Vizamyl (INN Flutemetamol F 18)

Failures to disclose NIH funding for four patents in the FDA Orange Book invented by William Klunk, Chester Mathis, Jr., and Yanming Wang, and assigned to the University of Pittsburgh

Knowledge Ecology International
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Introduction

Knowledge Ecology International (KEI) asks the National Institutes of Health (NIH) to investigate whether there has been a failure to disclose NIH research funding on four patents granted that list William E. Klunk, Chester A. Mathis, Jr., and Yanming Wang as inventors. All four patents are assigned to the University of Pittsburgh.

The patents are listed as the first four patents (out of five patents) in the FDA Orange Book for the drug Vizamyl (INN flutemetamol, marketed by GE Healthcare), a nuclear imaging agent for the visualization of β-amyloid neuritic plaque density in patients being evaluated for cognitive disorders such as Alzheimer's disease.

Each of the three inventors received numerous research grants and contracts from the NIH and other federal agencies.

According to the NIH RePORTER database, from 1988 to 2018, William Klunk was the principal investigator for grants obtained from the National Institute of Health, consisting of 52 projects, 35 sub-projects and a total funding amount of $47,209,483.

From 1986 to 2018, Chester A. Mathis, Jr. received NIH grants consisting of 31 projects and 12 subprojects with a total funding amount of $14,936,292.

From 2003 to 2013, Yanming Wang was listed as the principal investigator for 19 NIH projects involving $4,116,038 of funding.

Many of the NIH grants are directly related to the four patented inventions. In addition to the grants disclosed in the NIH RePORTER database, the inventors have disclosed additional research contracts or grants related to the invention from the NIH and the U.S. Department of Energy, in various academic papers describing the inventions.

The inventions are important. William Klunk and Chester Mathis received a $100,000 Potamkin Prize award in 2008 for their research on Alzheimer's disease. Specifically, the prize was awarded for the invention and development of Pittsburgh Compound B (PiB), a radioactive amyloid plaque imaging compound that enables visualization of the β-amyloid plaque deposits (which disrupt the function of brain cells) and distinguishes between the diagnosis of Alzheimer's disease and other types of dementia.[1]

Vizamyl is available in 10 or 30 mL multi-dose glass vials at a strength of 150 MBq/mL (4.05 mCi/mL), the price of 1 vial (5 mCi) is approximately $28,000. Medicare restricts reimbursements for the tests.[2]

KEI is asking the NIH to take title to the patents, which is an available remedy 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 University of Pittsburgh to correct the failure to disclose the NIH grants.

What Does Vizamyl Do?

GE Healthcare[3] provides the following information on Vizamyl:

> Vizamyl is an imaging drug (also called a tracer) that is injected into a person's bloodstream before a positron-emission tomography (PET) scan is performed. Currently, Vizamyl is the first-and-only imaging drug approved to provide color PET images that help your doctor estimate the amount of a protein called beta amyloid in the brain.
>
> Although most people will develop some beta amyloid in the brain during aging, those with Alzheimer's disease tend to develop more than those who do not have the disease.
>
> ...A short time after Vizamyl is injected into the bloodstream, it will attach to beta amyloid in the brain. An imaging device called a PET scanner will then take color images of the brain. A radiologist can use these images to estimate how much beta amyloid there is.

[1] Klunk and Mathis Win Prestigious Potamkin Prize For Alzheimer's Research. 2008
[2] Final Decision Memorandum for: CAG-00431N Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease, September 27, 2013. https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=265
[3] About Vizamyl. 2017

In 2010, the Centers for Disease Control reported an estimate of 5.4 million Americans affected by Alzheimer's, ranking the illness the "sixth leading cause of death among all adults and the fifth leading cause of death for those aged 65 or older".[4]

The Orange Book Patents for Vizamyl

The May 10, 2018 version of the FDA Orange Book lists five patents for Vizamyl. Four patents were assigned to the University of Pittsburgh and one was assigned to GE Healthcare Limited, in Buckinghamshire, Great Britain.

Table 1: The Orange Book Patents for Vizamyl

Patent Number	Grant	Expiration	Inventors	Assignee
7270800	9/18/2007	09/03/2025	Klunk; William E. (Pittsburgh, PA), Mathis, Jr.; Chester A. (Pittsburgh, PA), Wang; Yanming (Imperial, PA)	University of Pittsburgh
7351401	4/1/2008	01/24/2023	Klunk; William E. (Pittsburgh, PA), Mathis, Jr.; Chester A. (Pittsburgh, PA), Wang; Yanming (Imperial, PA)	University of Pittsburgh
8236282	8/8/2012	05/21/2024	Klunk; William E. (Pittsburgh, PA), Mathis, Jr.; Chester A. (Pittsburgh, PA), Wang; Yanming (Imperial, PA)	University of Pittsburgh
8691185	4/8/2014	01/24/2023	Klunk; William E. (Pittsburgh, PA), Mathis, Jr.; Chester A. (Pittsburgh, PA), Wang; Yanming (Imperial, PA)	University of Pittsburgh
8916131	12/23/2014	09/16/2028	Roed; Line (Oslo, NO), Peterson; Sarah Elizabeth (Amersham, GB)	GE Healthcare Limited (Buckinghamshire, GB)

The Klunk, Mathis, and Wang Patents that Failed to Disclose Federal Funding

The four University of Pittsburgh patents failed to disclose federal funding in the invention. The priority, file and grant dates, title, and abstract for the patents are listed in Table 2.

Table 2: The Four Amyloid Klunk, Mathis and Wang Patents

Patent Number	Priority Date	File Date	Grant Date	Title	Abstract
7270800	8/24/2000	3/14/2003	9/18/2007	Thioflavin derivatives for use in antemortem diagnosis of	This invention relates to novel thioflavin derivatives, methods of using the derivatives in, for example, in vivo imaging of patients having neuritic plaques, pharmaceutical compositions comprising the thioflavin

[4] Promoting Health and Independence for an Aging Population At A Glance 2017. September 12, 2017

				Alzheimer's disease and in vivo imaging and prevention of amyloid deposition	derivatives and method of synthesizing the compounds. The compounds find particular use in the diagnosis and treatment of patients having diseases where accumulation of neuritic plaques are prevalent. The disease states or maladies include but are not limited to Alzheimer's disease, familial Alzheimer's disease, Down's Syndrome and homozygotes for the apolipoprotein E4 allele.
7351401	8/24/2000	6/3/2004	4/01/2008	Thioflavin derivatives for use in the antemortem diagnosis of Alzheimers disease and in vivo imaging and prevention of amyloid deposition	This invention relates to novel thioflavin derivatives, methods of using the derivatives in, for example, in vivo imaging of patients having neuritic plaques, pharmaceutical compositions comprising the thioflavin derivatives and method of synthesizing the compounds. The compounds find particular use in the diagnosis and treatment of patients having diseases where accumulation of neuritic plaques are prevalent. The disease states or maladies include but are not limited to Alzheimer's Disease, familial Alzheimer's Disease, Down's Syndrome and homozygotes for the apolipoprotein E4 allele.
8236282	8/22/2003	9/30/2009	8/7/2012	Benzothiazole derivative compounds, compositions and uses	This invention provides benzothiazole derivative compounds, compositions comprising such compounds, methods of preparing such compounds, and methods of using such compounds for detecting amyloid deposit(s) and for diagnosing a disease, disorder or condition characterized by amyloid deposit(s).
8691185	08/22/2003	7/12/2012	4/8/2014	Benzothiazole derivative compounds, compositions and uses	This invention provides benzothiazole derivative compounds, compositions comprising such compounds, methods of preparing such compounds, and methods of using such compounds for detecting amyloid deposit(s) and for diagnosing a disease, disorder or condition characterized by amyloid deposit(s).

Note that all four patents have the same three inventors (Klunk, Mathis and Wang). The first two patents have the same title, abstract and priority date. The last two patents have the same title, abstract and priority date.

The 7,270,800 and 7,351,401 patents

The 7,270,800 and 7,351,401 patents have the same three inventors (Klunk, Mathis and Wang), title and abstract, with somewhat different claims. The inventions involve novel thioflavin derivatives, and their use in in vivo imaging, for diagnosis and treatment of patients having diseases where accumulation of neuritic plaques are prevalent, including but not limited to Alzheimer's disease. The priority date for both patents is August 24, 2000, and the filing dates were May 14, 2003 and June 3, 2004.

Table 3 lists eight NIH-funded projects by the University of Pittsburgh from 1988 to 1999 that list William Klunk as the Principal Investigator. This is the time leading up to the priority date for patents 7,270,800 and 7,351,401.

Table 3: NIH-Funded Projects to the University of Pittsburgh from Fiscal Years 1988 to 1999 Listing William Klunk as PI

Project Number	Title	FY	Agency	Amount
1 F32 AG005443 01	MOLECULAR PROBES FOR ALZHEIMER BETA-AMYLOID PROTEIN	1988	NIA	$27,000
5 F32 AG005443 02	MOLECULAR PROBES FOR ALZHEIMER BETA-AMYLOID PROTEIN	1989	NIA	$31,750
5 R01 AG005657 06	NMR STUDIES OF BRAIN AGING IN ALZHEIMER'S DISEASE	1990	NIA	$139,105
1 R29 MH053310 01A1	CLINICAL METABOLIC CORRELATION IN DEMENTIA BY PROTON NMR	1995	NIMH	$98,405
5 R29 MH053310 02	CLINICAL METABOLIC CORRELATION IN DEMENTIA BY PROTON NMR	1996	NIMH	$101,910
5 R29 MH053310 03	CLINICAL METABOLIC CORRELATION IN DEMENTIA BY PROTON NMR	1997	NIMH	$105,204
5 R29 MH053310 04	CLINICAL METABOLIC CORRELATION IN DEMENTIA BY PROTON NMR	1998	NIMH	$108,621
5 R29 MH053310 05	CLINICAL METABOLIC CORRELATION IN DEMENTIA BY PROTON NMR	1999	NIMH	$112,536

The budget end date for project 5R29MH053310-05 was June 30, 2000, less than two months before the priority date of the two patents. The abstract for that grant reads as follows:

Project Number: 5R29MH053310-05
Contact PI / Project Leader: Klunk, William E
Title: Clinical Metabolic Correlation In Dementia By Proton NMR
Awardee Organization: University Of Pittsburgh At Pittsburgh

Abstract Text:
This study proposes to perform a clinical-metabolic-neuropathological correlation in **dementia**, in particular, primary degenerative **dementia** of the **Alzheimer** type (AD). We will use clinical data on behavior, mood, function, and cognition obtained in the year preceding death as markers of severity. Proton nuclear **magnetic resonance spectroscopy** (1/H **MRS**) will be used to analyze 6 brain areas obtained at autopsy from 75 **Alzheimer's disease** (AD), 25 controls, and 15 non-AD demented controls over 5 years. The first goal is to broaden the metabolic understanding of AD and to delineate clinical-metabolic-neuropathological correlations in a way that may provide insights into the timing of pathogenetic events over the course of this dementing illness. The second goal is to provide a detailed in vitro database for future extensions of this study into 1/H **MRS** studies of living patients with AD. No such detailed database currently exists. The metabolites measurable by 1/H MRS include N-acetyl-L-aspartate (NAA), L-glutamate, GABA, glutamine, myo-inositol, choline- containing compounds, creative and others. NAA is important because it is a putative neuronal marker easily detected by **in vitro** and **in vivo** 1/H **MRS** and can give an estimate of neuronal survival. Much like senile plaques and **neurofibrillary tangles**, NAA can be considered a new candidate marker of the neuropathological severity of **dementia**. The excitatory and inhibitory

amino acids also play key roles in excitotoxic theories of several **dementias**. The choline-containing compounds include a phosphodiester which is a product of membrane degradation. In addition to determining differences between AD and control, demented non-AD brains will be examined to determine the **specificity** of the changes for AD. Clinical-metabolic and metabolic-neuropathologic correlations to NAA, **senile plaques**, and **neurofibrillary tangles** will be done in an attempt to determine which changes represent early, potentially causative, events and which changes are more likely secondary effects of neurodegeneration. In addition, a separately funded study will be analyzing the tissue by 31/P **MRS** and the levels of the membrane metabolites, phosphomonoesters and phosphodiesters, will be available for correlative studies as well. We hypothesize that markers of membrane proliferation and neuronal inhibition will be elevated early in the disease and decreased at later stages. In contrast, markers of membrane degeneration and excitotoxicity will be elevated at later stages. Preliminary results suggest that the i**n vitro** 1/H **MRS** studies proposed in this application could provide information that is valuable in both a diagnostic and pathophysiologic sense and be readily extended to non-invasive, longitudinal studies of living patients which could aid in monitoring the course of the illness and tracking efficacy of experimental therapies.

The 8,236,282 and 8,691,185 patents

The 8,236,282 and 8,691,185 patents have the same three inventors (Klunk, Mathis and Wang), title and abstract, with somewhat different claims. The inventions involve compositions and methods of preparing benzothiazole derivatives, for the detection and diagnosis of diseases characterized by amyloid deposits. The priority date for both patents is August 22, 2003. The filing dates were September 30, 2009 and July 12, 2012.

Table 4 lists four NIH-funded projects by the University of Pittsburgh from 2001 to 2002 that list William Klunk as the Principal Investigator.

Table 4: NIH-Funded Projects to the University of Pittsburgh from Fiscal Years 2001 to 2002 Listing William Klunk as PI

Project Number	Title	FY	Agency	Amount
1K02AG001039 01A1	PET IMAGING PROBES FOR AMYLOID IN ALZHEIMERS AND AGING	2001	NIA	$97,686
1R01AG020226 01	PET TRACERS TO MONITOR VACCINE AND IMMUNE THERAPY FOR AD	2001	NIA	$366,936
5K02AG001039 02	PET IMAGING PROBES FOR AMYLOID IN ALZHEIMERS AND AGING	2002	NIA	$97,686
5R01AG020226 02	PET TRACERS TO MONITOR VACCINE AND IMMUNE THERAPY FOR AD	2002	NIA	$353,050

The budget end date for project 5R01AG020226-02 was July 31, 2003, less than two months before the priority date for the 8,236,282 and 8,691,185 patents, and right before the filing of the 7,270,800 and 7,351,401 patents.

The abstract for that grant reads as follows:

Project Number: 5R01AG020226-02
Contact PI / Project Leader: Klunk, William E
Title: PET Tracers To Monitor Vaccine And Immune Therapy For AD
Awardee Organization: University Of Pittsburgh At Pittsburgh

Abstract Text:
DESCRIPTION (provided by the applicant): The deposition of beta-sheet fibrils in **Alzheimer's disease (AD)** brain has been hypothesized to be the primary cause of this devastating neurodegenerative disease. These deposits include the **amyloid-beta** (Abeta) protein in **plaques** and vascular amyloid and hyper-phosphorylated tau protein in neurofibrillary tangles, dystrophic neurites and neuropil threads. Despite the presence of this characteristic neuropathology and its critical importance in the pathophysiology of the disease, no non-invasive technique has been validated to assess the presence of these deposits in living patients. The absence of such a technique hinders early and presymptomatic diagnosis and will severely hinder the development of immune therapies aimed at prevention or reversal of beta-sheet fibril deposition. Over the past decade, our laboratory has worked to develop an in vivo **beta-sheet amyloid** fibril imaging agent. This work has resulted in a promising lead agent, [N-methyl-11C]2(-4'-methylaminophenyl-**benzothiazol**e (or [11C]BTA-1) which: 1) readily enters and clears from normal rodent and baboon brain; 2) binds to synthetic Abeta with nanomolar affinity; 3) specifically stains **plaques** and **tangles** in post-mortem AD brain; 4) binds to homogenates of post-mortem AD brain frontal cortex at >10-fold higher levels than aged control brain and non-AD demented brain samples, but shows no increased **binding** in AD **cerebellum**; and 5) shows no evidence of acute toxicity in preliminary studies. Furthermore, preliminary in vivo studies using APP transgenic mice and low resolution **PET scanning** show increased accumulation in the transgenic mice. In this study, we propose to validate the use of [11C]BTA-1 for in vivo **amyloid imaging** in PS/APP transgenic mice using a small animal microPET scanner. We will correlate in vivo results with: 1) quantitative immunohistochemical and histochemical measures of amyloid deposition; 2) Abeta ELISA; and 3) ex-vivo [11C]**BTA-1** levels and post-mortem [3H]**BTA-1** binding. We will show feasibility of longitudinal studies of the [11C]BTA-1/microPET technique in PS/APP mice and apply the technique to study an immune therapy protocol in these mice. Our goal is to provide a tool for use by investigators developing improved immune therapy protocols in transgenic mice, thus speeding progress in this area. However, because all of the techniques developed in this proposal apply directly to human studies, completion of this study will greatly speed the development of this technology for use in human studies of anti-amyloid therapies (immune therapy and secretase inhibitor therapies).

Description of the 7,270,800; 7,351,401; 8,236,282 and 8,691,185 patents

Thioflavin T is a benzothiazole compound, a fluorescent marker or a dye, that is used for the visualization and quantification of amyloid (misfolded protein aggregates found in the brains of patients diagnosed with Alzheimer's disease). Amyloids are made up of beta sheet fibrils or structures. The binding of Thioflavin T compounds to the amyloids' beta sheets displays a major increase in fluorescence intensity, allowing quantification of amyloids and diagnosis.[5]

In 2008, two of the patents' inventors, Klunk and Mathis, published a paper in the *Journal of Alzheimer Disease and Associated Disorders*, titled "Whatever happened to Pittsburgh Compound-A?"[6] The paper provides an overview of research undertaken in order to obtain the

[5] (2010). Biancalana M; Koide S. "Molecular mechanism of Thioflavin-T binding to amyloid fibrils" *Biochim Biophys Acta.* 1804(7):1405-12.
[6] (2008). Klunk WE; Mathis CA. "Whatever happened to Pittsburgh Compound-A?" *Alzheimer Dis Assoc Disord.* 22(3):198-203.

desired and most effective thioflavin derivative for the diagnosis of Alzheimer's disease. The following statements were provided:

> ". . . Pittsburgh Compound-A (PiA) represents one of the early thioflavin-T derivatives made in our amyloid-imaging tracer development program at the University of Pittsburgh.
>
> . . . For more than a decade, we struggled with manipulating the Congo red pharmacophore into a suitable positron emission tomography (PET) amyloid tracer with only limited success. This was primarily a result of the poor brain entry of this class of compounds.
>
> . . . The transition away from the Congo red derivatives such as the X-series began in November 1999. From that time through our present work with fluorine-18–labeled PiB derivatives, we have synthesized and tested over 350 thioflavin-T derivatives.
>
> . . . BTA-1 (PiA) was the seventh of the thioflavin-T derivatives and was first tested with in vitro binding studies and ex vivo mouse brain entry studies in April 2000, just 5 months into our thioflavin-T exploration program.
>
> . . . It is worth noting that we began the approval process for human studies simultaneously in Sweden and in the United States in 2001, understanding that it would take longer to begin our studies in Pittsburgh than it would to begin the Uppsala arm of this study. That process included toxicologic evaluation of the lead compound funded by a special National Institute on Aging (NIA) mechanism (NIA contract, N01- AG-9-2117).
>
> . . . NIA had already approved funding for toxicologic evaluation of Pittsburgh Compound-A, when the suggestion came up at our weekly chemistry meeting something to the effect of, "I've been looking at the data and thinking, and I don't think BTA-1 is the best compound. I think we should go with 6-OH-BTA-1 [the original name for PiB], because it is cleared from normal brain much better." It should not be surprising that this suggestion was initially met with a degree of inertia on both sides of the Atlantic.
>
> . . . PiB was the 23rd compound synthesized and tested in our thioflavin-T program in July 2000, so it had been on the (lab)books for more than a year before the first human study. The affinities of Pittsburgh Compound-A and PiB were never convincingly different in binding studies using Aβ fibrils or AD brain homogenates, but the more rapid clearance of PiB from normal animal brain was evident very early on.
>
> . . . The case was made as follows: when compared with several other proven dopamine and serotonin neuroreceptor radiotracers on "level ground," PiB fit the profile of a good tracer and Pittsburgh Compound-A did not."

The research paper further discloses how the correct thioflavin derivatives (PiA and PiB) were derived for the diagnosis of Alzheimer's disease, and notes some of the relevant time periods.

The following statements were made regarding funding:

> "Funding support for portions of the development program was provided by grants from The National Institutes of Health (R01 AG018402, P50 AG005133, K02 AG001039, R01 AG020226, R01 MH070729, K01 MH001976, R37 AG025516, P01 AG025204), the Alzheimer's Association (TLL-01-3381), GE Healthcare and the US Department of Energy (DE-FD02-03 ER63590)."

With the exception of grants R01 MH070729 and K01 MH001976 (PI Julie Price), all the other grants listed identified either William Klunk or Chester Mathis as the Principal Investigators.

Grant R01 AG018402
Using the NIH RePORTER database, we searched for the grant R01 AG018402. There were eight projects funded under grant R01 AG018402, where Chester Mathis was the Principal Investigator, from 2001 to 2010. The organization receiving the funding was the University of Pittsburgh.

Table 5: The Eight R01 AG018402 Projects Listing Chester Mathis as the PI and the University of Pittsburgh as the Institution

Project	Project Title	FY	Total Cost
1R01AG018402-01A1	AMYLOID IMAGING AGENTS FOR POSITRON EMISSION TOMOGRAPHY	2001	*$350,525*
5R01AG018402-02	AMYLOID IMAGING AGENTS FOR POSITRON EMISSION TOMOGRAPHY	2002	*$349,224*
5R01AG018402-03	AMYLOID IMAGING AGENTS FOR POSITRON EMISSION TOMOGRAPHY	2003	*$347,922*
5R01AG018402-04	AMYLOID IMAGING AGENTS FOR POSITRON EMISSION TOMOGRAPHY	2004	*$346,619*
2R01AG018402-05	AMYLOID IMAGING AGENTS FOR POSITION EMISSION TOMOGRAPHY	2007	*$339,851*
5R01AG018402-06	AMYLOID IMAGING AGENTS FOR POSITION EMISSION TOMOGRAPHY	2008	*$376,408*
5R01AG018402-07	AMYLOID IMAGING AGENTS FOR POSITION EMISSION TOMOGRAPHY	2009	*$394,437*

5R01AG018402-08	AMYLOID IMAGING AGENTS FOR POSITION EMISSION TOMOGRAPHY	2010	*$357,159*

Grant P50 AG005133

Using the NIH RePORTER database, we searched for the grant P50 AG005133. There were ten sub-projects funded under grant P50 AG005133, where William Klunk was the Principal Investigator, from 2005 to 2014.The organization receiving the funding was the University of Pittsburgh.

Table 6: The Ten P50 AG005133 Projects Listing William Klunk as the PI and the University of Pittsburgh as the Institution

Project	Project Title	FY	Total Cost
2P50AG005133-22	NATURAL HISTORY OF AMYLOID DEPOSITION IN FAMILIAL AD	2005	*$185,625*
5P50AG005133-23	NATURAL HISTORY OF AMYLOID DEPOSITION IN FAMILIAL AD	2006	*$128,746*
5P50AG005133-24	NATURAL HISTORY OF AMYLOID DEPOSITION IN FAMILIAL ALZHEIMERS DISEASE	2007	*$214,077*
5P50AG005133-25	NATURAL HISTORY OF AMYLOID DEPOSITION IN FAMILIAL ALZHEIMERS DISEASE	2008	*$215,088*
5P50AG005133-26	NATURAL HISTORY OF AMYLOID DEPOSITION IN FAMILIAL ALZHEIMERS DISEASE	2009	*$221,371*
2P50AG005133-27	NATURAL HISTORY OF AMYLOID DEPOSITION FAMILIAL AD	2010	*$171,025*
5P50AG005133-28	NATURAL HISTORY OF AMYLOID DEPOSITION FAMILIAL AD	2011	*$199,286*
5P50AG005133-29	NATURAL HISTORY OF AMYLOID DEPOSITION FAMILIAL AD	2012	*$182,113*
5P50AG005133-30	NATURAL HISTORY OF AMYLOID DEPOSITION FAMILIAL AD	2013	*$170,365*
5P50AG005133-31	NATURAL HISTORY OF AMYLOID DEPOSITION FAMILIAL AD	2014	*$182,280*

Grant K02 AG001039

Using the NIH RePORTER database, we searched for the grant K02 AG001039. There were five projects funded under grant K02 AG001039, where William Klunk was the Principal Investigator, from 2001 to 2005. The organization receiving the funding was the University of Pittsburgh.

Table 7: The Five K02 AG001039 Projects Listing William Klunk as the PI and the University of Pittsburgh as the Institution

Project	Project Title	FY	Total Cost
1K02AG001039-01A1	PET IMAGING PROBES FOR AMYLOID IN ALZHEIMERS AND AGING	2001	*$97,686*
5K02AG001039-02	PET IMAGING PROBES FOR AMYLOID IN ALZHEIMERS AND AGING	2002	*$97,686*
5K02AG001039-03	PET IMAGING PROBES FOR AMYLOID IN ALZHEIMERS AND AGING	2003	*$97,686*
5K02AG001039-04	PET IMAGING PROBES FOR AMYLOID IN ALZHEIMERS AND AGING	2004	*$97,686*
5K02AG001039-05	PET IMAGING PROBES FOR AMYLOID IN ALZHEIMERS AND AGING	2005	*$97,686*

Grant R01 AG020226

Using the NIH RePORTER database, we searched for the grant R01 AG020226. There were five projects funded under grant R01 AG020226, where William Klunk was the Principal Investigator, from 2001 to 2005. The organization receiving the funding was the University of Pittsburgh.

Table 8: The Five R01 AG020226 Projects Listing William Klunk as the PI and the University of Pittsburgh as the Institution

Project	Project Title	FY	Total Cost
1R01AG020226-01	PET TRACERS TO MONITOR VACCINE AND IMMUNE THERAPY FOR AD	2001	*$366,936*

5R01AG020226-02	PET TRACERS TO MONITOR VACCINE AND IMMUNE THERAPY FOR AD	2002	*$353,050*
5R01AG020226-03	PET TRACERS TO MONITOR VACCINE AND IMMUNE THERAPY FOR AD	2003	*$353,050*
5R01AG020226-04	PET TRACERS TO MONITOR VACCINE AND IMMUNE THERAPY FOR AD	2004	*$353,050*
5R01AG020226-05	PET TRACERS TO MONITOR VACCINE AND IMMUNE THERAPY FOR AD	2005	*$353,050*

Grant R37 AG025516

Using the NIH RePORTER database, we searched for the grant R37 AG025516. There were eleven projects funded under grant R37 AG025516, where William Klunk was the Principal Investigator, from 2005 to 2014. The organization receiving the funding was the University of Pittsburgh.

Table 9: The Eleven R37 AG025516 Projects Listing William Klunk as the PI and the University of Pittsburgh as the Institution

Project	Project Title	FY	Total Cost
1R37AG025516-01	AMYLOID PATHOLOGY AND COGNITION IN NORMAL ELDERLY	2005	*$430,155*
5R37AG025516-02	AMYLOID PATHOLOGY AND COGNITION IN NORMAL ELDERLY	2006	*$459,594*
5R37AG025516-03	AMYLOID PATHOLOGY AND COGNITION IN NORMAL ELDERLY	2007	*$459,409*
5R37AG025516-04	AMYLOID PATHOLOGY AND COGNITION IN NORMAL ELDERLY	2008	*$449,361*
3R37AG025516-05S1	AMYLOID PATHOLOGY AND COGNITION IN NORMAL ELDERLY	2009	*$5,000*

5R37AG025516-05	AMYLOID PATHOLOGY AND COGNITION IN NORMAL ELDERLY	2009	*$362,933*
4R37AG025516-06	AMYLOID PATHOLOGY AND COGNITION IN NORMAL ELDERLY	2010	*$473,345*
5R37AG025516-07	AMYLOID PATHOLOGY AND COGNITION IN NORMAL ELDERLY	2011	*$481,954*
5R37AG025516-08	AMYLOID PATHOLOGY AND COGNITION IN NORMAL ELDERLY	2012	*$480,423*
5R37AG025516-09	AMYLOID PATHOLOGY AND COGNITION IN NORMAL ELDERLY	2013	*$441,934*
5R37AG025516-10	AMYLOID PATHOLOGY AND COGNITION IN NORMAL ELDERLY	2014	*$227,443*

Grant P01 AG025204

Using the NIH RePORTER database, we searched for the grant P01 AG025204. There were 36 projects funded under grant P01 AG025204, where William Klunk was the Principal Investigator, from 2005 to 2018. The organization receiving the funding was the University of Pittsburgh.

Of interest are the nineteen grants listed from years 2005-2012, prior to the filing dates for two of the patents.

Table 10: The Nineteen P01 AG025204 Projects Listing William Klunk as the PI and the University of Pittsburgh as the Institution

Project	Project Title	FY	Total Cost
1P01AG025204-01	CROSS-SECTIONAL ASSESSMENT OF IN VIVO AMYLOID IN MCI AND AD	2005	*$157,425*
5P01AG025204-02	CROSS-SECTIONAL ASSESSMENT OF IN VIVO AMYLOID IN MCI AND AD	2006	*$172,602*
5P01AG025204-03	CROSS-SECTIONAL ASSESSMENT OF IN VIVO AMYLOID IN MCI AND AD	2007	*$298,271*
3P01AG025204-04S1	IN VIVOPIB PET AMYLOID IMAGING: NORMALS, MCI & DEMENTIA	2008	*$142,645*

5P01AG025204-04	CROSS-SECTIONAL ASSESSMENT OF IN VIVO AMYLOID IN MCI AND AD	2008	*$259,127*
5P01AG025204-04	IN VIVOPIB PET AMYLOID IMAGING: NORMALS, MCI & DEMENTIA	2008	*$1,031,916*
5P01AG025204-05	CROSS-SECTIONAL ASSESSMENT OF IN VIVO AMYLOID IN MCI AND AD	2009	*$360,047*
5P01AG025204-05	IN VIVOPIB PET AMYLOID IMAGING: NORMALS, MCI & DEMENTIA	2009	*$1,151,713*
2P01AG025204-06	ADMINISTRATIVE CORE	2010	*$129,363*
2P01AG0252040-06	MODULATORS OF COGNITIVE TRANSIFION FROM MCI TO AD	2010	*$301,836*
2P01AG025204-06	IN VIVO PIB PET AMYLOID IMAGING: NORMALS, MCI & DEMENTIA	2010	*$1,538,583*
5P01AG025204-07	ADMINISTRATIVE CORE	2011	*$126,512*
5P01AG025204-07	MODULATORS OF COGNITIVE TRANSIFION FROM MCI TO AD	2011	*$346,486*
5P01AG025204-07	QUANTITATIVE NEUROPATHOLOGICAL CORRELATES OF IN VIVO PIB RETENTION	2011	*$292,634*
5P01AG025204-07	IN VIVO PIB PET AMYLOID IMAGING: NORMALS, MCI & DEMENTIA	2011	*$1,482,584*
5P01AG025204-08	ADMINISTRATIVE CORE	2012	*$126,424*
5P01AG025204-08	MODULATORS OF COGNITIVE TRANSIFION FROM MCI TO AD	2012	*$337,923*
5P01AG025204-08	QUANTITATIVE NEUROPATHOLOGICAL CORRELATES OF IN VIVO PIB RETENTION	2012	*$287,620*
5P01AG025204-08	IN VIVO PIB PET AMYLOID IMAGING: NORMALS, MCI & DEMENTIA	2012	*$1,420,069*

Additional Notes on Research Grants from the National Institutes of Health

NIH Grants to William Klunk Cited in a 2003 Paper

In 2003, the patents' inventors, Klunk, Mathis and Wang, published a paper in the journal *Proceedings of the National Academy of Sciences of the United States of America* along with seven co-authors, titled "Four-dimensional multiphoton imaging of brain entry, amyloid binding, and clearance of an amyloid-beta ligand in transgenic mice."[7] The paper made disclosures regarding funding, including NIH grants to Mathis and Klunk:

> "...This work supported by National Institutes of Health Grants AG08487 (to B.T.H.), AG18402 (**to C.A.M.**), AG01039 (**to W.E.K.**), AG20226 (**to W.E.K.**), AG15453 (to B.T.H.), EB00768 (to B.J.B.), and AG020570 (to B.J.B.), an Alzheimer Association Pioneer Award (to B.T.H.), Alzheimer Association Grants IIRG-95-076 (to W.E.K.), TLL-01-3381 (to W.E.K.), and NIRG-00-2355 (to Y.W.), and Institute for the Study of Aging/American Federation for Aging Research Grant 210304 (to Y.W.)."

The abstract for Bacskai *et al.* 2003 reads as follows:

> "The lack of a specific biomarker makes preclinical diagnosis of **Alzheimer's disease** (AD) impossible, and it precludes assessment of therapies aimed at preventing or reversing the course of the disease. The development of a tool that enables direct, quantitative detection of the **amyloid-beta deposits** found in the disease would provide an excellent biomarker. This article demonstrates the real-time biodistribution kinetics of an imaging agent in transgenic mouse models of **AD**. Using multiphoton microscopy, **Pittsburgh compound B (PIB)** was imaged with sub-μm resolution in the brains of living transgenic mice during peripheral administration. **PIB** entered the brain quickly and labeled **amyloid deposits** within minutes. The nonspecific **binding** was cleared rapidly, whereas specific labeling was prolonged. WT mice showed rapid brain entry and clearance of **PIB** without any binding. These results demonstrate that the compound **PIB** has the properties required for a good amyloid-imaging agent in humans with or at risk for **AD**."

NIH Grants to Chester Mathis Cited in a 2004 Paper

In 2004, the patents inventors, Klunk, Mathis and Wang, published a paper in the journal *Annals of Neurology* along with eighteen co-authors, titled "Imaging brain amyloid in Alzheimer's

[7] (2003). Bacskai BJ; Hickey GA; Skoch J; Kajdasz ST; Wang Y; Huang GF; Mathis CA; Klunk WE; Hyman BT. "Four-dimensional multiphoton imaging of brain entry, amyloid binding, and clearance of an amyloid-beta ligand in transgenic mice." *Proc Natl Acad Sci U S A.* 100(21):12462-7.

disease with Pittsburgh Compound-B."[8] PubMed provides the following information on the grant support:

> "Grant support
> AG 01039/AG/NIA NIH HHS/United States
> **AG 05133/AG/NIA NIH HHS/United States**
> **AG 18402/AG/NIA NIH HHS/United States**
> AG 20226/AG/NIA NIH HHS/United States"

The abstract for Klunk *et al.* 2004 reads as follows:

> "This report describes the first human study of a novel **amyloid**-**imaging positron emission tomography (PET)** tracer, termed **Pittsburgh Compound-B (PIB)**, in 16 patients with diagnosed mild **AD** and 9 controls. Compared with controls, **AD** patients typically showed marked retention of **PIB** in areas of association cortex known to contain large amounts of amyloid deposits in **AD**. In the **AD** patient group, **PIB** retention was increased most prominently in frontal cortex (1.94-fold, p = 0.0001). Large increases also were observed in parietal (1.71-fold, p = 0.0002), temporal (1.52-fold, p = 0.002), and occipital (1.54-fold, p = 0.002) cortex and the striatum (1.76-fold, p = 0.0001). **PIB** retention was equivalent in AD patients and controls in areas known to be relatively unaffected by **amyloid** deposition (such as subcortical white matter, pons, and cerebellum). Studies in three young (21 years) and six older healthy controls (69.5 ± 11 years) showed low PIB retention in cortical areas and no significant group differences between young and older controls. In cortical areas, PIB retention correlated inversely with cerebral glucose metabolism determined with 18F-fluorodeoxyglucose. This relationship was most robust in the parietal cortex (r = −0.72; p = 0.0001). The results suggest that **PET** imaging with the novel tracer, PIB, can provide quantitative information on **amyloid deposits** in living subjects.

NIH Grants to Yanming Wang

In 2004, the patents' inventors, Klunk, Mathis and Wang, published a paper in the *Journal of Molecular Neuroscience* along with four co-authors, titled "development of a PET/SPECT agent for amyloid imaging in Alzheimer's disease."[9] PubMed provides the following information on the grant support:

[8] (2004). Klunk WE; Engler H; Nordberg A; Wang Y; Blomqvist G; Holt DP; Bergström M; Savitcheva I; Huang GF; Estrada S; Ausén B; Debnath ML; Barletta J; Price JC; Sandell J; Lopresti BJ; Wall A; Koivisto P; Antoni G; Mathis CA; Långström B. "Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B." *Ann Neurol.* 55(3):306-19.

[9] (2004). Wang Y; Klunk WE; Debnath ML; Huang GF; Holt DP; Shao L; Mathis CA. "Development of a PET/SPECT agent for amyloid imaging in Alzheimer's disease." *J Mol Neurosci.* 24(1):55-62.

> "Grant support
> AG01039/AG/NIA NIH HHS/United States
> AG05133/AG/NIA NIH HHS/United States
> AG18402/AG/NIA NIH HHS/United States
> AG20226/AG/NIA NIH HHS/United States
> **AG22048-01A1/AG/NIA NIH HHS/United States**"

The abstract for Wang *et al.* 2004 reads as follows:

> "In the search for a cure for **Alzheimer's disease (AD)**, efforts have been focused on preventing or reversing **amyloid deposition** in the **brain**. Efficacy evaluation of these antiamyloid therapies would greatly benefit from development of a tool for the **in vivo** detection and quantitation of **amyloid deposits** in the brain. Toward this goal, we have developed a series of **benzothiazole derivatives** as **amyloid-imaging agents** for **positron emission tomography (PET)**. To extend the potential of these **amyloid-imaging agents** for routine clinical studies, we also set out to develop iodinated **benzothiazole derivatives** that could be used as dual agents for either PET or the complementary s**ingle photon emission computed tomography (SPECT)**. Such dual agents would permit **PET** or **SPECT** studies using radiotracers with the same chemical identity but labeled with different radionuclides. This would facilitate the validation of clinical **SPECT** studies, based on quantitative **PET** studies. In this work we report the synthesis and biological evaluation of a potent, selective, and brain-permeable benzothiazole compound, 2-(3'-iodo-4'-methylaminophenyl)-6-hydroxy-benzothialzole, termed 6-OH-BTA-1-3'-I (4), which can be **radiolabeled** with either positron-emitting carbon-11 or single photon-emitting iodine-125/iodine-123. The synthesis and radiolabeling of [125I]4 or [11C]4 were achieved through direct iodination with sodium [125I]iodide in the presence of chloramine T or through radiomethylation with [11C]CH3I. **In vitro amyloid binding** assays indicated that [125I]4 bound to **amyloid deposits** in a saturable manner and exhibited affinities in the nanomolar concentration range. Binding studies of [125I]4 to postmortem human brain homogenates also showed preference of binding to frontal cortex in the **AD** homogenates relative to age-matched control **homogenates** or **cerebellum** from either **AD** or control. **In vivo** pharmacokinetic studies in normal mice following iv injection of [11C]4 indicated that the **radioligand** entered the **brain** readily at early time points and cleared from the **brain** rapidly at later time points with a 2- to 30-min ratio >3. These results suggest that the new radioiodinated **benzothiazole ligand** might be useful as a surrogate marker for the in vivo quantitation of **amyloid deposition** in human brain for use with either **PET** or **SPECT**."

According to the NIH RePORTER database, Yanming Wang received a total of $602,463 to support five projects that mention amyloid and involve diagnostics tests for dementia and/or Alzheimer's disease.

Table 11: Five NIH Grants to Yanming Wang from 2003-2007 Mentioning Amyloid-based Screening for Alzheimer's and Dementia

Grant Number	Title	Budget Start Date	Budget End Date	Agency
1K25AG022048-01A1	QUANTITATIVE IMAGING OF AMYLOID DEPOSITS IN AD AND AGING	9/30/2003	8/31/2004	NIA
7K25AG022048-02	QUANTITATIVE IMAGING OF AMYLOID DEPOSITS IN AD AND AGING	9/15/2004	8/31/2005	NIA
5K25AG022048-03	QUANTITATIVE IMAGING OF AMYLOID DEPOSITS IN AD AND AGING	9/1/2005	7/14/2006	NIA
7K25AG022048-04	QUANTITATIVE IMAGING OF AMYLOID DEPOSITS IN AD AND AGING	9/1/2006	8/31/2007	NIA
5K25AG022048-05	QUANTITATIVE IMAGING OF AMYLOID DEPOSITS IN AD AND AGING	9/1/2007	8/31/2008	NIA

Why the Wang Grants are Related to the Inventions

The abstracts given for the grants are as follows:

The Abstract for the Wang Amyloid Grants listed in Table 11

1K25AG022048-01A1, 7K25AG022048-02, 5K25AG022048-03, 7K25AG022048-04 and 5K25AG022048-05

DESCRIPTION (provided by applicant): In this application for a Mentored Quantitative Research Career Development Award (K25), the candidate's research and career development plans are described. The project is designed to customize the educational and research activities for the candidate to achieve two major goals. The immediate goal is for the candidate to continue his research in **amyloid imaging** in **Alzheimer's disease** and aging. The long-term goal is for the candidate to acquire advanced biomedical research skills and develop as an independent researcher in aging-related biomedical imaging. To achieve these goals, the candidate will obtain further trainings in neuroscience, biostatistics, pharmacology, and pharmacokinetics as well as in responsible conduct of biomedical and clinical research. He will also acquire related knowledge through journal clubs, research seminars, lectures, and conferences, and through interaction with other investigators and trainees. The practical skills in biomedical imaging will primarily be obtained through the proposed microPET studies under the guidance of Drs. Mathis and Klunk at the University of Pittsburgh. In this proposed research, the candidate plans to use microPET to evaluate amyloid-imaging agents in transgenic mice models of **amyloid deposition**. This will allow us for the first time to evaluate the in vivo binding specificity and pharmacokinetic profiles of lead compounds in a CNS model that mimics the future human studies. Therefore, this project will satisfy the following specific aims: 1) rationally design and synthesize a selected array of amyloid-binding agents; 2) evaluate the new compounds for in vitro binding affinity and specificity for amyloid deposits; 3) evaluate selected compounds in ex vivo studies of brain entry, crearance; and metabolism in normal control mice with no amyloid deposits in the brain; 4) use microPET to assess the in vivo properties of selected compounds in amyloid-containing transgenic mouse models to determine **in vivo**

binding specificity and detailed pharmacokinetic profiles. The overall goal of our research is to identify potent, selective, and brain permeable amyloid probes suitable for in vivo human studies.

The patents listed above in Table 2 provide several key terms/words that appear to be the subject matter of the grants listed in Table 11, including, to mention a few:

- These facts have little implications for **amyloid imaging** studies in which an extremely minute amount of the high specific activity radiolabelled dye would be directly injected into the blood stream. (PAGE 4, PATENT 7,351,401)
- The disease states or maladies include but are not limited to **Alzheimer's Disease**, familial **Alzheimer's Disease**, Down's Syndrome and homozygotes for the apolipoprotein E4 allele. (ABSTRACT, PATENT 7270800)
- **In Vivo** Baboon Imaging Studies (PAGE 17, PATENT 8,236,282)
- In allowing the temporal sequence of **amyloid deposition** to be followed, the inventive compound may further be used to correlate **amyloid deposition** with the onset of clinical symptoms associated with a disease, disorder or condition. (PAGE 5, PATENT 8,236,282)
- This study reflects **brain entry** and clearance from normal brain tissue. (PAGE 16, PATENT 8,236,282)

The Vizamyl Prices

Vizamyl injection is available in 10 or 30 mL multi-dose glass vial at a strength of 150 MBq/mL (4.05 mCi/mL). The price of 1 vial (5 mCi) is approximately $28,000.[10]

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 (UPSPTO). 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."

[10] https://www.rxgo.com/drug/vizamyl-coupon

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 possesses 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.

For a more detailed discussion of the specific statutory, regulatory and contractual obligations to disclose federal funding in patented inventions, and the remedies when funding is not disclosed, see: KEI Briefing Note 2018:1.

ANNEX 1: Select News Reports and Other Background on Vizamyl

About Alzheimer's disease. Alzheimer's Association.

2014. Scott Lerman. GE Healthcare Announces European Union Approval of VIZAMYL™ (Flutemetamol (18F) Solution for Injection) for PET Imaging of Beta Amyloid Plaque in Suspected Alzheimer's Disease. *Business Wire*. September 1, 2014.

2015. Lauren Dubinsky. GE's Vizamyl improves diagnostic confidence for early-onset dementia. *DOTmed*. July 22, 2015.

ANNEX 2: NIH Grants to the University of Pittsburgh with William E. Klunk Listed as Principal Investigator, with Search Term "Amyloid"

The search term for NIH RePORTER database: "Text Search: amyloid (and); Search in: Projects, AdminIC: All; Principal Investigator / Project Leader: Klunk; William; Fiscal Year: All Fiscal Years."

Project Number	Project Title	Fiscal Year	FY Cost
1F32AG005443-01	Molecular Probes For Alzheimer Beta-amyloid Protein	1988	$27,000
5F32AG005443-02	Molecular Probes For Alzheimer Beta-amyloid Protein	1989	$31,750
1K02AG001039-01A1	Pet Imaging Probes For Amyloid In Alzheimers And Aging	2001	$97,686
1R01AG020226-01	Pet Tracers To Monitor Vaccine And Immune Therapy For AD	2001	$366,936
5K02AG001039-02	Pet Imaging Probes For Amyloid In Alzheimers And Aging	2002	$97,686
5R01AG020226-02	Pet Tracers To Monitor Vaccine And Immune Therapy For AD	2002	$353,050
5K02AG001039-03	Pet Imaging Probes For Amyloid In Alzheimers And Aging	2003	$97,686
5R01AG020226-03	Pet Tracers To Monitor Vaccine And Immune Therapy For AD	2003	$353,050
5R01AG020226-04	Pet Tracers To Monitor Vaccine And Immune Therapy For AD	2004	$353,050
5K02AG001039-04	Pet Imaging Probes For Amyloid In Alzheimers And Aging	2004	$97,686
5K02AG001039-05	Pet Imaging Probes For Amyloid In Alzheimers And Aging	2005	$97,686
1R37AG025516-01	Amyloid Pathology And Cognition In Normal Elderly	2005	$430,155
1P01AG025204-01	Cross-sectional Assessment Of In Vivo Amyloid In Mci And AD	2005	$157,425
2P50AG005133-22	Natural History Of Amyloid Deposition In Familial AD	2005	$185,625
5R01AG020226-05	Pet Tracers To Monitor Vaccine And Immune Therapy For AD	2005	$353,050
5P50AG005133-23	Natural History Of Amyloid Deposition In Familial AD	2006	$128,746
5P01AG025204-02	Cross-sectional Assessment Of In Vivo Amyloid In Mci And AD	2006	$172,602
1U01AG028526-01	Amyloid-lowering Small Molecule Ab-binding Agents In AD	2006	$459,078
5R37AG025516-02	Amyloid Pathology And Cognition In Normal Elderly	2006	$459,594
5P01AG025204-03	Cross-sectional Assessment Of In Vivo Amyloid In Mci And AD	2007	$298,271
5U01AG028526-02	Amyloid-lowering Small Molecule Ab-binding Agents In AD	2007	$450,738
5P50AG005133-24	Natural History Of Amyloid Deposition In Familial Alzheimers Disease	2007	$214,077
5R37AG025516-03	Amyloid Pathology And Cognition In Normal Elderly	2007	$459,409
5R37AG025516-04	Amyloid Pathology And Cognition In Normal Elderly	2008	$449,361
5P50AG005133-25	Natural History Of Amyloid Deposition In Familial Alzheimers Disease	2008	$215,088
3P01AG025204-04S1	In Vivopib Pet Amyloid Imaging: Normals; Mci & Dementia	2008	$142,645
5P01AG025204-04	In Vivopib Pet Amyloid Imaging: Normals; Mci & Dementia	2008	$1,031,916
5U01AG028526-03	Amyloid-lowering Small Molecule Ab-binding Agents In AD	2008	$454,087
5P01AG025204-04	Cross-sectional Assessment Of In Vivo Amyloid In Mci And AD	2008	$259,127

5P50AG005133-26	Natural History Of Amyloid Deposition In Familial Alzheimers Disease	2009	$221,371
5P01AG025204-05	In Vivopib Pet Amyloid Imaging: Normals; Mci & Dementia	2009	$1,151,713
5U01AG028526-04	Amyloid-lowering Small Molecule Ab-binding Agents In AD	2009	$466,821
5R37AG025516-05	Amyloid Pathology And Cognition In Normal Elderly	2009	$362,933
5P01AG025204-05	Cross-sectional Assessment Of In Vivo Amyloid In Mci And AD	2009	$360,047
3R37AG025516-05S1	Amyloid Pathology And Cognition In Normal Elderly	2009	$5,000
2P01AG025204-06	Modulators Of Cognitive Transifion From Mci To AD	2010	$301,836
4R37AG025516-06	Amyloid Pathology And Cognition In Normal Elderly	2010	$473,345
2P01AG025204-06	In Vivo Pib Pet Amyloid Imaging: Normals; Mci & Dementia	2010	$1,538,583
5U01AG028526-05	Amyloid-lowering Small Molecule Ab-binding Agents In AD	2010	$504,093
5P01AG025204-07	In Vivo Pib Pet Amyloid Imaging: Normals; Mci & Dementia	2011	$1,482,584
5R37AG025516-07	Amyloid Pathology And Cognition In Normal Elderly	2011	$481,954
5P50AG005133-28	Natural History Of Amyloid Deposition Familial Ad	2011	$199,286
5P50AG005133-29	Natural History Of Amyloid Deposition Familial Ad	2012	$182,113
5P01AG025204-08	Administrative Core	2012	$126,424
5P01AG025204-08	Modulators Of Cognitive Transifion From Mci To Ad	2012	$337,923
5P01AG025204-08	Quantitative Neuropathological Correlates Of In Vivo Pib Retention	2012	$287,620
5R37AG025516-08	Amyloid Pathology And Cognition In Normal Elderly	2012	$480,423
5P01AG025204-08	In Vivo Pib Pet Amyloid Imaging: Normals; Mci & Dementia	2012	$1,420,069
5R37AG025516-09	Amyloid Pathology And Cognition In Normal Elderly	2013	$441,934
5P01AG025204-09	Modulators Of Cognitive Transifion From Mci To Ad	2013	$267,813
5P01AG025204-09	Administrative Core	2013	$113,777
5P01AG025204-09	Quantitative Neuropathological Correlates Of In Vivo Pib Retention	2013	$274,558
5P01AG025204-09	In Vivo Pib Pet Amyloid Imaging: Normals; Mci & Dementia	2013	$1,295,247
5P50AG005133-30	Natural History Of Amyloid Deposition Familial Ad	2013	$170,365
2RF1AG025516-11	Amyloid Pathology And Cognition In Normal Elderly	2014	$2,701,818
5P01AG025204-10	Administrative Core	2014	$126,259
5P01AG025204-10	Modulators Of Cognitive Transifion From Mci To Ad	2014	$175,638
5P01AG025204-10	Quantitative Neuropathological Correlates Of In Vivo Pib Retention	2014	$286,635
5P01AG025204-10	In Vivo Pib Pet Amyloid Imaging: Normals; Mci & Dementia	2014	$1,146,355
5R37AG025516-10	Amyloid Pathology And Cognition In Normal Elderly	2014	$227,443
5P50AG005133-31	Natural History Of Amyloid Deposition Familial Ad	2014	$182,280

1U01AG051406-01	Neurodegeneration In Aging Down Syndrome (niad): A Longitudinal Study Of Cognition And Biomarkers Of Alzheimer's Disease	2015	$3,656,559
2P01AG025204-11A1	Imaging Pathophysiology In Aging And Neurodegeneration	2016	$1,998,101
3RF1AG025516-11S1	Amyloid Pathology And Cognition In Normal Elderly	2016	$782,946
5U01AG051406-02	Neurodegeneration In Aging Down Syndrome (niad): A Longitudinal Study Of Cognition And Biomarkers Of Alzheimer's Disease	2016	$3,556,865
3U01AG051406-03S1	Neurodegeneration In Aging Down Syndrome (niad): A Longitudinal Study Of Cognition And Biomarkers Of Alzheimer's Disease	2017	$158,939
5P01AG025204-12	Imaging Pathophysiology In Aging And Neurodegeneration	2017	$2,020,576
3U01AG051406-03S2	Neurodegeneration In Aging Down Syndrome (niad): A Longitudinal Study Of Cognition And Biomarkers Of Alzheimer's Disease	2017	$163,334
5U01AG051406-03	Neurodegeneration In Aging Down Syndrome (niad): A Longitudinal Study Of Cognition And Biomarkers Of Alzheimer's Disease	2017	$3,623,562

ANNEX 3: Eighteen Patents Assigned to the University of Pittsburgh that List William E. Klunk as the Inventor

Note: only one patent disclosed federal funding.

Patent Number	Title
9,833,458	Thioflavin derivatives for use in the antemortem diagnosis of Alzheimer's disease and in vivo imaging and prevention of amyloid deposition
9,808,541	Thioflavin derivatives for use in antemortem diagnosis of Alzheimer's disease and in vivo imaging and prevention of amyloid deposition
9,134,328	Methods of using benzothiazole derivative compounds and compositions
8,911,707	Thioflavin derivatives for use in antemortem diagnosis of alzheimer's disease and in vivo imaging and prevention of amyloid deposition
8,691,185	Benzothiazole derivative compounds, compositions and uses
8,580,229	Amyloid imaging as a surrogate marker for efficacy of anti-amyloid therapies

8,404,213	Thioflavin derivatives for use in antemortem diagnosis of Alzheimer's disease and in vivo imaging and prevention of amyloid deposition
8,343,457	Amyloid imaging as a surrogate marker for efficacy of anti-amyloid therapies
8,236,282	Benzothiazole derivative compounds, compositions and uses
8,147,798	Amyloid imaging as a surrogate marker for efficacy of anti-amyloid therapies
8,138,360	Isotopically-labeled benzofuran compounds as imaging agents for amyloidogenic proteins
7,854,920	Thioflavin derivatives for use in antemortem diagnosis of alzheimer's disease and in vivo imaging and prevention of amyloid deposition
7,351,401	Thioflavin derivatives for use in the antemortem diagnosis of Alzheimers disease and in vivo imaging and prevention of amyloid deposition
7,270,800	Thioflavin derivatives for use in antemortem diagnosis of Alzheimer's disease and in vivo imaging and prevention of amyloid deposition
6,417,178	Amyloid binding nitrogen-linked compounds for the antemortem diagnosis of alzheimer's disease, in vivo imaging and prevention of amyloid deposits
6,168,776	Alkyl, alkenyl and alkynyl Chrysamine G derivatives for the antemortem diagnosis of Alzheimer's disease and in vivo imaging and prevention of amyloid deposition
6,133,259	Alkyl, alkenyl and alkynyl chrysamine G derivatives for inhibition of cell degeneration and toxicity associated with amyloid deposition
6,1144,175	Compound for the antemortem diagnosis of Alzheimer's Disease and in vivo imaging and prevention of amyloid deposition

ANNEX 4: NIH Grants to the University of Pittsburgh with Chester A. Mathis Listed as Principal Investigator, with Search Term "Amyloid"

The search term for NIH RePORTER database: "Text Search: amyloid (and); Search in: Projects, AdminIC: All; Principal Investigator / Project Leader: Mathis; Chester; Fiscal Year: All Fiscal Years."

Project Number	Project Title	Agency	FY	FY Cost
1R01AG018402-01A1	Amyloid Imaging Agents For Positron Emission Tomography	NIA	2001	$350,525
5R01AG018402-02	Amyloid Imaging Agents For Positron Emission Tomography	NIA	2002	$349,224
5R01AG018402-03	Amyloid Imaging Agents For Positron Emission Tomography	NIA	2003	$347,922
5R01AG018402-04	Amyloid Imaging Agents For Positron Emission Tomography	NIA	2004	$346,619
2R01AG018402-05	Amyloid Imaging Agents For Position Emission Tomography	NIA	2007	$339,851
5R01AG018402-06	Amyloid Imaging Agents For Position Emission Tomography	NIA	2008	$376,408
5R01AG018402-07	Amyloid Imaging Agents For Position Emission Tomography	NIA	2009	$394,437
5R01AG018402-08	Amyloid Imaging Agents For Position Emission Tomography	NIA	2010	$357,159
1S10RR028324-01	Siemens Eclipse Hp Cyclotron For Pet Imaging Research	NCRR	2010	$2,688,777
2P50AG005133-32	Project 2: Pet Imaging Of Tau In Elderly Controls; Mci; And Ad	NIA	2015	$137,119
5P50AG005133-33	Project 2: Pet Imaging Of Tau In Elderly Controls; Mci; And Ad	NIA	2016	$137,119
5P50AG005133-34	Project 2: Pet Imaging Of Tau In Elderly Controls; Mci; And Ad	NIA	2017	$137,119