#">Compositions for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01CA105216	9102760	<a href="#">Compositions for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01CA105216	8975071	<a href="#">Compositions for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01CA105216	8911993	<a href="#">Compositions for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01CA105216	9133436	<a href="#">ICOS critically regulates the expansion and function of inflammatory human Th17 cells</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01CA105216	9572836	<a href="#">Methods for assessing the suitability of transduced T cells for administration</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01CA105216	8916381	<a href="#">Methods for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01CA105216	9101584	<a href="#">Methods for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01CA105216	8906682	<a href="#">Methods for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01CA105216	9328156	<a href="#">Use of chimeric antigen receptor-modified T cells to treat cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH

Table 4 presents the 12 patents in the RePorter search for NIH grant R01CA105216. The patents with a blue background are the 2014 patents.

**Table 4: The RePorter Designated Patents for Grant R01CA105216**

NIH Grant	Patent	Title	Grantee	Federal rights disclosed on patent
R01CA105216	7,754,482	Artificial antigen presenting cells and uses therefor	UNIVERSITY OF PENNSYLVANIA	R21 AI060477, R01 CA105216 R01 AI 057838
R01CA105216	8,722,400	Artificial antigen presenting cells and uses therefor	UNIVERSITY OF PENNSYLVANIA	R21 AI060477, R01 CA105216 R01 AI057858
R01CA105216	8,906,682	Methods for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	K24 CA11787901, R01CA120409, 1R01CA105216,

				R01AI057838 RO11113482
R01CA105216	8,911,993	Compositions for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	K24 CA11787901, R01CA120409, 1R01CA105216, R01AI057838 RO11113482
R01CA105216	8,916,381	Methods for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	None
R01CA105216	8,975,071	Compositions for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	None
R01CA105216	9,101,584	Methods for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	None
R01CA105216	9,102,760	Compositions for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	None
R01CA105216	9,102,761	Compositions for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	None
R01CA105216	9,133,436	ICOS critically regulates the expansion and function of inflammatory human Th17 cells	UNIVERSITY OF PENNSYLVANIA	5R01CA105216, 1R01CA120409, 5P01CA066726 R01A1057838
R01CA105216	9,328,156	Use of chimeric antigen receptor-modified T cells to treat cancer	UNIVERSITY OF PENNSYLVANIA	K24 CA11787901, R01CA120409, 1R01CA105216, R01AI057838 RO11113482
R01CA105216	9,572,836	Methods for assessing the suitability of transduced T cells for administration	UNIVERSITY OF PENNSYLVANIA	K24 CA11787901, 1PN2-EY016586, 1R01CA105216, 1R01CA120409, R01AI057838, RO1113482

*The NIH RePORTER website shows that the 2014 Patents share an identical “Core NIH Project Number” for NIH grant number R01AI057838*

Chimeric antigen receptors are composed of different segments having distinct functions in antigen recognition, signaling and co-stimulation. Understanding the right combination of these segments is important in the function of the CAR and, the activation and survival of the T cell. T cell activation enables these to multiply and allows for the cells to respond to tumors they recognize. The NIH funded project R01AI057838 entitled “Regulation of Human T Cell Activation by the CD28 Family” aims to discern the mechanism behind antigen-dependent signaling pathways responsible for survival and anti-tumor functions so that clinicians can better control therapeutic T cells. Specifically this project studies signaling and activation through

CD28 and ICOS. The R01AI057838 grant is connected to 12 patents including the 2014 patents. Embodiments of second generation CARs described in the 2014 patents incorporate co-stimulatory fragments, such as CD28 and ICOS, into their intracellular domains. Additionally, published results relevant to the 2014 patents appear in articles supported by the R01AI057838 grant. Scientific articles of particular interest are; "Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo", "The inducible costimulator (ICOS) is critical for the development of human T(H)17 cells" and "CD28 costimulation is essential for human T regulatory expansion and function".<sup>21, 22, 23</sup> The R01AI057838 project grant was awarded to Dr. James L Riley at University of Pennsylvania, from 2004 to 2008. The total amount of funding for these four years was \$1,731,361.<sup>24</sup>

**Figure 2: Screenshot of NIH-RePORTER Results (taken October 11, 2017) of Patents Connected to Grant Number R01AI057838.**

Core NIH Project Number	Patent Number	Patent Title	Patent Owner	Primary Agency
R01AI057838	7754482	<a href="#">Artificial antigen presenting cells and uses therefor</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01AI057838	8722400	<a href="#">Artificial antigen presenting cells and uses therefor</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01AI057838	8975071	<a href="#">Compositions for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01AI057838	9102761	<a href="#">Compositions for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01AI057838	8911993	<a href="#">Compositions for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01AI057838	9102760	<a href="#">Compositions for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01AI057838	9133436	<a href="#">ICOS critically regulates the expansion and function of inflammatory human Th17 cells</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01AI057838	9572836	<a href="#">Methods for assessing the suitability of transduced T cells for administration</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01AI057838	8916381	<a href="#">Methods for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01AI057838	9101584	<a href="#">Methods for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01AI057838	8906682	<a href="#">Methods for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
R01AI057838	9328156	<a href="#">Use of chimeric antigen receptor-modified T cells to treat cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH

<sup>21</sup> Milone MC et al. Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo. Mol Ther. Aug 2009

<sup>22</sup> Paulos CM et al. The inducible costimulator (ICOS) is critical for the development of human T(H)17 cells. Sci Transl Med. Oct 2010

<sup>23</sup> Golovina TN et al. CD28 costimulation is essential for human T regulatory expansion and function. J Immunol. Aug 2008

<sup>24</sup> <https://projectreporter.nih.gov>



We checked the patent disclosures on the twelve patents identified by RePorter as relevant to NIH Grant R01A1057838. As reported in Table 5, all disclosed federal funding except for the five “2014” patents.

**Table 5: The 12 RePorter-Designated Patents for Grant R01A1057838**

NIH Grant	Patent	Title	Grantee	Federal rights disclosed on patent
R01AI057838	9,572,836	Methods for assessing the suitability of transduced T cells for administration	UNIVERSITY OF PENNSYLVANIA	K24 CA11787901, 1PN2-EY016586, 1R01CA105216, 1R01CA120409, RO1AI057838, RO1113482,
R01AI057838	9,328,156	Use of chimeric antigen receptor-modified T cells to treat cancer	UNIVERSITY OF PENNSYLVANIA	K24 CA11787901, R01CA120409, 1R01CA105216, RO1AI057838, RO1113482
R01AI057838	9,133,436	ICOS critically regulates the expansion and function of inflammatory human Th17 cells	UNIVERSITY OF PENNSYLVANIA	5R01CA105216, 1R01CA120409, 5P01CA066726, R01A1057838
R01AI057838	9,102,761	Compositions for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	None
R01AI057838	9,102,760	Compositions for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	None
R01AI057838	9,101,584	Methods for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	None
R01AI057838	8,975,071	Compositions for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	None
R01AI057838	8,916,381	Methods for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	None
R01AI057838	8,911,993	Compositions for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	K24 CA11787901, R01CA120409, 1R01CA105216, RO1AI057838, RO1113482
R01AI057838	8,906,682	Methods for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	K24 CA11787901, R01CA120409, 1R01CA105216, RO1AI057838, RO1113482
R01AI057838	8,722,400	Artificial antigen presenting cells and	UNIVERSITY OF	R21 AI060477,



		uses therefor	PENNSYLVANIA	R01 CA105216, R01 AI057858.
R01AI057838	7,754,482	Artificial antigen presenting cells and uses therefor	UNIVERSITY OF PENNSYLVANIA	R21 AI060477, R01 CA105216, R01 AI 057838

*The NIH RePORTER website shows that the 2014 Patents share an identical “Core NIH Project Number” for NIH grant number K24CA117879*

Nine patents, including the 2014 patents, are affiliated with the K24CA117879 “Mid-career Investigator Award in Allogeneic Adoptive Immunotherapy” project (Figure 3). Dr. David Porter, from the University of Pennsylvania, was awarded \$777,980 between 2006 and 2010, to conduct research under this project. K42 mid-career grants are awarded to clinicians for “patient-oriented research”.<sup>25</sup> The research conducted under this grant applied to cellular immunotherapy against cancer. Importantly, grant K24CA117879 supported the crucial but small 2011 UPenn clinical study with Dr. June, “Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia” (NCT01029366) that demonstrated the potential of their CAR T cell therapy in leukemia. Shortly after this study, Novartis gave UPenn funding towards a research center in exchange for exclusive worldwide rights to CARs developed at UPenn.<sup>26</sup>

**Figure 3: Screenshot of NIH-RePORTER Results (taken October 11, 2017) of Patents Connected to Grant Number K24CA117879.**

The screenshot displays the NIH RePORTER search results for patents connected to grant number K24CA117879. The interface includes a search bar, navigation tabs (PROJECTS, PUBLICATIONS, PATENTS, CLINICAL STUDIES, DATA & VISUALIZE, MAP, NEWS & MORE), and an EXPORT button. A message indicates that there are 9 connections of patents to projects matching the search criteria. The results are presented in a table with the following columns: Core NIH Project Number, Patent Number, Patent Title, Patent Owner, and Primary Agency.

Core NIH Project Number	Patent Number	Patent Title	Patent Owner	Primary Agency
K24CA117879	8911993	<a href="#">Compositions for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
K24CA117879	8975071	<a href="#">Compositions for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
K24CA117879	9102760	<a href="#">Compositions for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
K24CA117879	9102761	<a href="#">Compositions for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
K24CA117879	9572836	<a href="#">Methods for assessing the suitability of transduced T cells for administration</a>	UNIVERSITY OF PENNSYLVANIA	NIH
K24CA117879	9101584	<a href="#">Methods for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
K24CA117879	8916381	<a href="#">Methods for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
K24CA117879	8906682	<a href="#">Methods for treatment of cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH
K24CA117879	9328156	<a href="#">Use of chimeric antigen receptor-modified T cells to treat cancer</a>	UNIVERSITY OF PENNSYLVANIA	NIH

<sup>25</sup> [https://grants.nih.gov/grants/funding/funding\\_program.htm](https://grants.nih.gov/grants/funding/funding_program.htm)

<sup>26</sup> <https://www.elsevier.com/connect/penn-and-novartis-collaborate-on-new-cancer-drug>

We checked the patent disclosures on the nine patents identified by RePorter as relevant to NIH Grant **K24CA117879**. As reported in Table 6, all disclosed federal funding exception for the five “2014” patents.

**Table 6: The 9 RePorter Designated Patents for Grant K24CA117879.**

NIH Grant	Patent	Title	Grantee	Federal rights disclosed on patent
K24CA117879	9572836	Methods for assessing the suitability of transduced T cells for administration	UNIVERSITY OF PENNSYLVANIA	K24 CA11787901, 1PN2-EY016586, 1R01CA105216, 1R01CA120409, RO1AI057838, RO1113482
K24CA117879	9328156	Use of chimeric antigen receptor-modified T cells to treat cancer	UNIVERSITY OF PENNSYLVANIA	K24 CA11787901, R01CA120409, 1R01CA105216, RO1AI057838, RO1113482
K24CA117879	9102761	Compositions for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	None
K24CA117879	9102760	Compositions for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	None
K24CA117879	9101584	Methods for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	None
K24CA117879	8975071	Compositions for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	None
K24CA117879	8916381	Methods for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	None
K24CA117879	8911993	Compositions for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	K24 CA11787901, R01CA120409, 1R01CA105216, RO1AI057838, RO1113482
K24CA117879	8906682	Methods for treatment of cancer	UNIVERSITY OF PENNSYLVANIA	K24 CA11787901, R01CA120409, 1R01CA105216, RO1AI057838, RO1113482

### **III. In the Case of a Failure to Disclose, the Government May Reclaim the Invention**

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**” (emphasis added).

In the past, the federal government has utilized its authority to claim title in subject inventions that have not been properly disclosed, as in the case of *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 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.”).

In *Campbell Plastics*, the court found that the contract was clear and unambiguous, but moreover the government’s claim to title was “buttressed by the policy considerations behind the Bayh-Dole Act.” *Id.* at 1248. These include, specifically under 35 U.S.C. § 200, the need “to ensure that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions.”

### **IV. Conclusion**

We believe that there is sufficient evidence to warrant an investigation into this matter. If the 2014 patents are subject inventions under the Bayh-Dole Act, UPenn has an affirmative obligation to disclose the inventions to the government and to explicitly state the government’s rights in the patents. The 2014 patents appear to have failed to do so in spite of the abundant evidence suggesting that they are subject inventions.

The failure to disclose government rights in a subject invention does a disservice to taxpayers, consumers and patients.

We request a meeting at your earliest convenience to discuss this matter in further detail.

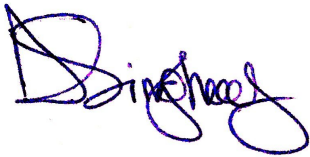
Sincerely,



James Love  
Director  
Knowledge Ecology International  
[james.love@keionline.org](mailto:james.love@keionline.org)



Andrew S. Goldman, Esq.  
Counsel, Policy and Legal Affairs  
[andrew.goldman@keionline.org](mailto:andrew.goldman@keionline.org)



Diane Singhroy  
Scientific and Technical Advisor  
[diane.singhroy@keionline.org](mailto:diane.singhroy@keionline.org)

Cc:  
Gary M. Beck, Advisor for External Affairs, HHS  
Ann Hammersla, Director of OPERA's Division of Extramural Inventions and Technology  
Resources, NIH