Rydapt (INN midostaurin)

Failures to disclose government funding for patents granted to James Griffin and assigned to Dana-Farber Cancer Institute in the FDA Orange Book

Knowledge Ecology International
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Table of Contents

Introduction

Knowledge Ecology International (KEI) asks the Department of Health and Human Services (DHHS) to investigate a failure to disclose National Institutes of Health (NIH) research funding on two patents granted to James D. Griffin as the lead inventor, and assigned to a single entity, Dana-Farber Cancer Institute.

Patents 7,973,031 and 8,222,244 are listed as the first two patents (out of three patents) in the FDA Orange Book for the drug Rydapt (INN midostaurin), used for the treatment of acute myeloid leukemia (AML), myelodysplastic syndrome and advanced systemic mastocytosis (ASM).

The cost of Rydapt depends upon the indication and patient weight. For a typical patient, the cost for the treatment of AML is $195,405 per year, and for ASM, $390,811 per year. In both cases, the high cost is a barrier to access and a fiscal strain on health systems.

From 1985 to 2017, James Griffin was the principal investigator for 46 projects and 25 sub projects funded by the NIH totalling $44 million. All of the grants involve research on leukemia.

KEI is asking the NIH to take title to the patents, which is a remedy available under the Bayh-Dole Act for non-disclosure of federal funding of patented inventions. At a minimum, the Department of Health and Human Services should require the Dana-Farber Cancer Institute to correct the failure to disclose the relevant NIH grants.

What Is Midostaurin?

Midostaurin is a multi-targeted protein kinase inhibitor that was synthesized by Giorgio Caravatti in 1986,[1] originally encoded as CGP 41251 and later known as PKC421, as part of a drug discovery program aimed toward optimizing the inhibitory activity of staurosporine, a natural product isolated from Streptomyces staurosporeus, against protein kinase C (PKC). To investigate its potential as a PKC inhibitor, studies were conducted revealing midostaurin's ability to inhibit cell proliferation (by interfering with cell-cycle activity) and inhibit solid tumor growth (by displaying antiproliferative activity).[2,3] Following oral administration, midostaurin

[1] Caravatti G, Meyer T, Fredenhagen A, et al. Inhibitory activity and selectivity of staurosporine derivatives towards protein kinase C. Bioorg Med Chem Lett. 1994;4(3):399–404.
[2] Ikegami Y, Yano S, Nakao K. Antitumor effect of CGP41251, a new selective protein kinase C inhibitor, on human non-small cell lung cancer cells. Jpn J Pharmacol. 1996;70(1):65-72.
[3] Ikegami Y, Yano S, Nakao K. Effects of the new selective protein kinase C inhibitor 4′-N-benzoyl staurosporine on cell cycle distribution and growth inhibition in human small cell lung cancer cells. Arzneimittelforschung. 1996;46(2):201-204

produces active metabolites that target the protein kinase C family including serine-threonine and tyrosine kinases.[4]

What Does Rydapt Do?

On April 28, 2017 the FDA approved Rydapt (INN midostaurin) for the following indications:

- Newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.

- Aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).

The FDA released the following statement:[5]

> "Rydapt is the first targeted therapy to treat patients with AML, in combination with chemotherapy," said Richard Pazdur, M.D., acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research and director of the FDA's Oncology Center of Excellence. "The ability to detect the gene mutation with a diagnostic test means doctors can identify specific patients who may benefit from this treatment. ...The safety and efficacy of Rydapt for patients with AML were studied in a randomized trial of 717 patients who had not been treated previously for AML."

The Dana-Farber Cancer Institute issued its own press release, titled "Backed by Dana-Farber research, FDA approves new AML drug," which stated:[6]

> "A targeted drug whose clinical testing was led by Richard Stone, MD, of Dana-Farber Cancer Institute, has become the first new treatment for newly diagnosed acute myeloid leukemia (AML) in more than 25 years. . . The drug, midostaurin (Rydapt®), was approved by the U.S. Food and Drug Administration (FDA) as a combination treatment, with chemotherapy, for adult patients newly diagnosed with AML that carries a mutation in the gene FLT3. Such patients account for roughly a third of the 21,000 Americans

[4] Manley PW, Caravatti G, Furet P, Roesel J, Tran P, Wagner T. Comparison of the profile of the AML drug midostaurin (Rydapt(R) as a kinase inhibitor with those of its predominant primary human metabolites. Blood. 2017:130(suppl 1). Abstract 1383

[5] Press Release. FDA approves new combination treatment for acute myeloid leukemia. FDA. April 28, 2017

[6] Press Release. Backed by Dana-Farber research, FDA approves new AML drug. Dana-Farber Cancer Institute. April 28, 2017.

diagnosed annually with AML, a rare and aggressive disease of the blood and bone marrow."

The Cost of Rydapt

According to Reuters, the list price at introduction was $7,495 for 56 25mg capsules, or $133.84 per capsule.[7]

An AML patient would typically receive 50mg twice a day (4 capsules), and the AMS patient would typically receive 100 mg twice a day (8 capsules).

The cost of the treatment depend upon the indication.

For AML, the cost would be $535.36 per day and $195,405.36 per year.

For an AMS patient, the cost is $1070.71 per day and $390,810.71 per year.

The Orange Book Patents for Rydapt

The March 19, 2018 version of the FDA Orange Book lists three patents for Rydapt. Two were assigned to Novartis AG (Basel, CH) and Dana-Farber Cancer Institute and one was assigned to solely to Novartis AG.

Table 1: The Orange Book patents for Rydapt

Patent number	Date filed	Date granted	Expiration	Inventors	Assignee
7973031	10/29/2002	7/5/2011	10/17/2024	Griffin; James D (Brookline, MA), Manley; Paul W (Arlesheim, CH)	Novartis AG (Basel, CH) Dana-Farber Cancer Institute Inc (Boston, MA)
8222244	5/17/2011	7/17/2012	10/29/2022	Griffin; James D (Brookline, MA), Manley; Paul W (Arlesheim, CH)	Novartis AG (Basel, CH) Dana-Farber Cancer Institute Inc. (Boston, MA)
8575146	6/17/2004	11/5/2013	12/2/2030	Coutre; Steven (Stanford, CA)	Novartis AG (Basel, CH)

[7] Reuters Staff. U.S. FDA approves Novartis' Leukemia Treatment. April 28, 2017.

The Griffin Patents that Failed to Disclose Federal Funding

The patents assigned to Novartis AG and the Dana-Farber Cancer Institute that failed to report NIH funding are listed in Table 2.

Table 2: The two FLT3 Griffin patents

Patent number	Priority date	Date filed	Date granted	Title
7973031	2001-10-30	10/29/2002	7/5/2011	Staurosporine derivatives as inhibitors of FLT3 receptor tyrosine kinase activity
8222244	2001-10-30	5/17/2011	7/17/2012	Staurosporine derivatives as inhibitors of FLT3 receptor tyrosine kinase activity

Note, the two patents have the exact same title and the same priority date of October 30, 2001. The first patent was filed in 2002, but not granted until 2011. The second patent was filed May 17, 2011.

On June 21, 2017, Novartis filed for an application for a patent term extension for patent 7,973,031, requesting an additional 1183 days.

On June 21, 2017, Novartis also requested a patent term extension for patent 8,222,244, for an additional 994 days.

The James Griffin Research Grants from the National Institutes of Health

NIH Grants for which James Griffin was a Principal Investigator

According to the National Institutes of Health RePORTER database, from 1985 to 2012 James Griffin was the principal investigator for grants involving 42 projects and 17 sub-projects awarded to the Dana-Farber Cancer Institute, with a total of $32,655,809 in NIH funding.

Griffin received funding from the National Cancer Institute, the National Institute of Diabetes and Digestive and Kidney Diseases and the National Heart, Lung and Blood Institute every fiscal year from 1985 to 2012.

From 2014 to 2017, James Griffin was the principal investigator for NIH grants to the Brigham and Women’s Hospital involving 4 projects and 8 sub projects involving $11,297,311.

A list of all 71 NIH projects and subprojects identifying James Griffin as principal investigator is attached as an Annex.

Of particular interest are the periods of funding from 1996 to 2001, leading up to the priority date for both patents, and from 2009 to 2011, leading up to the filing of the second patent.

Table 3: Funding by fiscal year for 71 NIH funded projects and subprojects listing James Griffin as the principal investigator, from 1985 to 2017

Year	Projects	Sub Projects	Total funding
1985	1		$127,387
1986	1		$116,972
1987	1		$155,176
1988	2		$267,469
1989	2		$329,404
1990	2		$382,739
1991	2		$468,263
1992	2		$485,919
1993	2		$525,493
1994	2		$512,094
1995	2		$533,957
1996	3		$2,534,049
1997	2	2	$2,701,141
1998	2	4	$3,232,873
1999	2	3	$3,023,890
2000	2	2	$2,755,613
2001	2	1	$1,515,995
2002	1		$298,972
2003	1		$355,929
2004	1		$355,929
2005	1		$355,929
2006	1		$347,565
2007	1		$337,486
2008		1	$302,258
2009	1	1	$2,678,257

2010	1	1	$2,724,533
2011	1	1	$2,605,102
2012	1	1	$2,625,415
2013			
2014	1	2	$2,881,926
2015	1	2	$2,806,128
2016	1	2	$2,805,172
2017	1	2	$2,804,085
Totals	46	25	$43,953,120
Subtotal, 1996 to 2001	13	12	$15,763,561
Subtotal, 2009 to 2011	3	3	$8,007,892
Annual Average, 1996 to 2001			$2,627,260
Annual Average, 2009 to 2011			$2,669,297

Note that from 1996 to 2001, James Griffin was the principal investigator for grants averaging $2.6 million per year, or $7,198 per day, from the NIH, to study leukemia. This included, for example, six grants with the title “Novel Therapeutic Strategies in Leukemia and Lymphoma,” with a total grant amount of $11,122,975.

Table 4: NIH grants from 1996 to 2001 with title: “Novel Therapeutic Strategies in Leukemia and Lymphoma.”

Project	Title	PI	Institution	Fiscal Year	NIH funding
1 P01 CA066996 01A1	Novel Therapeutic Strategies In Leukemia And Lymphoma	Griffin, James Douglas	Dana-farber Cancer Institute	1996	$2,004,678

5 P01 CA066996 02	Novel Therapeutic Strategies In Leukemia And Lymphoma	Griffin, James Douglas	Dana-farber Cancer Institute	1997	$1,990,293
5 P01 CA066996 03	Novel Therapeutic Strategies In Leukemia And Lymphoma	Griffin, James Douglas	Dana-farber Cancer Institute	1998	$2,057,110
5 P01 CA066996 04	Novel Therapeutic Strategies In Leukemia And Lymphoma	Griffin, James Douglas	Dana-farber Cancer Institute	1999	$2,035,202
5 P01 CA066996 05	Novel Therapeutic Strategies In Leukemia And Lymphoma	Griffin, James Douglas	Dana-farber Cancer Institute	2000	$2,102,745
3 P01 CA066996 05S1	Novel Therapeutic Strategies In Leukemia And Lymphoma	Griffin, James Douglas	Dana-farber Cancer Institute	2001	$932,947

These grants were cited in at least six papers published by James Griffin from 2002 to 2007, describing the elements of the patented inventions, including two papers that mention PCK412 (midostaurin) in the title of the paper.

Table 5: Seven papers published from 2002 to 2007 describing the role of FLT3 and PTK inhibitors for the treatment of leukemia cells.

Publication date	Citation	Authors	Disclosures
2002 June 1	(2002). Inhibition of mutant FLT3 receptors in leukemia cells by the small molecule tyrosine kinase inhibitor PKC412. Cancer Cell. 1 (5), 433-443.	Weisberg, E., Boulton, C., Kelly, L.M., Manley, P., Fabbro, D., Meyer, T., Gilliland, G., Griffin, J.D.	This work was supported in part by NIH PO1 CA66996 (D.G.G. and J.D.G.), a Leukemia and Lymphoma Society Specialized Center of Research Grant 7059 (D.G.G. and J.D.G.), and NIH PO1 DK50654 (D.G.G. and J.D.G.).
2002 Aug 13	(2002). The roles of FLT3 in hematopoiesis and leukemia. Blood. 100 (5), 1532-1542.	Gilliland, D.G., Griffin, J.D.	Supported in part by National Institutes of Health (NIH) PO1 CA66996 (D.G.G. and J.D.G.), a Leukemia and Lymphoma Society Specialized Center of Research Grant 7059 (D.G.G. and J.D.G.), and NIH PO1 DK5654 (D.G.G. and J.D.G.). D.G.G. is an Associate Investigator of

			the Howard Hughes Medical Institute.
2003 Feb 27	(2003). Inhibition of FLT3 in MLL: Validation of a therapeutic target identified by gene expression based classification. Cancer Cell. 3 (2), 173-183.	Armstrong, S.A., Kung, A.L., Mabon, M.E., Silverman, L.B., Stam, R.W., Den Boer, M.L., Pieters, R., Kersey, J.H., Sallan, S.E., Fletcher, J.A., Golub, T.R., Griffin, J.D., Korsmeyer, S.J.	This work was supported in part by NIH grants PO1 CA68484 and KO8 CA92551 and an American Society of Hematology Fellow Scholar Award (S.A.A.)
2004 Mar 2	(2004). Combination of rapamycin and protein tyrosine kinase (PTK) inhibitors for the treatment of leukemias caused by oncogenic PTKs. Proceedings of the National Academy of Sciences of the United States of America. 101 (9), 3130-3135.	Mohi, M.G., Boulton, C., Gu, T.L., Sternberg, D.W., Neuberg, D., Griffin, J.D., Gilliland, D.G., Neel, B.G.	This work was supported by National Institutes of Health Grants R01 DK50654 and PO1 DK50693 (to B.G.N.) and PO1 CA66996 (to J.D.G. and D.G.G.). D.G.G. is an Associate Investigator of the Howard Hughes Medical Institute. M.G.M. is supported by a fellowship from the Leukemia and Lymphoma Society.
2004 Sep 1	(2004) Identifying and characterizing a novel activating mutation of the FLT3 tyrosine kinase in AML. Blood. 104 (6), 1855-1858.	Jiang, J., Paez, J.G., Lee, J.C., Bo, R., Stone, R.M., DeAngelo, D.J., Galinsky, I., Wolpin, B.M., Jonasova, A., Herman, P., Fox, E.A., Boggon, T.J., Eck, M.J., Weisberg, E., Griffin, J.D., Gilliland, D.G., Meyerson, M., Sellers, W.R.	Supported by the Poduska Family Foundation, by the Claudia-Adams Barr Foundation (M.M. and W.R.S), by National Institutes of Health grant DK50654 and CA66996, and by the Leukemia and Lymphoma Society (D.G.G.). D.G.G. is an Associate Investigator of the Howard Hughes Medical Institute.
2004 Dec 20	(2005). Patients with acute myeloid leukemia and an activating mutation in FLT3 respond to a small-molecule FLT3 tyrosine kinase inhibitor, PKC412. Blood. 105 (1), 54-60.	Stone, R.M., DeAngelo, D.J., Klimek, V., Galinsky, I., Estey, E., Nimer, S.D., Grandin, W., Lebwohl, D., Wang, Y., Cohen, P., Fox, E.A., Neuberg, D., Clark, J., Gilliland, D.G., Griffin, J.D.	Supported in part by a Leukemia and Lymphoma Society SCOR grant (R.M.S., D.J.D., D.G.D., J.D.G.) and Leukemia and Lymphoma Society grants (V.K. and S.D.N.) and by National Institutes of Health grant PO1 CA66996-06.
2007 Jul 9	(2007). Potentiation of antileukemic therapies by Smac mimetic, LBW242: effects on mutant FLT3-expressing cells. Molecular Cancer Therapy. 6 (7), 1951-1961.	Weisberg, E., Kung, A.L., Wright, R.D., Moreno, D., Catley, L., Ray, A., Zawel, L., Tran, M., Cools, J., Gilliland, G., Mitsiades, C., McMillin, D.W., Jiang, J., Hall-Meyers, E., Griffin, J.D.	J.D. Griffin is supported by NIH grant CA66996 and a Specialized Center of Research Award from the Leukemia and Lymphoma Society. J.D. Griffin is also supported by NIH grants CA36167 and DK50654. L. Zawel and M. Tran are employees of Novartis Pharma AG, Basel, Switzerland. J.D. Griffin has a financial interest with Novartis Pharma AG.

Note that Griffin also cited support from NIH grants CA36167 and DK50654.

There were at least 24 projects funded under grant CA306167 where Griffin was the principal investigator from 1985 to 2007, of which 23 are included in the NIH RePORTer database. We are attaching the titles and links to the 23 CA306167 grants as an Annex.

There were seven DK50654 grants, and these are listed in Table 6.

Table 6: Seven DK050654 projects listing James Griffin as the PI and Dana-Farber as the institution.

Project	Project Title	FY	Funding IC	Total cost
1 P01 DK050654 01A1	Signal Transduction Pathways In Stable Phase Chronic Myeloid Leukemia Cells	1996	NIDDK	Unavailable
1 P01 DK050654 02	Signal Transduction Pathways In Stable Phase Chronic Myeloid Leukemia Cells	1997	NIDDK	$210,597
3 P01 DK050654 03S1	Signal Transduction Pathways In Stable Phase Chronic Myeloid Leukemia Cells	1998	NIDDK	$198,808
5 P01 DK050654 03	Signal Transduction Pathways In Stable Phase Chronic Myeloid Leukemia Cells	1998	NIDDK	$198,808
5 P01 DK050654 04	Signal Transduction Pathways In Stable Phase Chronic Myeloid Leukemia Cells	1999	NIDDK	$198,808
5 P01 DK050654 05	Signal Transduction Pathways In Stable Phase Chronic Myeloid Leukemia Cells	2000	NIDDK	$148,636
3 P01 DK050654 05S1	Signal Transduction Pathways In Stable Phase Chronic Myeloid Leukemia Cells	2001	NIDDK	$296,752

There are several other grants that appear to be related to the inventions in the Rydapt patents, including the second patent, 8,222,244, which was filed on May 17, 2011.

For example, the CA066996 projects listed in Table 7, totalling $8.3 million and averaging more than $2 million per year, are particularly relevant. Several elements of the grant abstracts are directly related to the claims for patent 8,222,244.

Table 7: CA066996 grants from 2008 to 2011

Project	Title	Fiscal Year	Cost
P01 CA066996 11A1	Tyrosine Kinase Oncogenes In Acute Myeloid Leukemias	2008	$302,258
P01 CA066996 12	Tyrosine Kinase Oncogenes In Acute Myeloid Leukemias	2009	$311,047
P01 CA066996 12	Development Of Novel Therapeutic Strategies In Human Leukemias	2009	$2,367,210

P01 CA066996 13	Tyrosine Kinase Oncogenes In Acute Myeloid Leukemias	2010	$315,567
P01 CA066996 13	Development Of Novel Therapeutic Strategies In Human Leukemias	2010	$2,408,966
P01 CA066996 14	Tyrosine Kinase Oncogenes In Acute Myeloid Leukemias	2011	$298,834
P01 CA066996 14	Development Of Novel Therapeutic Strategies In Human Leukemias	2011	$2,306,268

James Griffin's research directly related to the patented invention was robustly supported by the NIH during the years preceding the dates for the priority and the filing of both patents.

Requested Remedies for Non-disclosure

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; (2) 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.

After establishing a failure by the patent holder to disclose the federal funding, an agency may choose to require the patent holders to provide a disclosure to iEdison and to submit a Certificate of Correction to the United States Patent and Trademark (USPTO). The agency also has consequential remedies. In particular, a 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."

The disclosure itself is an acknowledgement that the federal government has certain rights in the patents, and that the patent holder has certain obligations. When federal funding is involved, the patent owner has an obligation to manufacture the invention substantially within the United States and to make the invention "available to the public on reasonable terms." The federal government obtains a worldwide royalty-free right to use the patent, and may grant a compulsory license to the patent under the Bayh-Dole march-in provisions of 35 U.S.C. § 203(a).

The failure to make a timely disclosure of the federal funding should be seen as an attempt to evade these responsibilities and as a denial of the government's rights in the invention.

KEI recommends that the federal government take title to the invention, since the lesser remedy of requiring late disclosure has not, in the past, provided an adequate incentive for patent holders to comply with the disclosure obligations.

See the Annex attached as a PDF file and also published as KEI Briefing Note 2018:1, regarding the discussion of the specific statutory, regulatory and contractual obligations to disclose federal funding in patented inventions, and the remedies when funding is not disclosed.

Attachments:

ANNEX: James Griffin's 71 NIH Funded Projects
ANNEX: Griffin's CA36167 Grants, from NIH REPORTER
ANNEX: KEI-Briefing-Note-2018-1