UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

RIGEL PHARMACEUTICALS, INC.,

Petitioner,

v.

SERVIER PHARMACEUTICALS LLC

Patent Owner.

Case IPR2022-01423
U.S. Patent No. 10,610,125

PETITION FOR *INTER PARTES* REVIEW

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I. INTRODUCTION

Petitioner respectfully requests *inter partes* review ("IPR") of Claims 1-5 and 9-12 (the "Challenged Claims") of U.S. Patent No. 10,610,125 (EX1001, "the '125 Patent").

The '125 Patent purports to claim the use of ***any*** IDH1 inhibitor in the treatment of IDH1-mutant Acute Myeloid Leukemia ("AML"). However, the Challenged Claims of the '125 Patent are not entitled to the claims of priority to applications filed in 2010 and earlier, because the applications filed at those times do not provide sufficient written description to support the broad Challenged Claims. Accordingly, because the Challenged Claims of '125 Patent cannot be entitled to any priority dates before July 11, 2013, they are invalid over 2012 publications by Popovici-Muller, and over a 2011 publication to Dang (which is the publication of the international application of which the '125 Patent is a grandchild continuation).

The Board should institute trial and cancel the Challenged Claims.

II. MANDATORY NOTICES

A. Real Party-In-Interest (37 C.F.R. §42.8(b)(1))

The petitioner in this proceeding is Rigel Pharmaceuticals, Inc. ("Rigel" or "Petitioner") and Rigel is the real party-in-interest. There are no other real parties-in-interest.

B. Related Matters (37 C.F.R. §42.8(b)(2))

Petitioner identifies U.S. Provisional Patent Applications Nos. 61/160,253; 61/160,665; 61/173,518; 61/180,609; 61/220,543; 61/227,649; 61/229,689; 61/253,820; and 61/266,929 (all lapsed); International Patent Application no. PCT/US2010/027253 (lapsed); and U.S. Patent Applications No. 13/256,396 (abandoned); 13/443,012 (abandoned); 13/939,519 (abandoned); and 16/790,860 (pending) as related administrative matters.

There are no district court or other *inter partes* review proceedings currently involving the '125 Patent or its Related Matters.

C. Counsel (37 C.F.R. §42.8(b)(3)) and Service Information (37 C.F.R. §42.8(b)(3)-(4))

Petitioner designates Paul H. Berghoff (Reg. No. 30,243) as lead counsel for this matter, and designates James L. Lovsin (Reg. No. 69,550) and James V. Suggs (Reg. No. 50,419) as back-up counsel for this matter.

Post mailings and hand deliveries for lead and back-up counsel should be addressed to: McDonnell Boehnen Hulbert and Berghoff LLP, 300 South Wacker Drive, Chicago, IL, 60606. (Telephone: 312-913-0001; Fax: 312-913-0002).

Pursuant to 37 C.F.R. §42.8(b)(4), Petitioner consents to e-mail service at: docketing@mbhb.com, and RigelIPR@mbhb.com.

For compliance with 37 C.F.R. §42.10(b), a Power of Attorney is filed concurrently herewith.

III. PAYMENT OF FEES

The undersigned authorizes the Office to charge the fee required by 37 C.F.R. §42.15(a) and any additional fees to Deposit Account 132490.

IV. REQUIREMENTS FOR IPR

A. Grounds for Standing

Petitioner certifies that the ’125 Patent is available for IPR and that Petitioner is not barred or estopped from requesting IPR on the following grounds.

B. Identification of Challenge

1. The Specific Art on Which the Challenge is Based

This Petition relies on the prior art identified below.[1] This Petition also relies on expert declarations of Professor David J. Sherman (EX1003; CV of Professor Sherman provided as EX1004) and Doctor Leslie Oleksowicz (EX1005; CV of Doctor Oleksowicz provided as EX1006).

Name	Exhibit	Relevant Date(s)	Prior Art category
Dang'243	1009	September 2010	§102(a)(1)
PM'678	1010	January 2012	§102(a)(1)
PM 2012	1011	September 2012	§102(a)(1)

2. Statutory Grounds on Which the Challenge is Based

The above-identified prior art renders the Challenged Claims unpatentable based on the following grounds:

[1] These references have publication dates after March 13, 2009, the earliest priority date claimed by the '125 Patent. Petitioner describes in Section VII, *infra*, that the Challenged Claims are not entitled to the 2009 and 2010 priority dates.

Ground	Statute	Art Cited	Claims Challenged
1	35 U.S.C. §102	PM'678	1-5 and 6-12
2	35 U.S.C. §102	PM 2012 in view of PM'678	1-5 and 6-12
3	35 U.S.C. §103	PM'678, or PM 2012 in view of PM'678, in view of Dang'243	12
4	35 U.S.C. §102	Dang'243	1-5 and 6-12

3. Discretionary Denial is Not Warranted

Petitioner respectfully submits that the Board should not exercise its discretion under 35 U.S.C. §§314(a) or 325(d) to deny this Petition.

a) No prior petitions or parallel litigation

The '125 Patent has not been challenged in any prior IPR petition, and Patent Owner has not asserted the '125 Patent against Petition in any co-pending litigation. As such, none of the discretionary factors in *General Plastic Indus. Co., Ltd. v. Canon Kabsuhiki Kaisha*, IPR2016-01357, Paper 19 at 16 (PTAB Sep., 6, 2016) (Section II.B.4.i precedential) or in *Apple Inc. v. Fintiv, Inc.*, IPR2020-0019, Paper 11 (PTAB Mar. 20, 2020) applies to this Petition, therefore discretionary denial under §§314 and 325(d) is not warranted.

b) The *Advanced Bionics* test favors institution

The Petition satisfies the two-part test of *Advanced Bionics, LLC v. Med-El Elektromedizinische Gerate GMBH*, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential). First, none of the evidence and arguments in the Petition that the Challenged Claims are not entitled to any priority date was previously presented to or otherwise considered by the Office. The '125 Patent issued from U.S. Patent Application No. 15/589,615 ("the '615 Application"). The Examiner never addressed the '615 Application's priority claim on the record during examination and there is "no basis to presume" that the '615 Application is "necessarily entitled to the filing date of its provisional application." *Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375, 1380 (Fed. Cir. 2015).

Moreover, while U.S. Patent Application Publication 2013/0184222 was cited during prosecution, the corresponding international publication, Popovici-Muller et al., WO 2012/009678 ("PM'678") was not; this difference is critical, as the publication date of the document cited during prosecution was after the July 11, 2013 Application filing date, while the PM'678 publication was more than a year before. Accordingly, the Grounds raised by this Petition are not the same or substantially the same as the arguments raised during the prosecution of the '125 Patent.

Second, even if one assumes *arguendo* that the arguments in the Petition were previously presented or substantially the same (they were not), the Examiner erred in a manner material to the patentability of the Challenged Claims. As a critical example, the Examiner committed errors of law by misapplying Federal Circuit case law regarding the lack of written description of genus claims with respect to these genus applications in determining the proper effective filing date of the claims, including *Idenix Pharm. LLC v. Gilead Sci. Inc.*, 941 F.3d 1149 (Fed. Cir. 2019) and *Abbvie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed. Cir. 2014). During prosecution of the '125 Patent, the Examiner also did not have the benefit of *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330 (Fed. Cir. 2021) (invalidating genus claims for lack of written description). Accordingly, the Examiner did not properly assess the content of the disclosure of the 2009 and 2010 priority applications in comparison to the claims and failed to determine that the claims were not entitled to early priority dates.

Without an understanding of any proper priority date, the Office did not properly consider the teachings of Dang'243, PM'678 and PM 2012 from among the hundreds references cited. Thus, the Board should not exercise its discretion to deny institution of this Petition under §325(d).

V. BACKGROUND

A. Overview of Technology

Isocitrate dehydrogenase 1 ("IDH1," found in the cytosol and peroxisomes) and isocitrate dehydrogenase 2 ("IDH2," found in mitochondria) are homodimeric isoenzymes involved in a major pathway for cellular NADPH generation through the oxidative decarboxylation of isocitrate to α-ketoglutarate ("αKG"). EX1014, 2. Sherman Dec., ¶ 55.

Mutations of IDH1 and IDH2 were identified in various brain tumors in 2008 and early 2009, and in August 2009 mutations of IDH1 were identified in AML patient samples. *See, e.g.*, EX1007, 7-8; EX1015, 1; 1017, 1, 4; 1016, 1-2. The mutation in IDH generates an oncometabolite product, 2-hydroxyglutarate ("2HG"), which has more recently been linked to the disruption of metabolic and epigenetic mechanisms responsible for cellular differentiation and is understood to be an early and critical contributor to oncogenesis. *Id.* at 2. Sherman Dec., ¶ 56.

In recent times, two mutant IDH inhibitors ivosidenib, (mutant IDH1 inhibitor) and enasidenib (mutant IDH2 inhibitor), have been FDA-approved for IDH-mutant relapsed or refractory acute myeloid leukemia (AML) based on phase 1 safety and efficacy data and continue to be studied in clinical trials in relating to

malignancies, as well as in glioma, cholangiocarcinoma, and chondrosarcoma. EX1014, 9. Sherman Dec., ¶ 57.

B. The '125 Patent

The '125 Patent relates generally to "[m]ethods of treating and evaluating subjects having neoactive mutants." EX1001, Abstract. The inventors assert that they "have discovered, inter alia, a neoactivity associated with IDH [i.e., isocitrate dehydrogenase] mutants and that the product of the neoactivity can be significantly elevated in cancer cells." *Id.* at 1:52-54. They further assert the discovery "that certain mutated forms of an enzyme (e.g., IDH1 or IDH2) have a gain of function, referred to as a neoactivity, which can be targeted in the treatment of a cell proliferation-related disorder such as cancer." *Id.* at 38:29-33. The lone independent claim recites:

> 1. A method of treating a subject having acute myelogenous leukemia (AML) characterized by the presence of a mutant isocitrate dehydrogenase 1 enzyme (IDH1) or a mutant isocitrate dehydrogenase 2 enzyme (IDH2), wherein the mutant IDH1 or mutant IDH2 has the ability to convert alpha-ketoglutarate to 2-hydroxyglutarate (2HG), the method comprising administering to the subject a therapeutically effective amount of a small molecule inhibitor of said mutant IDH1 or mutant IDH2.

Id. at 431:57-67. Sherman Dec., ¶ 58.

The '125 Patent specification begins with a single paragraph background section that identifies the biochemical role of isocitrate dehydrogenases. EX1001, 1:30-45. The Summary of the Invention section begins with a statement that "[t]he inventors have discovered, inter alia, a neoactivity associated with IDH mutants and that the product of the neoactivity can be significantly elevated in cancer cells." *Id*. at 1:52-54. Generally, "[d]isclosed herein are methods and compositions for treating, and methods of evaluating, subjects having or at risk for a disorder, e.g., a cell proliferation-related disorder characterized by a neoactivity in a metabolic pathway enzyme, e.g., IDH neoactivity." *Id.* at 1:55-59. The inventors surmise a general underlying mechanism:

> While not wishing to be bound by theory it is believed that the balance between the production and elimination of neoactive product, e.g., 2HG, e.g., R-2HG, is important in disease. Neoactive mutants, to varying degrees for varying mutations, increase the level of neoactive product, while other processes, e.g., in the case of 2HG, e.g., R-2HG, enzymatic degradation of 2HG, e.g., by 2HG dehydrogenase, reduce the level of neoactive product. An incorrect balance is associated with disease. In embodiments, the net result of a neoactive mutation at IDH1 or IDH2 result in increased levels, in affected cells, of neoactive product, 2HG, e.g., R-2HG,

Id. at 2:29-40. Sherman Dec., ¶ 59.

Columns 2-33 provide a series of repetitive "embodiments" and "aspects" that set out various methods of treatment and methods for diagnosis of cell-proliferation disorders characterized by a somatic mutation in a metabolic pathway enzyme. This section begins with:

> Accordingly, in one aspect, the invention features, a method of treating a subject having a cell proliferation-related disorder, e.g., a disorder characterized by unwanted cell proliferation, e.g., cancer, or a precancerous disorder. The cell proliferation-related disorder is characterized by a somatic mutation in a metabolic pathway enzyme. The mutation is associated with a neoactivity that results in the production of a neoactivity product. The method comprises: administering to the subject a therapeutically effective amount of a therapeutic agent described herein, e.g., a therapeutic agent that decreases the level of neoactivity product encoded by a selected or mutant somatic allele, e.g., an inhibitor of a neoactivity of the metabolic pathway enzyme (the neoactive enzyme), a therapeutic agent that ameliorates an unwanted affect [sic] of the neoactivity product, or a nucleic acid based inhibitor, e.g., a dRNA which targets the neoactive enzyme mRNA, to thereby treat the subject.

EX1001, 4157. The "embodiments" following this recite a number of metabolic pathways, mutations, mutant IDH1 and IDH2 species, general types of therapeutic agents, and disorders to be treated. *Id.* at 2:58-33:54. Sherman Dec., ¶ 60.

The Detailed Description section focuses on mutant IDH1 and mutant IDH2 that have a particular "neoactivity" – the ability to convert αKG to 2HG. EX1001, 38:29-40:52. Detection of 2HG in patients is described as a way to diagnose, prognose, select an inhibitor or monitor treatment efficacy. *Id.* at 40:53-43:31. Sherman Dec., ¶ 61.

Methods of treatment are described:

> Described herein are methods of treating a cell proliferation-related disorder, e.g., a cancer, e.g., a glioma, e.g., by inhibiting a neoactivity of a mutant enzyme, e.g., an enzyme in a metabolic pathway, e.g., a metabolic pathway leading to fatty acid biosynthesis, glycolysis, glutaminolysis, the pentose phosphate shunt, the nucleotide biosynthetic pathway, or the fatty acid biosynthetic pathway, e.g., IDH1 or IDH2. The cancer can be characterized by the presence of a neoactivity, such as a gain of function in one or more mutant enzymes (e.g., an enzyme in the metabolic pathway, e.g., a metabolic pathway leading to fatty acid biosynthesis, glycolysis, glutaminolysis, the pentose phosphate shunt, the nucleotide biosynthetic pathway, or the fatty acid biosynthetic pathway e.g., IDH1 or IDH2). In some embodiments, the gain of function is the conversion of α-ketoglutarate to 2-hydroxyglutarate, e.g., R-2-hydroxyglutarate.

EX1001, 43:31-48. Sherman Dec., ¶ 62.

The specification then purports to describe suitable compounds for therapeutic use. A number of general methods for identifying suitable compounds are provided. EX1001, 43:49-44:51. "Compounds that inhibit a neoactivity, *e.g.*, a neoactivity described herein, can include, e.g., small molecule, nucleic acid, protein and antibody." *Id.* at 44:52-54. Small molecules are described:

> Exemplary small molecules include, e.g, small molecules that bind to enzymes and decrease their activity, e.g., a neoactivity described herein. The binding of an inhibitor can stop a substrate from entering the enzyme's active site and/or hinder the enzyme from catalyzing its reaction. Inhibitor binding is either reversible or irreversible. Irreversible inhibitors usually react with the enzyme and change it chemically. These inhibitors can modify key amino acid residues needed for enzymatic activity. In contrast, reversible inhibitors bind non-covalently and different types of inhibition are produced depending on whether these inhibitors bind the enzyme, the enzyme-substrate complex, or both.

Id. at 44:55-67. The specification exemplifies micromolar-range inhibition of enzyme αKG→2HG activity by five compounds of four different structural classes; and provides a measurement of isocitrate→αKG activity by oxalomalate. *Id.* at 72:30-54, 122:38-125:29. Oxalosuccinate and oxalofumarate are also suggested as inhibitors, as are two chemical genera and 92 compounds apparently

falling into one of the genera. *Id.* at 45:1-67, 125:30-148:67. Moreover, a list of references disclosing several wild-type IDH inhibitors is provided; these are said to be "[e]xemplary candidate compounds, which can be tested for inhibition of a neoactivity described herein (e.g., a neoactivity associated with mutant IDH1)." *Id.* 46:16-31. However, no such testing is provided. Nucleic acids are also described. *Id.* at 49:51-56:44. Sherman Dec., ¶ 63.

A general discussion of pharmaceutical formulations and combination therapies are provided. EX1001, 56:45-66:39, 69:36-47. Sherman Dec., ¶ 64.

The specification suggests that a wide variety of disorders can be treated or evaluated by the methods described, including virtually any kind of cancer. EX1001, 66:40-69:35. Sherman Dec., ¶ 65.

The specification concludes with a number of examples. Examples 1 and 2 explore the biochemistry of mutant IDH1, including the identification of the "neoactivity" of the conversion of αKG to 2HG. EX1001, 69:51-84:26. Example 3 provide suggestions for metabolomics analysis of IDH1 and for evaluation of IDH1 as a cancer target. *Id.* at 84:28-61. Example 5 describes a variety if siRNAs that "can be evaluated" for the ability to silence a mutated IDH. *Id.* at 84:63-113:17. Example 6 describes the solving of a crystal structure of IDH1R132H bound to αKG, NADPH and Ca^{2+}. *Id.* at 113:18-122:35. Example 9 provides

compounds as described above. *Id.* at 122:37-144:67. Example 10 describes the NADPH catalytic activity of IDH2R172K. *Id.* at149:1-16. Example 11 describes that 2HG accumulates in AML with IDH mutations. *Id*. at 149:17-155:17; 156:1-17. The rest of the specification is a sequence listing. *Id.* at cols. 156-432. Sherman Dec., ¶ 66.

C. Prosecution History of the '125 Patent

1. Prosecution History of the '125 Patent Itself

A copy of the file history of the '125 Patent is provided as EX1002. The underlying patent application was filed on May 8, 2017. EX1002, 1238, 274, 1472. It is a great-grandchild through two intervening continuations of a U.S. National Stage entry of a PCT application filed in 2010, which in turn claims priority to nine provisional applications going back to an earliest claimed priority date of March 13, 2009. EX1002, 1468.

The originally-filed claims were similar to claim 1 of the '125 Patent as issued, but recited treatment of "a cancer" instead of AML, using "an inhibitor" instead of "a small molecule inhibitor." *Id.* at 1460. In the first Office Action, the Examiner rejected most of the claims as being obvious, primarily over Zernicka-Goetz (provided as EX1018), which teaches therapy of cancers having mutated genes by inhibiting gene expression with a double-stranded RNA inhibitor, in view

of Yan, which teaches that mutant IDH1, present in certain cancers like certain gliomas, has the ability to convert alpha-ketoglutarate to 2-hydroxyglutarate ("2HG"). EX1002, 165-170.

In response, the Applicant amended the claims to recite the use of "small molecule" inhibitors, noting that the definition in the text limited "small molecules" to less than 1000 Da in molecular weight. *Id.* at 156, 158-160.

In a second Office Action, the Examiner based prior art rejections on Vogelstein, noting its teachings of the presence of mutant IDH1 and IDH2 in certain cancers, of the neoactivity of such mutants in making 2HG, and of suggestion of treatment of such cancers by inhibiting the relevant IDH. *Id.* at 93-101. For a dependent claim reciting AML in particular, the Office relied upon Kang (provided as EX1019). *Id.* at 97.

In response, the Applicant amended the claims to recite only the treatment of AML, arguing that "Vogelstein and Kang suggest that IDH mutations are not present in AML," and so "[c]onsequently, at the time of the filing of the instant application, a person of skill in the art would find no motivation in either Vogelstein or Kang, alone or in combination" to practice the claimed method of treating IDH-mutant AML. *Id.* at 84, 87.

The Examiner allowed the application after the Applicant overcame the double patenting rejection based on U.S. Patent no. 9982309 by submitting a Terminal Disclaimer. *Id.* at 19, 59, 68.

2. Prosecution History of the Parent Patent Applications

As noted above, the ’125 Patent is part of a chain of applications asserting priority claims extending back to March 2009. EX1001, front page. The ’125 Patent itself issued from the ’615 Application, which was a continuation of U.S. Patent Application no. 13/939,519 (“the 2013 Application,” filed July 11, 2013, excerpted file history provided as EX1020), which in turn was a continuation of U.S. Patent Application no. 13/256,396 (“the 2010 National Stage,” excerpted file history provided as EX1021), which was a U.S. National Stage entry of International Patent Application no. PCT/US2010/027253 (“the 2010 Application,” filed March 12, 2010; refer to EX1009 for text). The 2010 Application claimed the benefit of priority of nine provisional applications with filing dates extending back to March 13, 2009.

In the 2010 National Stage and the 2013 Application, the Applicant pursued claims chiefly related to diagnosis of subjects with respect to IDH1/IDH2 neoactivity. *See* EX1021, 328; EX1020, 73, 164, 297. Both of these applications were abandoned, variously after rejections on the basis of written description with

respect to the scope of mutant IDHs claimed, enablement with respect to correlation of 2HG with disease, and non-statutory subject matter. *See* EX1021, 1-2, 14-21; EX1020, 1-10.

D. Asserted Prior Art

The Challenged Claims are unpatentable, based on the references described below.

1. Dang'243

Dang'243 (EX1009) was published on September 16, 2010. Accordingly, it is prior art under §102(a)(1) for purposes of this Petition, as the earliest possible effective filing date of the Challenged Claims is July 11, 2013.[2] Sherman Dec., ¶ 85.

Dang'243 is a publication of the original international stage application of which the '125 Patent is a grandchild continuation. It has substantively identical disclosure to the intervening 2013 Application and the '125 Patent itself. It is the publication of the 2010 Application; this Petition refers to the 2010 Application

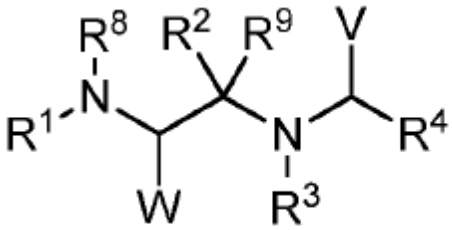
[2] Petitioner does not admit that the Challenged Claims are entitled to any of their claimed priority dates, or even that they are adequately supported by the specification of the '125 Patent itself as of its filing date.

when discussing support for the claims, and Dang'243 when discussing the effect of the document as prior art. Sherman Dec., ¶ 86.

2. PM'678

PM'678 (EX1010) was published on January 19, 2012. Accordingly, it is prior art under §102(a)(1) for purposes of this Petition, as the earliest possible effective filing date of the Challenged Claims is July 11, 2013.

PM'678 describes methods of treating IDH1-mutant cancers with certain structurally-defined compounds:

> Described herein are methods of treating a cancer characterized by the presence of a mutant allele of IDH1. The methods comprise the step of administering to a subject in need thereof a compound of formula I, or a pharmaceutically acceptable salt thereof, wherein:
>
> 
>
> formula I
>
> ….
>
> The compound of formula I inhibits mutant IDH1, particularly mutant IDH1 having alpha hydroxyl neoactivity.

EX1010, 3-4. The specification describes a number of subgenera of compounds, as well as 386 particular compounds. EX1010, 8-67. AML (specifically

IDH1R132H-mutant AML), is identified as a disorder that can be treated by administration of the compounds of the disclosure. *See*, *e.g.*, EX1010, 83-84. The specification provides IDH1R132H inhibition enzymatic assay data, and in many cases IDH1R132H inhibition cellular assay data, for the compounds. EX1010, 236-245. A number of the compounds are reported to have IC_{50} values for inhibition of no more than 100 nM in enzymatic assays, and no more than 250 nM in cellular assays. *Id*. Sherman Dec., ¶ 87.

3. PM 2012

PM 2012 is a September 2012 publication by the original applicant of the '125 Patent describing "the First Potent Inhibitors of Mutant IDH1 That Lower Tumor 2-HG in Vivo." EX1011, 1. The journal in which it was published by an established publisher, and was widely disseminated and would have been accessible to persons in the field of medicinal chemistry, drug development, and cancer therapeutics at least as of the end of the month of its listed publication date.[3] Sherman Dec., ¶ 88.

[3] The same is true for all cited publications bearing publication dates before March 2010. *See* Sherman Dec, *passim*.

It describes the state of the art with respect to mutant IDH1 inhibitors and their applicability to glioma and AML:

> The implication of a role for IDH in cancer was revealed after somatic mutations in IDH1 were identified through a genome wide mutation analysis in glioblastoma. This landmark study was followed by high throughput sequencing, which revealed the presence of mutations in IDH1 in more than 70% of grade II−III gliomas and secondary glioblastomas, as well as in approximately 10−15% of patients with acute myeloid leukemia (AML). These somatic mutations were found at a key arginine residue belonging to the catalytic triad found in the enzyme's active site (R132 for IDH1). This active site mutation results in loss-of-function for the oxidative decarboxylation of isocitrate and confers a novel gain-of-function for the production of the oncometabolite D-2-hydroxyglutarate (2-HG). Further characterization of the mutation showed that overexpression of mutant IDH1 in U87-MG, a human glioblastoma cell line, resulted in 100-fold elevated levels of 2-HG relative to the same cells expressing vector alone (data not shown). Recently, it was demonstrated that 2-HG is a competitive inhibitor of multiple α-KG-dependent dioxygenases, including histone and DNA demethylases, and several studies have shown that 2-HG producing IDH mutants are involved in global histone and DNA methylation alterations which may contribute to tumorigenesis through epigenetic rewiring. Taken together, these

> findings implicate mutant IDH1 as an oncogene and a ***compelling drug target for new therapies for glioma and AML patients***.

EX1011, 1 (emphasis added, citations omitted). PM 2012 identified compound 1 as an initial lead.

> Detailed kinetic mechanism-of action studies showed compound 1 binding to be reversible and behaving as competitive inhibitor with respect to α-KG and uncompetitive with respect to NADPH (data not shown). Given its attractive chemical structure and well-defined inhibitory properties, we selected this compound as a starting point for further optimization.

Id. Sherman Dec., ¶ 89.

A variety of compounds were tested with the goal of elucidating structure-activity relationships. Some findings were made with respect to the particular phenylglycine molecules studied. EX1011, 2-5. Sherman Dec., ¶ 90.

This work "led to the identification of 35, the first reported R132H IDH1 inhibitor to show robust in vivo reduction of 2-HG levels in a tumor xenograft model." EX1011, 2. PM 2012 concludes that its "results demonstrated that tumor 2-HG inhibition correlated with the duration of drug exposure and that robust tumor 2-HG inhibition is achievable with adequate and sustainable drug exposure." EX1011, 5. Sherman Dec., ¶ 91.

Notably, Table 3 reports IDH1R132H inhibition data, in enzyme and cell assays, for a variety of compounds; many had IC_{50} values in enzyme assays below 100 nM. EX 1011, 3. Sherman Dec., ¶ 92.

VI. LEVEL OF ORDINARY SKILL IN THE ART

As of all relevant earliest effective filing dates of the Challenged Claims, a person having ordinary skill in the art ("POSA") in the field of the '125 Patent (i.e., small molecule inhibitors of mutant IDH and therapeutic uses thereof) would have had the skill sets of a team comprising a medicinal chemist having a broad array of experience including synthetic chemistry, conducting enzyme inhibition assays and understanding of cancer treatment; and a physician experienced in treating patients for AML. The physician on the team would have had an M.D., and is not only board-certified in Internal Medicine, but also a board certified Hematologist/Oncologist following a minimum of three years of training in an ABIM (American Board of Internal Medicine) approved program. The medicinal chemist would have had a Ph.D. in organic chemistry or biochemistry and at least three years of experience working in the field of small molecule drug discovery and development. Sherman Dec., ¶¶ 93-94.

VII. CLAIM CONSTRUCTION

Claims are construed in accordance with the *Phillips* standard as would be applied in district court. 37 C.F.R. §42.200(b).

The claim term "small molecule" would be understood to mean a compound having a molecular weight no more than 1000 Daltons, as this is the definition urged by the Applicant to overcome a rejection during prosecution. EX1002, 156-159; *see also* EX1001, 4:23-25. Sherman Dec., ¶ 95.

Petitioner submits that the other terms recited in the Challenged Claims can be given their ordinary and customary meaning, as would have been understood by a POSA based on the specification. Thus, no express constructions are needed for the Board to institute the IPR and cancel the Challenged Claims. Sherman Dec., ¶ 96.

VIII. GROUNDS OF UNPATENTABILITY

A. The Challenged Claims are not entitled to any priority date

1. Legal Standards for Priority

In order to rely on the filing date of an earlier application, 35 U.S.C. §120 requires that the earlier application include a disclosure that complies with the written description requirement of 35 U.S.C. §112. *Lockwood v. Am Airlines, Inc.*, 107 F.3d 1565, 1571-72 (Fed. Cir. 1997).

The written description requirement of 35 U.S.C. §112 provides, in pertinent part, that "[t]he specification shall contain a written description of the invention." That requirement is satisfied only if the inventor "convey[s] with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate[s] that by disclosure in the specification of the patent." *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1348 (Fed. Cir. 2011) (internal quotation omitted).

The written description requirement incentivizes "actual invention," *id.,* and thus "[a] mere wish or plan for obtaining the claimed invention is not adequate written description," *Id.* at 1348 (internal quotation omitted). When an inventor expressly claims a specific result, case law requires that the result must be supported by adequate disclosure in the specification. *Nuvo Pharmaceuticals v. Dr. Reddy's Laboratories*, 923 F.3d 1368, 1384 (Fed. Cir. 2019) (finding lack of written description when "the inventor chose to claim the therapeutic effectiveness of uncoated PPI, but he did not adequately describe the efficacy of uncoated PPI so as to demonstrate to ordinarily skilled artisans that he possessed and actually invented what he claimed.").

To satisfy the written description requirement when a genus is claimed, the specification must disclose either "a representative number of species falling

within the scope of the genus or structural features common to the members of the genus." *Ariad Pharms., Inc. v. Eli Lilly Co.*, 598 F.3d 1336, 1349-50 (Fed. Cir. 2010) (en banc). "For generic claims, we have set forth a number of factors for evaluating the adequacy of the disclosure, including the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue." *Id.* at 1351 (internal quotation omitted, alteration in original). For genus claims using functional language, like the mutant IDH1/IDH2 inhibitory function of the small molecule compounds claimed here, the written description "must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus." *Id.* at 1349. Generally, the representative number of species falling within the scope of the genus or structural features common to the members of the genus must allow "one of skill in the art can visualize or recognize the members of the genus." *Id.* at 1350 (internal quotation omitted).

The Federal Circuit has repeatedly held that genus claims with unsupported, functional genus limitations fail to satisfy the written description requirement. *See, e.g.*, *Juno*, 10 F.4th at 1339-40 (Fed. Cir. 2021) (invalidating genus claims directed to antibody fragments that bind to any target); *Idenix Pharm.*, 941 F.3d at 1164

(invalidating genus claims directed to nucleosides that are effective at treating a disease); *Abbvie*, 759 F.3d at 1301 (invalidating genus claims directed to antibodies defined by neutralizing activity to an antigen).

2. There can be no valid priority claim before July 11, 2013

The Challenged Claims are entitled to no priority claim before the July 11, 2013 filing date of the 2013 Application, as neither the 2010 Application nor the provisional applications satisfy the written description requirement of §112 with respect those Challenged Claims.[4] Sherman Dec., ¶ 99.

a) The state of the art as of March 2010

As of the March 12, 2010 filing date of the 2010 Application, the fields of mutant IDH inhibitors and treatment of AML with mutant IDH inhibitors were still in their infancy. It was only in August 2009 that the discovery of mutant IDH1 in AML was published. EX1007, 1. Sherman Dec., ¶ 100.

Mardis identified IDH1 mutations at R132 in 15/187 AML samples studied:

[4] Again, Petitioner does not concede that the Challenged Claims are entitled to the filing date of the 2013 Application, or that they are supported by the specification of the ’125 Patent itself as of its filing date.

> We then genotyped the tier 1 mutations in 187 additional samples from patients with AML whose clinical characteristics have been described previously (Table 2 in the Supplementary Appendix). The *NPM*c mutation was previously shown to be present in 43 of 180 samples (23.9%), and activating *NRAS* mutations were present in 17 of 182 samples (9.3%). We observed mutations in *IDH1*, which were predicted to cause substitution of the arginine residue at position 132, in 16 of 188 samples: R132C in 8 samples, R132H in 7 samples, and R132S in 1 sample (Table 2 in the Supplementary Appendix).

Id. at 5-9 (citations omitted). Mardis also infers that mutant IDH1 is somehow "important" for pathogenicity:

> The best test of the relevance of individual mutations for pathogenesis (in the absence of functional validation) is recurrence in other AML samples or other cancers. Of the 12 tier 1 mutations, 3 (occurring in NPM1, NRAS, and IDH1) were recurrent in patients with AML and therefore were likely to be important in the pathogenesis of this tumor.

Id. at 8. Sherman Dec., ¶ 101.

While the roles of mutant IDH1 in AML are now better understood, the situation was less clear as of March of 2010. Throughout most of 2009, there was little published about the mechanism of pathogenesis with respect to mutant IDH

in AML. Yan found reduced wild-type catalytic activity (i.e., conversion of isocitrate to αKG) in glioma cells exhibiting IDH1R132H and a few IDH2R172 mutants, and found increased survival times for patients having mutant IDH gliomas. EX1016, 6-8. Zhao found that in mutant IDH1R132H-, IDH1R132S- and IDH1R132C-mutant gliomas there was a link between loss of wild-type activity and increased levels of hypoxia-inducible factor subunit HIF-1α. EX1012, 1. Sherman Dec., ¶ 102.

Dang 2009, published in December 2009, identified the so-called "neoactivity" of R132 mutant IDH1, i.e., that 2HG is formed from αKG. EX1024, 1. Indeed, this appears to be the experimental work underlying much of the '125 Patent disclosure. *See* EX1001, cols. 69-84. While Dang 2009 suggested that "inhibition of 2HG production by mutant IDH1 might slow or halt conversion of lower-grade glioma into lethal secondary glioblastoma, changing the course of the disease," EX1024, 5, there is no evidence showing that this would be the case and no suggestion made with respect to any other types of cancer, let alone AML. And in fact, Frezza in January 2010 questioned Dang 2009's suggestion that 2HG was an "onco-metabolite." EX1052, 2. Sherman Dec., ¶ 103.

Gross, working with Dang, in February 2010 published a more detailed study of AML, in which IDH1R132H, IDH1R132C, IDH1R132G and

IDH2R172K mutants were detected in patient AML samples and correlated with an increased amount of 2HG as compared to wild-type enzymes. This work also appears in the '125 Patent. *See* EX1001, 149:15-155:5. Notably, "there does not seem to be an effect of IDH1/2 mutation status on most clinical characteristics or treatment response in AML." EX1022, 3. The authors here, many of whom are listed as inventors on the '125 Patent, do not suggest that inhibition of IDH1R132 mutants is in fact therapeutically useful; rather, "[f]urther functional and mechanistic work will be required to understand the underlying biology driving the acquisition of these mutations, and to determine whether mutants of IDH1 R132 and IDH2 R172 may be useful therapeutic targets." *Id* at 5. Sherman Dec., ¶ 104.

As of March 12, 2010, there was not much in the open literature providing druggable compounds that might inhibit mutant IDH1. Vogelstein describes the presence of mutant IDH1 in gliomas, and suggests use of IDH1 inhibitors such as oxalomalate in inhibition. EX1008, 135. There were, in fact, a handful of wild-type IDH inhibitors known as of March 2010, as noted by the citation of references as describing "candidate compounds, which can be tested for inhibition." EX1001, 46:16-32. However, none had been demonstrated to inhibit mutant IDH1. This is especially important, given that the activity and structure of the mutant IDH1 was known to be different from that of the wild-type enzyme. For example, Zhao

teaches that the mutant has much lower isocitrate→αKG activity than the wild-type enzyme, and that the conformation of the mutant enzyme is different than that of the wild-type enzyme. EX1012, 3. Dang 2009 and the 2010 Application report the αKG→2HG activity of the mutants. EX1009, 109-112. EX1024, 1, 2-3. And the 2010 Application describes two important features in the change of R132 to histidine in the IDH1R132H: the effect on catalytic conformation equilibrium and the reorganization of the active site. EX1009, 141-142. Sherman Dec., ¶ 105.

b) The scope of the Challenged Claims is broad

Claim 1 recites a method for treating ***any*** AML having a mutant IDH1 or mutant IDH2 that has the ability to convert αKG to 2HG. Claim 2 limits this by requiring binding to IDH1R132X or IDH2R172X. EX1001, 432:57-59. Claim 3 requires that the mutation be an IDH1 mutation, while claims 4 and 5 require various IDH1R132X mutations. EX1001, 432:60-67. Sherman Dec., ¶ 107.

Claim 1 recites administering to the subject a therapeutically effective amount of a small molecule inhibitor of said mutant IDH1 or mutant IDH2. The small molecule inhibitor is ***not structurally defined*** (other than being a "small molecule" less than 1000 Da in molecular weight). None of claims 2-5 and 9-12 further limits the structure of the small molecule inhibitor. Sherman Dec., ¶ 108.

Claim 1 recites that the small molecule inhibitor is an "inhibitor of said mutant IDH1 or mutant IDH2." EX1001, 431:66-67. None of claims 1, 3-5 and 9-12 limits the actual function of the inhibitor with regard to its target, *e.g.*, whether it inhibits the activity of the mutant enzyme in converting isocitrate to αKG (i.e., analogous to the wild-type enzyme), the activity of the mutant enzyme in converting αKG to 2HG (the particular example of a "neoactivity" discussed in the specification), both of these activities, or some other activity entirely. Only claim 2 requires that the inhibitor inhibits the ability to convert αKG to 2HG. Sherman Dec., ¶ 109.

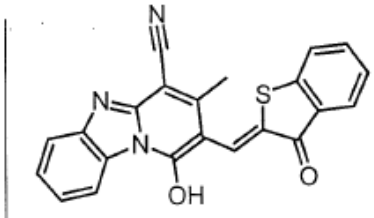
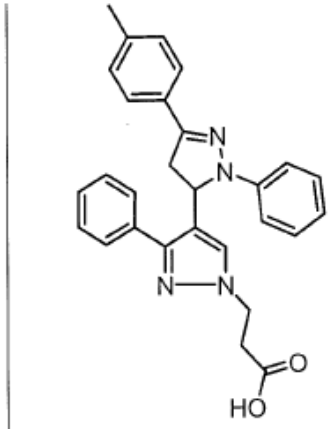
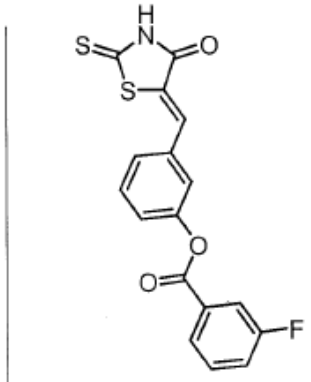
Claims 9-12 depend from claim 1 and recite methods in which the mutant IDH1 or mutant IDH2 is detected, e.g., in a sample from the subject or by sequencing a nucleic acid from an affected cell. EX1001, 433:7-17. These, too, are broadly recited. Sherman Dec., ¶ 110.

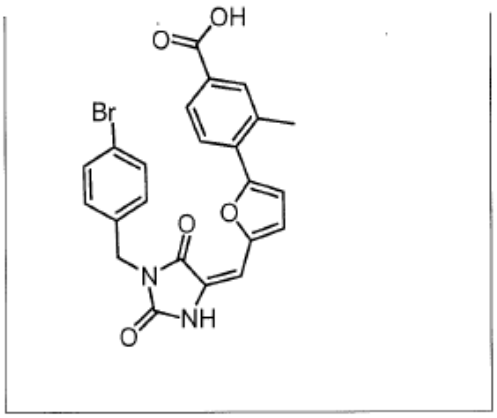
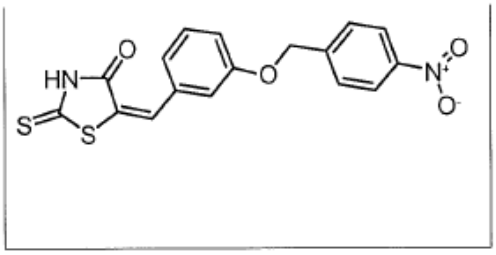
c) The effective disclosure of the 2010 Application and of the provisional applications with respect claimed compounds is much narrower than that claimed

The claims of the '125 Patent purport to cover ***any*** small molecule inhibitor of mutant IDH1/IDH2 with the recited activity. *Id.* But the actual disclosure effectively provided by the 2010 Application is not nearly as broad as the scope of the claims. Sherman Dec., ¶ 111.

There is scant disclosure of such small molecule inhibitors of mutant IDH1/IDH2 in the 2010 Application. There are five compounds, of widely varying structures, for which some degree of inhibition of an IDH1R132H mutant is demonstrated:

Table 24a

STRUCTURE	LDHa IC50	LDHb IC50	**ICDH IC50 (uM) @ 4 uM (10x Km) NADPH**	ICDH IC50 (uM) @ 40 uM NADPH	IC50 Ratio (40/4)	IDH1wt IC50 @ 1x Km (uM)
	25.43	64.07	5.74	>100	17.42	**16.22**
	5.92	17.40	12.26	41.40	3.38	**NO inhibition**
	8.61	>100	12.79	14.70	1.15	**19.23**

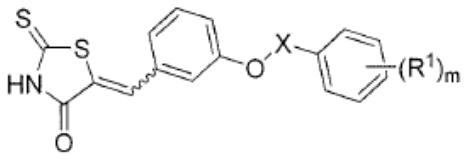
	33.75	>100	14.98	19.17	1.28	**46.83**
	12.76	>100	23.80	33.16	1.39	**69.33**

EX1009, 156-158. But only the first compound in the table provides an IC_{50} value less than 10 μM under the most favorable conditions tested. Sherman Dec., ¶ 112.

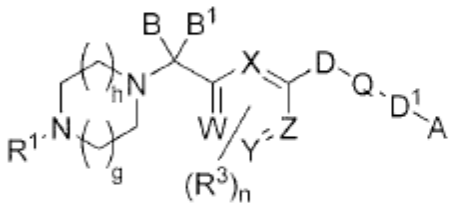
The 2010 Application also asserts oxalomalate, oxalofumarate, and oxalosuccinate as small molecule inhibitors of mutant IDH1. EX1009, 64-65. There are data provided for inhibition of the isocitrate➔αKG activity of IDH1R132H and IDH1R132S. *Id.* at 20-21 (FIGS. 17A-17C). But no further information is provided with respect to the mutants' αKG➔2HG neoactivity. Sherman Dec., ¶ 113.

There are other compounds described in the specification, but critically, without any data or other meaningful information demonstrating activity. Table

24b purports to describe "[a]dditional exemplary compounds that inhibit IDH1R132H." EX1009, 157-175. While there are 92 such compounds listed, no inhibitory data or other information is provided, and none of these compounds is structurally similar to the five compounds for which data are provided. *Id.* Two broad genera of compounds are also provided. First, a genus that appears to encompass the 5-benzylidene-2-thioxothiazolidin-4-one structures of two of the tested compounds of Table 24a, based on Formula (X) below, and second, a genus that appears to encompass the compounds of Table 24b, based on Formula (XI) below:



Formula (X)



(XI)

Id. at 65-66. No inhibitory data are provided for any of these compounds,[5] and there are no indications regarding what structural features might be important for activity. Sherman Dec., ¶ 114.

[5] In a parallel application, originally published as WO2011072174 (EX1023), inhibitory data are provided for these compounds. But this was not included in the

Finally, the specification states:

> Exemplary candidate compounds, which ***can be tested*** for inhibitin of a neoactivity described herein (e.g., a neoactivity associated with mutant IDH1), are described in the following references, each of which are incorporated herein by reference: Bioorganic & Medicinal Chemistry (2008), 16(7), 3580-3586; Free Radical Biology & Medicine (2007), 42(1), 44-51; KR 2005036293 A; Applied and Environmental Microbiology (2005), 71(9), 5465-5475; KR 2002095553 A; U.S. Pat. Appl. US 2004067234 Al; PCT Int. Appl. (2002), WO 2002033063 Al; Journal of Organic Chemistry (1996), 61(14), 4527-4531; Biochimica et Biophysica Acta, Enzymology (1976), 452(2), 302-9; Journal of Biological Chemistry (1975), 250(16), 6351-4; Bollettino - Societa Italiana di Biologia Sperimentale (1972), 48(23), 1031-5; Journal of Biological Chemistry (1969), 244(20), 5709-12.

EX1009, 66-67 (emphasis added). These publications relate generally to the few wild-type IDH inhibitors known at the time.[6] The text notes that these are merely

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specification of 2010 Publication, and so is not available as part of the written description here. Sherman Dec., ¶ 116.n.4.

[6] Professor Sherman considered all of these but the "Bollettino - Societa Italiana di Biologia Sperimentale (1972), 48(23), 1031-5" reference. Sherman Dec., ¶ 115.n.5

"candidate compounds" that "***can be tested*** for inhibition of a neoactivity." *Id.* (emphasis added). There are no data that suggest that they inhibit any activity of a mutant IDH, be it the wild-type activity (isocitrate➔αKG) or the neoactivity (αKG➔2HG).[7] Sherman Dec., ¶ 115.

d) The scope of claims with respect to the small molecule inhibitor compounds is not supported by the 2010 Application

As noted above, the "small molecule inhibitor" is not claimed structurally in any of the Challenged Claims. Rather, it is claimed only by its function. Sherman Dec., ¶ 116.

[7] The underlying provisional applications are incorporated by reference into the 2010 Application. EX1009, 1, 2. In provisional applications up to July 29, 2009, there is disclosure of alpha-ketoglutarates as potential inhibitors, citing Gottleib. EX1025, 52. No inhibitory data or other information is provided in the provisional applications, and the cited reference is silent about IDH1, stating only that its compounds activate HIFα hydroxylase. EX1026, 1, 7. This disclosure is not included in the provisionals beyond July 29, 2009. Other than this, the provisionals provide no more information than the 2010 Application. Sherman Dec., ¶ 115.n.6

While the claims of the '125 Patent purport to reach out to ***any*** small molecule inhibitor of mutant IDH1/IDH2 with the recited activity, the actual disclosure of the 2010 Application provides actual mutant IDH1 inhibition data for only six compounds: five compounds (Table 24a) of varying structure for which inhibition of the αKG➔2HG neoactivity of IDH1R132H is demonstrated (and only one of those at an IC_{50} below 10 μM), and oxalomalate, for which inhibition of the wild-type isocitrate➔αKG activity (but not neoactivity) is demonstrated for IDH1R132H and IDH1R132S. EX1009, 156-158. Sherman Dec., ¶ 117.

There are a number of prophetic compounds described in Table 24b – but without inhibitory data, a POSA would have no way of understanding which compounds, if any, were actually inhibitory, and which structural features of the compounds were important for inhibition. Accordingly, these compounds, without inhibitory data or structural details, do not provide a meaningful disclosures to a POSA with respect to inhibition of any particular mutant enzyme. Rather, they suggest, at best, a plan of compounds that "can be tested" for activity and might (or might not) work in therapy of mutant IDH1/IDH2 AML. The same is true for the genera described in the specification. Sherman Dec., ¶ 118.

Neither does the reference to the known wild-type IDH inhibitors that "can be tested" for mutant IDH inhibition provide any meaningful information to a

POSA. Given the differences in activity between the wild-type and mutant enzymes, and the differences in the structures of the active sites of the mutant enzymes as demonstrated by crystallography, there could have been no expectation that any particular wild-type inhibitor would inhibit mutant activity, be it the wild-type activity (isocitrate➔αKG) or the neoactivity (αKG➔2HG). Here, too, the disclosure provides more of a suggestion for further research than an actual teaching demonstrating possession of the entire class of mutant IDH1/IDH2 inhibitors. Sherman Dec., ¶ 119.

As of 2010, the field of mutant IDHs, and especially the inhibition thereof, was still in its infancy. IDH mutations had been reported in brain cancers in 2008, and in AML only in August 2009. *See* EX1007, 1. While there were some inhibitors of wild-type IDHs known, there was no information available to a POSA regarding inhibition of mutant IDH1 and mutant IDH2. This is not a case where inhibitors of the mutant enzymes were generally known and appreciated as a well-understood and well-mapped class of compounds, and the invention is a new use for these old compounds. Rather, the field of mutant IDH inhibitors was undeveloped. Sherman Dec., ¶ 120.

The scope of claims 1 and 9-12 with respect to compounds is functionally defined as any small molecule compound that inhibits a mutant IDH1/IDH2 that

can convert αKG to 2HG. This would be understood to include any activity, i.e., the wild-type activity (isocitrate➔αKG) or the disclosed neoactivity (αKG➔2HG), or some other activity entirely. Sherman Dec., ¶ 121.

The scope is not supported by the disclosure of the 2010 Application in view of the state of the art in March 2010. At the time, mutant IDH inhibitors were not known to a POSA. And the specification provides only six compounds: five that are shown to inhibit the αKG➔2HG neoactivity of IDH1R132H, and oxalomalate, shown to inhibit the wild-type activity of IDH1R132H and IDH1R132S. These six compounds are of five different compound structural types, and there is nothing in the specification suggesting what structural motifs are important for activity. There are a number of other compounds baldly asserted to be inhibitory, but without data and an identification of degree of inhibition, a POSA is left guessing as to which would work, if any. Sherman Dec., ¶ 122.

While this scant disclosure may (or may not) provide support for the particular compounds for which data are provided, in the nascent field of mutant IDH inhibitors, it does not demonstrate possession of the broad class of mutant IDH1/IDH2 inhibitors defined solely by function that can be used to treat IDH1-mutant AML. The five compounds for which data are provided have IC_{50} values for IDH1R132H inhibition of 5-25 μM. These are of four different molecular

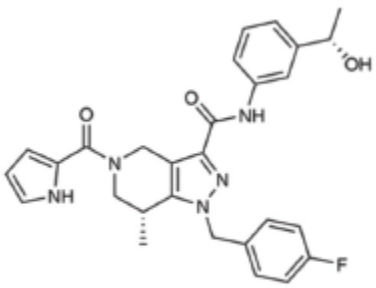
scaffolds, and there is nothing in the specification indicating how one might modify these to get to a compound of high enough activity to be considered a useful drug (typically below 100 nM IC_{50}, desirably closer to 10 or less). Moreover the five compounds of Table 24a are small molecules in that they are no more than 1000 Da in molecular weight. But as they are generally polycyclic aromatic compounds, they would be expected to be hydrophobic and poorly soluble, making them difficult to administer therapeutically. And the last compound in the table bears a nitro group, which is generally disfavored as it is typically bioconverted to an amine, which here would form an aniline moiety which can presenting toxicity issues. Sherman Dec., ¶ 123.

And while the claim covers inhibition of both mutant IDH1 and mutant IDH2, data are provided only for inhibition of mutant IDH1; there is nothing from which a POSA would recognize that the inventors possessed inhibitors for mutant IDH2. Even the data provided for mutant IDH1 is provided only with respect to mutants at R132; in fact, these are the only mutants identified in the specification with respect to AML. In contrast, the claims purport to cover any mutant at any position having the αKG➔2HG neoactivity. Matteo 2017 demonstrates that there are in fact a number of IDH1 mutants at different positions that provide a degree of such neoactivity, *see* EX1051, 1, yet there is nothing in the specification

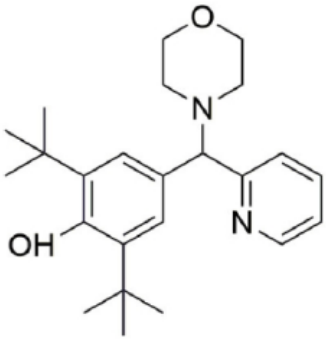
suggesting how such mutants could be inhibited. Moreover, while the data in the specification are said to suggest that inhibition of the production of 2HG can be useful in therapy, there is no information suggesting a link between any other activity of a mutant IDH and AML, and so nothing suggesting that inhibition of any other activity could be used therapeutically. That is, even the claimed function is also much broader than that demonstrated by the specification. Sherman Dec., ¶ 124.

Here, the disclosure of the 2010 Application provides neoactivity (production of 2HG) inhibition data for only five IDH1R132H inhibiting compounds in Table 24a; inhibition of the normal wild-type activity (production of αKG) is also provided for oxalomalate. EX1009 at 156-158. There are other compounds asserted to be mutant inhibitors, e.g., in Table 24b, Formula (X) and Formula (XI), EX1009, 158-176, but since no inhibition data or other information demonstrating inhibition are provided, a POSA would have no real guidance as to which, if any, of these compounds, are actually inhibitors of any mutant IDH1 or IDH2. The disclosure of wild-type IDH inhibitors that "can be tested" for inhibition of mutant IDH1 or IDH2 likewise provides no meaningful information to a POSA. The handful of tested compounds described in the 2010 Application, even together with the disclosure of untested compounds as described, is ***not***

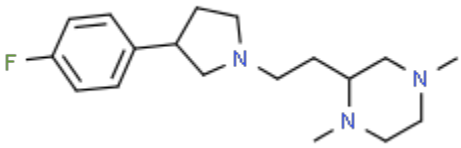
representative of the functionally-defined genus, especially given that it spans a wide variety of different compound types, including phenyglycines as described by Popovici-Muller and coworkers EX1011, 1, 2. The functionally-defined genus also includes more recently-discovered compounds of entirely different structures, such as those below:



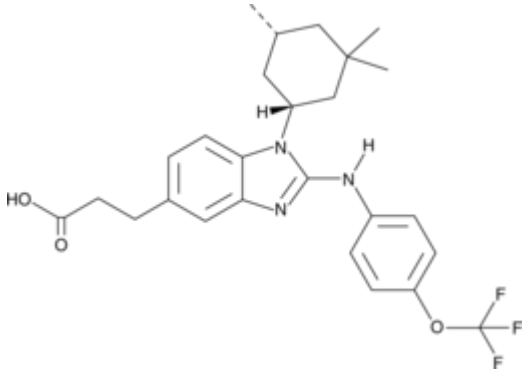
GSK321



DC_H31



HMS101



BAY 1436032

See, EX1038, 3 (DC_H31); EX1039, 9 (GSK 321); EX1040, 5 (HMS101, Fig. 3E); EX1041, 1 (BAY 1436032); EX1042, 1 (BAY 1436032). Sherman Dec., ¶ 125.

Moreover, there are multiple mechanisms for inhibition at play in even the compounds known as of 2013. Compound 1 of PM 2012 was shown to reversibly bind to IDH1R132H, behaving as a competitive inhibitor with respect to αKG, while being uncompetitive with respect to NADPH. EX1011, 1, 2. This suggests binding to the site where αKG binds. *Id.* In contrast, Dang'243 discloses that the first compound in Table 24a, having a very different structure from that of compound 1 of PM 2012, is competitive with NADPH, indicating binding to the site where NADPH binds. EX1009, at 156-158. This indicates that inhibition of R132-mutant IDH1 is not a simple single-substrate lock-and-key mechanism, but is rather something more nuanced and complex. This difference in mechanisms, as well as the possibility of other mechanisms, such as allosteric binding in which the inhibitor binds in a position that is different than the active site. Allosteric inhibitors can change enzyme conformation, which further suggests that the compounds taught by the 2012 Application cannot be generally representative of the class of mutant IDH1 inhibitors. Sherman Dec., ¶ 126.

Nowhere does the 2010 Application provide any inkling of ***structural features common to the genus*** of IDH1 inhibitors. There are five compounds, of four different structural types, tested for inhibition of 2HG neoactivity; and one (different still) compound for which data for inhibition of αKG production is

provided. While there are other compounds mentioned, there are no data or other information to suggest actual activity, and thus no way for a POSA to use them to discern what common structural features may be important for inhibition. The information provided does not describe structural features common to the members of the genus sufficient for a POSA to visualize or recognize mutant IDH1 inhibitory compounds as compared to other compounds. Sherman Dec., ¶ 127. See, e.g., *Idenix Pharms.*, 941 F.3d at 1164 (noting that without an explanation of "what makes them effective, or why," "a [POSA] is deprived of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same result"); *AbbVie*, 759 F.3d at 1301-02.

The mutant IDH1R132H inhibitors disclosed in the specification have relatively low activity – the best has an IC_{50} of just over 5 μM under the conditions tested, while others have IC_{50}s in the 10-25 μM range. EX1009, 156-158. In contrast, typical enzyme-inhibiting drugs have IC_{50} values in the mid-low nM range – about 2-3 orders of magnitude more powerful than these compounds. For example, the "first potent inhibitors" of PM 2012 have IC_{50} values below 100 nM, and ivosidenib was shown to have an IC_{50} value in the low single digits nM. EX1011, 3; EX1058, 3. A POSA could have had no reasonable expectation that compounds operating in the 5-25 μM range of IC_{50} values would have been useful

in treatment of AML. Rather, given their relatively weak inhibition values, a POSA would have needed further experimental evidence to conclude that these inhibitors could be useful in treatment. This is not present in the 2010 Application or in the state of the art as of March 2010. This further suggests that the inventors did not possess a method of treatment of IDH-mutant AML. Sherman Dec., ¶ 128; Oleksowicz Dec., ¶ 103.

"A written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." *Regents of the Univ. of Cal. v. Eli Lilly & Co.,* 119 F.3d 1559, 1568 (Fed. Cir. 1997) (internal quotation omitted). Here, the chemical genus of mutant IDH1 inhibitors is not precisely defined, and there are not enough representative examples or common structural features provided for a POSA to be able to distinguish functionally-defined mutant IDH1 inhibitors from other materials. In 2009, the field of mutant IDH inhibitors was immature, if it existed at all, as there was no prior art describing mutant IDH inhibitors and no other knowledge in the field. And while there might be some degree of predictability in making very minor changes to a molecular structure, generally what compounds might inhibit an enzyme is, even now, considered to be rather

unpredictable. *See*, *e.g.*, EX1013, 1. The information provided in the specification might in fact support a claim that is narrowly drawn to particular chemical structures – but not a claim in which a therapeutic compound is defined solely by function. And the low activity of the compounds exemplified calls into question their operability in therapy. Claims 1 and 9-12 cannot be accorded the priority date of the 2010 Application because the specification does not provide adequate written description of the functionally-defined inhibitor compounds as broadly as they are claimed. Sherman Dec., ¶ 129.

Claim 2 recites that "inhibitor binds to IDH1R132X or IDH2R172X and inhibits the ability to convert alpha-ketoglutarate to 2-HG." EX1001, 432:57-59. This claim restricts the scope of the inhibition to inhibition of the αKG➔2HG neoactivity, and the scope of the position of binding to residue R132 of IDH1 and residue R172 of IDH2. Claim 2 suffers from similar issues with respect to the scope of the inhibitor as does claim 1 as described above: there are only five compounds shown to inhibit the αKG➔2HG neoactivity of IDH1R132H, without anything suggesting a correlation between structure and function. As described above, this is not sufficient to support a claim broadly to an inhibitor described solely by function, especially given the structural diversity of later-discovered inhibitors. Moreover, while there are a handful of compounds demonstrated to

inhibit the αKG➔2HG neoactivity of a mutant IDH1, there is nothing showing inhibition of αKG➔2HG neoactivity of any IDH2. For similar reasons to those described above with respect to claims 1 and 9-12, claim 2 cannot be accorded the priority date of the 2010 Application. Sherman Dec., ¶ 130.

Claim 3 requires that the cancer is characterized by an IDH1 mutation. EX1001, 432:60-61. The shortcomings described above with respect to claim 1 directed to IDH2 do not apply, but all others do, especially with respect to the scope of the inhibitor compound claimed, the scope of the activity inhibited, and the scope of the IDH1 mutations encompassed by the claim. For similar reasons to those described above with respect to claims 1 and 9-12, claim 3 cannot be accorded the priority date of the international application. Sherman Dec., ¶ 131.

Claims 4 and 5 depend from claim 3 and require particular mutations at residue R132. EX1001, 432:62-67. The shortcomings described above with respect to IDH2 and the position of the mutation do not apply, but all others do, especially with respect to scope of the inhibitor compound claimed and the scope of the activity inhibited. For similar reasons to those described above with respect to claims 1 and 9-12, claims 4 and 5 cannot be accorded the priority date of the 2010 Application. Sherman Dec., ¶ 132.

e) The disclosure of the 2010 Application does not provide sufficient information to demonstrate possession of methods for treating IDH1-mutant AML

Moreover, while the disclosure of the 2010 Application does identify the "neoactivity" of IDH1R132 mutants as the conversion of αHG to 2HG, it provides no data or other information demonstrating or suggesting to a POSA that inhibition of IDH1 would be useful in treating AML. Oleksowicz Dec., ¶ 90.

The 2010 Application describes the presence of mutant IDH1 in various cancers, including AML. *See*, *e.g.*, EX1009, 177-184. It describes experimental work suggesting that the mutant IDH1 converts αHG to 2HG, which is a different activity than the wild-type enzyme. EX1009, 100-121. It also describes ways to identify patients having such cancers, e.g., through DNA sequencing, or through detection of 2HG, as well as methods that one might use to determine why GBM patients carrying IDH1R132 mutations have a survival advantage, and to evaluate IDH1 as a cancer target, but no data are shown. EX1009, *e.g.*, 2-3, 4-5, 8-9, 25, 27, 121-122, 177-184, 185 (claim 1), 188-190 (claims 18, 21, 23). X-ray crystallographic work was described, showing how the change of the wild-type R132 histidine changed the conformation of the enzyme. EX1009, 141-155. Oleksowicz Dec., ¶ 91.

Even if a suitable inhibitor of mutant IDH1 were available as of March 2010, there is not enough information in the specification and in the state of the art to provide a POSA in March 2010 any indication that the inventors had achieved this goal or otherwise had intellectual possession of the invention. While there are data in the 2010 Application suggesting modest inhibition of the αKG-2HG neoactivity of IDH1R132H, EX1009, 156-158, there are no data suggesting that such inhibition has any therapeutic consequence. Oleksowicz Dec., ¶ 92.

There is, of course, text formally proposing treatment of IDH1-mutant AML using an inhibitor of mutant IDH1. *See*, *e.g.*, EX1009, 4-9 and *passim*. This is not dispositive, as "[t]he appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy" §112, ¶ 1 because it may not both put others on notice of the scope of the claimed invention and demonstrate possession of that invention. *Enzo Biochem Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 968-69 (Fed. Cir. 2002); see also *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1346-47 (Fed. Cir. 2005) (finding original claim 21 to lack written description support because "nothing in claim 21 or the specification constitutes an adequate and enabling description of all seamless DWTs"). And without some indication in the specification or in the state of the art tying inhibition IDH1 neoactivity or a reduction in amounts of 2HG to some

therapeutic benefit, a POSA in March 2010 would not have understood the inventors to actually possess an operational method of treatment. Oleksowicz Dec., ¶ 93.

It is true that, as of March 2010, 2HG was known to be present in IDH1R132X-mutant AML patient samples, as described in various references described above and the 2010 Application itself. But this does not demonstrate that 2HG production or IDH1R132X is necessarily a therapeutic target. In many cases a mutant pathway is identified in a cancer but is therapeutically useless because it does not "drive" cancer, i.e., it is merely a "passenger." Oleksowicz Dec., ¶¶ 94-97 (describing c-KIT and BRAF as examples of mutations that drive some types of cancer but not others.

Thus, while the presence of 2HG in IDH-mutant AML might have been an interesting observation suitable for further study, this alone would not have suggested any oncogenic role of 2HG or that inhibition of the mutant IDH might have any therapeutic affect for AML. Rather, as of March 2010, there was no established link to AML that implied that the inhibition of the αKG→2KG conversion would have any helpful effect on AML. Oleksowicz Dec., ¶ 98.

The 2010 Application does provide some ideas about therapeutic utility: EX1009, 118-119. This text largely discusses correlations between 2HG and brain

tumors, and with respect to actual therapeutic use suggests only that "[i]nhibition of 2HG production by mutant IDH1 might slow or halt conversion of lower grade glioma into lethal secondary glioblastoma, changing the course of the disease." EX1009, 119. This does not provide any suggestion with respect to AML. Oleksowicz Dec., ¶ 99.

There are in this passage of the 2010 Application a few theories about ROS, HIF1a, and NMDA receptor agonism. Here, too, the text suggests mechanisms that might be worth further study, but does not provide any indication that the inventors possessed a method for treating IDH1-mutant AML. The statement that "[r]egardless of mechanism, it appears likely that the gain-of-function ability of cells to produce 2HG as a result of R132 mutations in IDH1 contributes to tumorigenesis," *id.*, is mere speculation. Without an understanding of mechanism, it is difficult to understand whether the production of 2HG is oncogenic, or rather merely coincidental. This is especially true given the observation that IDH1-mutant glioma patients have a better survival rate than wild-type IDH1 glioma patients. EX1016, 8. Oleksowicz Dec., ¶ 100.

At this time AML was understood to be a difficult disorder to address therapeutically. *See*, *e.g.*, EX1057, 1. And while many of the ideas in this passage from the 2010 Application might represent interesting ideas worthy of further

study, nothing here provides any certainty that inhibition of mutant IDH1 would have any therapeutic effect for AML. Oleksowicz Dec., ¶ 101.

At least some of the inventors would appear to agree. In Gross, inventors Dang, Fantin, Gross, Jang and Jin state that, as of February 2010, "[f]urther functional and mechanistic work will be required to understand the underlying biology driving the acquisition of these mutations, and to determine whether mutants of IDH1 R132 and IDH2 R172 may be useful therapeutic targets." EX1022, 5. Here, the inventors confirm that more work was needed to provide an actual therapeutic method. Oleksowicz Dec., ¶ 102.

Moreover, as noted above the mutant IDH1R132H inhibitors disclosed in the specification have relatively low activity, and given their relatively weak inhibition values, a POSA would have needed experimental evidence suggesting successful treatment to understand that these inhibitors could be useful in treatment. This is not present in the 2010 Application. This further suggests that the inventors did not possess a method of treatment of IDH-mutant AML. Oleksowicz Dec., ¶ 103.

The teachings of the specification in view of the state of the art as of March 2010 do not demonstrate that the inventors had achieved a method for treating IDH1-mutant AML, even if a mutant IDH1 inhibitor were provided. Critically, neither the 2010 Application nor the state of the art establishes any link between

inhibition of mutant IDH or reduction of amounts of 2HG with treatment of IDH-mutant AML – and without this link, mere inhibition of mutant IDH or reduction of amounts of 2HG cannot be said to be therapeutically useful. At best, the inventors had identified something – the presence of 2HG in IDH-mutant AML – that warranted further study. This is merely a wish or a plan for further research, and not a properly described invention. Oleksowicz Dec., ¶ 104.

Claim 1 recites generally the treatment of an AML characterized by a mutant IDH1/IDH2 that has the ability to convert αKG→2HG. EX1001, 431:57-67. Claims 9-12 depend ultimately from claim 1 and recite steps to detection of mutant IDH1/IDH2, EX1001, 433:7-17, and thus have the same scope as claim 1 with respect to the treatment step. Claims 1 and 9-12 cannot be accorded the priority date of the 2010 Application because it there was no established link between reduction of amounts of 2HG or the inhibition of mutant IDH1/IDH2 and any therapeutic effect. Without this, a POSA would not have recognized that such a treatment method was possessed. Oleksowicz Dec., ¶ 105.

Claim 2 recites that "inhibitor binds to IDH1R132X or IDH2R172X and inhibits the ability to convert alpha-ketoglutarate to 2-HG." EX1001, 432:57-59. This claim restricts the scope of the inhibition to inhibition of the αKG→2HG neoactivity, and the scope of the position of binding to residue R132 of IDH1 and

residue R172 of IDH2. Claim 3 requires that the cancer is characterized by an IDH1 mutation. EX1001, 432:60-61. Claims 4 and 5 depend from claim 3 and require particular mutations at residue R132. EX1001, 432:62-67. These claims likewise cannot be accorded the priority date of the 2010 Application because there was no established link between reduction of amounts of 2HG or the inhibition of mutant IDH1 and any therapeutic effect. Oleksowicz Dec., ¶ 106.

Thus, for this additional reason, none of the Challenged Claims is entitled to the filing date of the 2010 Application. The effective filing date of the claims can be no earlier than July 11, 2013. Oleksowicz Dec., ¶ 107.

f) Neither do the provisional applications support the Challenged Claims

Other than the disclosure of alpha-ketoglutarates in provisional applications July 29, 2009 and earlier (addressed above), there is no more information in the provisional applications than is in the 2010 Application. See EX1025, EX1043, EX1044, EX1045, EX1046, EX1047, EX1048, EX1049, EX1050. Accordingly, for the same reasons as described for the 2010 Application, the Challenged Claims cannot be accorded the priority date of any of the provisional applications. Sherman Dec., ¶ 133; Oleksowicz Dec. ¶ 108.

g) There can be no valid priority date before July 11, 2013

Accordingly, the applications filed in 2009 and 2010 do not provide adequate written description support for the Challenged Claims. The effective filing date of the claims can be no earlier than July 11, 2013.[8] Sherman Dec., ¶ 134; Oleksowicz Dec. ¶ 109.

B. Ground 1: PM'678 anticipates the Challenged Claims

PM'678 is a 2012 published patent application by the original applicant of the '125 Patent, describing phenylglycine-based inhibitors of mutant IDH1. Many of these compounds are the same as those described in PM 2012. Sherman Dec., ¶ 135.

Because the earliest effective filing date possible for the Challenged Claims is in 2013, PM'678 anticipates the Challenged Claims. *See, e.g.*, *Dr. Reddy's Labs. S.A. v. Indivor UK Ltd.*, IPR2019-00329, Paper 49 at 11-12 (PTAB June 2, 2020), *aff'd* 18 F.4th 1323 (Fed. Cir. 2021).

[8] Petitioner does not admit that the Challenged Claims are entitled to priority claims to the 2013 filing date of the parent application, or even that they are adequately supported by the specification of the '125 Patent itself as of its 2017 filing date.

1. Claim 1

As described above, claim 1 is entitled to a priority date no earlier than July 11, 2013. Sherman Dec., ¶ 136.

Claim 1 is anticipated by PM'678. It discloses throughout the treatment of AML characterized by a mutant IDH1 having the ability to convert αKG to 2HG. *See*, *e.g.*, EX1010, 3-4, 77-80, 83-84. Sherman Dec., ¶ 137.

PM'678 discloses that the treatment can be performed by using therapeutic amount of a small molecule inhibitor of the mutant IDH1. *See*, e.g., EX1010, 14-26, 28-66. Data are provided showing inhibition of mutant IDH1R132H for most of the exemplified compounds. *Id.* at 236-245. PM'678 highlights a number of compounds from Table 1 and Table 2 of the specification, many of which have sub-100 nM IC_{50} values for inhibition of IDH1R132H. *Id.* at 29-67. Sherman Dec., ¶ 138.

A POSA would have understood PM'678 to teach the treatment of AML characterized by a mutant IDH1 that has the ability to convert α-KG to 2HG, specifically IDH1R132H, using an effective amount of any of the specifically-identified inhibitors. Accordingly, PM'678 anticipates claim 1. Sherman Dec., ¶ 139.

Moreover, PM 2012 specifically exemplifies its compound 35 as "the first reported R132H IDH1 inhibitor to show robust in vivo reduction of 2-HG levels in a tumor xenograft model." EX1011, 2. This is the same as compound 165 in PM'678, which is one of the highlighted compounds, shown in PM'678 to have an IC_{50} of no more than 100 nM. EX1010, 40, 336-338. This compound was reported not only to be a potent inhibitor of IDH1R132H in vitro, but also to reduce amounts of 2HG in a mouse xenograft model. EX1011, 4, 5. Accordingly, compound 165 of PM'678 would have inherently had inhibitory activity in vivo. This further demonstrates anticipation, *i.e.*, with PM 2012 evidencing the inherent properties of compound 165. Sherman Dec., ¶ 140.

Accordingly, PM'678 discloses all limitations of Challenged Claim 1. Challenged Claim 1 is anticipated. Sherman Dec., ¶ 141.

2. Claims 2-5

Challenged Claims 2-5 depend ultimately from claim 1 and relate particularly to IDH1 mutants. They are anticipated or rendered obvious as demonstrated in the claim chart below.

Challenged Claim	**PM'678 Disclosure**
2. The method of claim 1, wherein the inhibitor binds to IDH1R132X or IDH2R172X and inhibits the ability to convert alpha-ketoglutarate to 2-HG.	In PM'678, various example compounds, including compound 165, are shown to inhibit the formation of αKG to 2HG in IDH1R132H, both in vitro and in cell assay. *See*, *e.g.*, EX1010, 236-245. PM 2012 demonstrates that compound 165 of PM'678 additionally exhibits robust in vivo reduction of 2HG levels in a tumor xenograft model. *See*, *e.g.*, EX1011, 2.
3. The method of claim 1, wherein the cancer is characterized by an IDH1 mutation. 4. The method of claim 3, wherein the IDH1 mutation is an IDH1R132X mutation.	Throughout, PM'678 discloses treatment of AML having an IDH1 mutation. *See*, *e.g.*, EX1010, 84. The example compounds were tested against an IDH1 mutant, specifically

5. The method of claim 3, wherein the IDH1 mutation is selected from R132H, R132C, R132S, R132G, R132L, and R132V.	IDH1R132H. *See*, *e.g.*, EX1010, 39, 84.

Sherman Dec., ¶ 142.

As PM'678 discloses each and every limitation of claims 2-5, they are likewise anticipated by PM'678 for reasons analogous to those described above for claim 1. Sherman Dec., ¶ 143.

3. Claims 9-12

Challenged Claims 9-12 depend ultimately from claim 1 and relate to methods in which the mutant IDH1 or mutant IDH2 is detected, e.g., in a sample from the subject or by sequencing a nucleic acid from an affected cell. They are anticipated as demonstrated in the claim chart below.

Challenged Claim	**PM'678 Disclosure**
9. The method of claim 1, wherein the mutant IDH1 or mutant IDH2 is detected in a sample obtained from the subject.	PM'678 discloses "prior to and/or after treatment with" a compound of the disclosure, "the step of evaluating the IDH1 genotype of the cancer." EX1010, 84.

10. The method of claim 9, wherein the sample comprises tissue or bodily fluid.	A POSA would have understood identification of the cancer to necessarily involve sampling the affected tissue of a subject, e.g., from bone marrow of the subject. And in any event, it would have been obvious to do so in order to evaluate the IDH1 genotype of the cancer.
11. The method of claim 1, wherein the mutant IDH1 or mutant IDH2 is detected by sequencing a nucleic acid from an affected cell that encodes the relevant amino acid(s) from the mutant IDH1 or mutant IDH2.	PM'678 discloses "prior to and/or after treatment with" a compound of the disclosure, "the step of evaluating the IDH1 genotype of the cancer." EX1010, 84. "This may be achieved by ordinary methods in the art, such as DNA sequencing, immuno analysis, and/or evaluation of the presence, distribution or level of 2HG." EX1010, 85.
12. The method of claim 11, wherein the sequencing is	A POSA would have understood DNA sequencing to involve PCR.

performed by polymerase chain reaction (PCR).	

Sherman Dec., ¶ 144.

As PM'678 discloses each and every limitation of Challenged Claims 9-12, they are likewise anticipated by PM'678. Sherman Dec., ¶ 145.

C. Ground 2: PM 2012 in view of PM'678 renders obvious the Challenged Claims

PM'2012 is a 2012 publication by many of the inventors listed on PM'678, describing phenylglycine-based inhibitors of mutant IDH1, describing "the First Potent Inhibitors of Mutant IDH1 That Lower Tumor 2-HG in Vivo." EX1011, 1. Sherman Dec., ¶ 146.

1. Claim 1

As described above, claim 1 is entitled to a priority date no earlier than July 11, 2013. Sherman Dec., ¶ 147.

Claim 1 is rendered obvious by PM 2012 in view of PM'678. PM 2012 suggests that mutant IDH1 is a "compelling drug target for new therapies for glioma and AML," and throughout discloses compounds that are strong inhibitors of IDH1R132H, many having IC_{50} values less than 100 μM. EX1011, 1, 2-5. Notably:

> In conclusion, we have discovered the first class of potent IDH1 mutant inhibitors through optimization of HTS hits. Compound 35 is a potent inhibitor of 2-HG production in U87 R132H cells and shows ~90% tumor 2-HG inhibition in vivo following three BID doses.

Id. at 5. Sherman Dec., ¶ 148.

As described above, PM'678 discloses throughout the treatment of AML characterized by a mutant IDH1 having the ability to convert αKG to 2HG. *See*, *e.g.*, EX1010, 3-4, 77-80, 83-84. PM'678 discloses that the treatment can be performed by using therapeutic amount of a small molecule inhibitor of the mutant IDH1. *See*, *e.g.*, *Id.* at 15-27, 29, 67. And in fact, compound 35 of PM 2012 is exemplified as compound 165 of PM'678. *See* EX1011, 1; EX1010, 39. Sherman Dec., ¶ 149.

A POSA would have had reason to use compound 35 of PM 2012 in the methods described in PM'678, based on PM'678's disclosure of the treatment of AML with such compounds. Doing so would result in the treatment of AML characterized by a mutant IDH1 with the ability to convert αKG to 2HG, specifically IDH1R132H, using an effective amount of compound 35. Accordingly, PM 2012 in view of PM'678 renders claim 1 obvious. Sherman Dec., ¶ 150.

2. Claims 2-5

Challenged Claims 2-5 depend ultimately from claim 1 and relate particularly to IDH1 mutants. They are rendered obvious as demonstrated in the claim chart below:

Challenged Claim	**PM 2012 and PM'678 Disclosure**
2. The method of claim 1, wherein the inhibitor binds to IDH1R132X or IDH2R172X and inhibits the ability to convert alpha-ketoglutarate to 2-HG.	In PM 2012, compound 35 is shown to inhibit the formation of αKG to 2HG in IDH1R132H, both in vitro and in cell assay. EX1011, 4. PM 2012 demonstrates that compound 35 additionally exhibits robust in vivo reduction of 2HG levels in a tumor xenograft model. *Id.* PM 2012 demonstrates that phenylglycine compound 1, analogous to compound 35, was a competitive inhibitor with respect to αKG, and thus would be understood to bind to the enzyme. *See Id.* at 1.
3. The method of claim 1, wherein the cancer is	Throughout, PM'678 discloses treatment of AML having an IDH1 mutation. *See*, e.g., EX1010, 3-4, 77-80, 83-84. The example

characterized by an IDH1 mutation. 4. The method of claim 3, wherein the IDH1 mutation is an IDH1R132X mutation. 5. The method of claim 3, wherein the IDH1 mutation is selected from R132H, R132C, R132S, R132G, R132L, and R132V.	compound 35 of PM 2012 was tested against an IDH1 mutant, specifically IDH1R132H. EX1011, 2-3.

Sherman Dec., ¶ 151.

As PM'678 and PM 2012 teach each and every limitation of claims 2-5, they are likewise rendered obvious by PM 2012 in view of PM'678, for reasons analogous to those described above for claim 1. Sherman Dec., ¶ 152.

3. Claims 9-12

Challenged Claims 9-12 depend ultimately from claim 1 and relate to methods in which the mutant IDH1 or mutant IDH2 is detected, e.g., in a sample

from the subject or by sequencing a nucleic acid from an affected cell. They are anticipated or rendered obvious as demonstrated in the claim chart below.

Challenged Claim	**PM'678 Disclosure**
9. The method of claim 1, wherein the mutant IDH1 or mutant IDH2 is detected in a sample obtained from the subject.	PM'678 discloses "prior to and/or after treatment with" a compound of the disclosure, "the step of evaluating the IDH1 genotype of the cancer." EX1010, 84-85.
10. The method of claim 9, wherein the sample comprises tissue or bodily fluid.	A POSA would have understood identification of the cancer to necessarily involve sampling the affected tissue of the subject, e.g., bone marrow. And in any event, it would have been obvious to do so in order to evaluate the IDH1 genotype of the cancer.
11. The method of claim 1, wherein the mutant IDH1 or mutant IDH2 is	PM'678 discloses "prior to and/or after treatment with" a compound of the

detected by sequencing a nucleic acid from an affected cell that encodes the relevant amino acid(s) from the mutant IDH1 or mutant IDH2.	disclosure, "the step of evaluating the IDH1 genotype of the cancer." EX1010, 84-85. "This may be achieved by ordinary methods in the art, such as DNA sequencing, immuno analysis, and/or evaluation of the presence, distribution or level of 2HG." EX1010, 85.
12. The method of claim 11, wherein the sequencing is performed by polymerase chain reaction (PCR).	A POSA would have understood DNA sequencing to involve PCR.

Sherman Dec., ¶ 153.

As the person of ordinary skill in the art would have had reason to use compound 35 of PM 2012 in the methods described in PM'678, and in doing so would meet each and every limitation of claims 9-12, they are likewise rendered obvious by PM 2012 and PM'678. Sherman Dec., ¶ 154.

D. Ground 3: PM'678 (optionally together with PM 2012) in view of Dang'243 renders obvious Challenged Claim 12

Claim 12 depends from claim 11 and recites that the sequencing is performed by polymerase chain reaction (PCR). Claim 11 is shown, as above, to be anticipated by PM'678, or rendered obvious by PM 2012 in view of PM'678. Dang'243 teaches that PCR can be used in the sequencing of DNA for genotyping. EX1009, 3, 101, 115. A POSA would have had reason to use the common technique of PCR for genotyping in the methods described by PM'678, and would have had every expectation of success in doing so, based on Dang'243. The subject matter of claim 12 would have been obvious in view of the combination of Dang'243 with the references described in Grounds 1 and 2. Sherman Dec., ¶ 155.

E. Ground 4: Dang'243 Anticipates Claims 1-5 and 9-12

Dang'243 is the publication of the grandparent international application in the claimed priority chain of the '125 Patent. It has substantively identical disclosure to the 2010 Application, to the intervening 2013 Application, and to the '125 Patent itself. Sherman Dec., ¶ 156.

Because the earliest effective filing date possible for the Challenged Claims is in 2013, Dang'243 anticipates the Challenged Claims. Sherman Dec., ¶ 157. *See, e.g.*, *Dr. Reddy's Labs.*, IPR2019-00329, Paper 49 at 11-12.

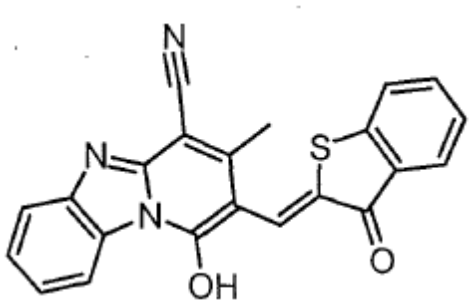
1. Claim 1

As described above, claim 1 is entitled to a priority date no earlier than July 2013 because the 2010 Application does not provide written description support for the claimed subject matter as of its March 2010 filing date. Sherman Dec., ¶ 158.

Claim 1 is anticipated by Dang'243. Dang'243 discloses throughout the treatment of AML having characterized by a mutant IDH1 having the ability to convert αKG to 2HG. *See*, e.g., EX1009, 32. This disclosure is in substantively identical detail to the description in the specification of the 2013 Application and the '125 Patent itself. Sherman Dec., ¶ 159.

Dang'243 throughout discloses the treatment of AML characterized by a mutant IDH1 that has the ability to convert αKG to 2HG. EX1009, *passim*, *e.g.*, EX1009, 4, 19, 56, 185-186 (claims 1, 3, 5, 6-9). Sherman Dec., ¶ 160.

Dang'243 discloses that the treatment can be performed by using therapeutic amount of a small molecule inhibitor of the mutant IDH1. *See*, *e.g.*, EX1009, 4, 6, 24 (specifically neoactivity, "binding with"), 56, 65-66, 185 (claim 1), 186 (claim 14). Dang'243 specifically recites as an example of a compound that inhibits IDH1R132H the first compound of Table 24a:



EX1009, 156-157. This compound had an IC_{50} of 5.74 μM when tested at 10x Km of NADPH, but is shifted significantly at 100x Km of NADPH, indicating it to be a direct NADPH-competitive inhibitor, EX1009, 156, which means that it competes for binding in the NADPH pocket of the enzyme. Sherman Dec., ¶ 161.

Accordingly, Dang'243 teaches all limitations of Challenged Claim 1. Challenged Claim 1 is anticipated. Sherman Dec., ¶ 162.

2. Claims 2-5

Challenged Claims 2-5 depend ultimately from claim 1 and relate particularly to IDH1 mutants. They are anticipated as demonstrated in the claim chart below:

Challenged Claim	**Dang'243 Disclosure**
2. The method of claim 1, wherein the inhibitor binds to IDH1R132X or IDH2R172X	In Dang'243, the first compound of Table 24a is shown to inhibit the conversion of αKG to 2HG by IDH1R132H (a specific example of

and inhibits the ability to convert alpha-ketoglutarate to 2-HG.	IDH1R132X) with an IC_{50} of 5.74 μM under the conditions tested. It was shown to be a direct NADPH-competitive inhibitor, and thus binds to IDH1R132H. EX1009, 156-157.
3. The method of claim 1, wherein the cancer is characterized by an IDH1 mutation.	Throughout, Dang'243 discloses treatment of AML having an IDH1 mutation. EX1009, *passim*, e.g., EX1009, 4, 19, 56, 185-186 (claims 1, 3, 5, 6-9). The IDH1 mutation for which the compounds of Table 24a were tested was IDH1R132H. EX1009, 156-157.
4. The method of claim 3, wherein the IDH1 mutation is an IDH1R132X mutation.	The only IDH1 mutations in AML identified by Dang'243 are IDH1R132X mutations. EX1009, 177-184. The IDH1R132X mutation for which the compounds of Table 24a were tested was IDH1R132H. EX1009, 156-157.
5. The method of claim 3, wherein the IDH1 mutation is selected from R132H, R132C,	Dang'243 identifies R132H, R132C, and R132G mutations in AML. EX1009, 181, 185. The IDH1R132X mutation for which the

R132S, R132G, R132L, and R132V.	compounds of Table 24a were tested was IDH1R132H. EX1009, 156-157.

Sherman Dec., ¶ 163.

As Dang'243 teaches each and every limitation of claims 2-5, they are likewise anticipated. Sherman Dec., ¶ 164.

3. Claims 9-12

Challenged Claims 9-12 depend ultimately from claim 1 and relate to methods in which the mutant IDH1 or mutant IDH2 is detected, e.g., in a sample from the subject or by sequencing a nucleic acid from an affected cell. As these methods are described identically as in the 2013 Application and the '125 Patent, they are anticipated as demonstrated in the claim chart below:

Challenged Claim	**Dang'243 Disclosure**
9. The method of claim 1, wherein the mutant IDH1 or mutant IDH2 is detected in a sample obtained from the subject.	Dang'243 discloses detection of mutant IDH1 in a sample from the subject. EX1009, *passim*, *e.g.*, 2-3, 4-5, 8-9,185 (claim 1), 188-190 (claims 18, 21, 23).

10. The method of claim 9, wherein the sample comprises tissue or bodily fluid.	Dang'243 discloses detection of mutant IDH1 in a tissue or bodily fluid sample from the subject. EX1009, *passim*, *e.g.*, 2-3, 4-5, 8-9, 177, 185 (claim 1), 188-190 (claims 18, 21, 23).
11. The method of claim 1, wherein the mutant IDH1 or mutant IDH2 is detected by sequencing a nucleic acid from an affected cell that encodes the relevant amino acid(s) from the mutant IDH1 or mutant IDH2.	Dang'243 discloses detection of mutant IDH1 in an affected cell by sequencing an encoding nucleic acid. *See*, *e.g.*, EX1009, 26, 27, 177-184.
12. The method of claim 11, wherein the sequencing is performed by polymerase chain reaction (PCR).	Dang'243 discloses use of PCR to identify cells having wild-type IDH1 vs. IDH1R132X mutants. EX1009, 115.

Sherman Dec., ¶ 165.

As Dang'243 discloses each and every limitation of claims 2-5, they are likewise anticipated. Sherman Dec., ¶ 166.

IX. NO SECONDARY CONSIDERATIONS

Petitioner is not aware of any evidence of secondary considerations suggesting that the subject matter of Claims 1-5 and 9-12 would not have been obvious. *See* Sherman Dec., ¶ 167. Petitioner reserves its right to address any such evidence that Patent Owner may later submit in this proceeding.

X. CONCLUSION

For the reasons set forth above, the Challenged Claims are anticipated or rendered obvious. *See* Sherman Dec., ¶ 169. There is a reasonable likelihood that Petitioner will prevail as to each of these Challenged Claims. Accordingly, trial should be instituted, and the Challenged Claims should be canceled as unpatentable.

Respectfully Submitted,

Dated: August 15, 2022

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LISTING OF CHALLENGED CLAIMS (37 C.F.R. §42.24(a)(1))

1. A method of treating a subject having acute myelogenous leukemia (AML) characterized by the presence of a mutant isocitrate dehydrogenase 1 enzyme (IDH1) or a mutant isocitrate dehydrogenase 2 enzyme (IDH2), wherein the mutant IDH1 or mutant IDH2 has the ability to convert alpha-ketoglutarate to 2-hydroxyglutarate (2HG), the method comprising administering to the subject a therapeutically effective amount of a small molecule inhibitor of said mutant IDH1 or mutant IDH2.

2. The method of claim 1, wherein the inhibitor binds to IDH1R132X or IDH2R172X and inhibits the ability to convert alpha-ketoglutarate to 2-HG.

3. The method of claim 1, wherein the cancer is characterized by an IDH1 mutation.

4. The method of claim 3, wherein the IDH1 mutation is an IDH1R132X mutation.

5. The method of claim 3, wherein the IDH1 mutation is selected from R132H, R132C, R132S, R132G, R132L, and R132V.

6-8. (not challenged)

9. The method of claim 1, wherein the mutant IDH1 or mutant IDH2 is detected in a sample obtained from the subject.

10. The method of claim 9, wherein the sample comprises tissue or bodily fluid.

11. The method of claim 1, wherein the mutant IDH1 or mutant IDH2 is detected by sequencing a nucleic acid from an affected cell that encodes the relevant amino acid(s) from the mutant IDH1 or mutant IDH2.

12. The method of claim 11, wherein the sequencing is performed by polymerase chain reaction (PCR).

CERTIFICATE OF SERVICE

The undersigned hereby certifies on this August 15, 2022, that a true and correct copies of the foregoing PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 10,610,125, Exhibits 1001-1058, and Petitioner's power of attorney were served in their entirety on the following parties via FedEx Express® or Express Mail:

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CERTIFICATION OF COMPLIANCE WITH TYPE-VOLUME LIMITS

This Petition includes 13,903 words, as counted by Microsoft Word, and is therefore in compliance with the word limit of 14,000 words established by 37 C.F.R. §42.24(a)(1)(i). Accordingly, pursuant to 37 C.F.R. §42.24(d), it is hereby certified that this Petition complies with the type-volume limits established for a petition requesting IPR.

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