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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte STANTON GERSON[1]

Appeal 2018-005600
Application 13/900,166
Technology Center 1600

Before ERIC B. GRIMES, RACHEL H. TOWNSEND, and CYNTHIA M. HARDMAN, *Administrative Patent Judges.*

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a method of treating cancer, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

STATEMENT OF THE CASE

"Chemotherapeutic agents can work in a number of ways." Spec. 4. For example, "uracil . . . can be incorporated into DNA of cancer cells by

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[1] Appellant identifies the real party in interest as Case Western Reserve University. Appeal Br. 3. We use the word Appellant to refer to "applicant" as defined in 37 C.F.R. § 1.42(a).

administering antimetabolite agents to the cancer cells[,] . . . leading to the inhibition of DNA replication." *Id*. ¶ 56. "In comparison to other anti-metabolites, pemetrexed is the most potent inducer of uracil incorporation into DNA." *Id*. ¶ 91.

"'[U]uracil DNA glycosyl[a]se' or 'UDG' . . . [is] a conserved DNA repair protein expressed in all types of human cells. It specifically removes uracil from DNA and protect[s] cells from cytotoxicity." *Id*. ¶ 54.

> The UDG enzyme hydrolyzes the N-glycosidic bond between the UDG substrate (e.g., uracil residue) and the deoxyribose sugar of the DNA backbone, liberating the UDG substrate and generating an abasic site (e.g., an apurinic or apyrimidinic (AP) site). . . . The AP site is further processed by a 5'-3' endonuclease (AP endonuclease (APE)) that . . . cleav[es] the phosphodiester bonds at the AP sites.

Id. ¶ 57. An "AP endonuclease inhibitor . . . inhibit[s] repair of DNA" in cancer cells treated with an antimetabolite agent. *Id*. ¶ 94. Methoxyamine is an AP endonuclease inhibitor. *Id*. ¶ 95.

Claims 1, 5, 8, 13–16, and 23–28 are on appeal. Claims 1 and 8, reproduced below, are illustrative:

Claim 1: A method of determining the susceptibility of human non-small cell lung cancer in a subject to treatment with pemetrexed that induces or promotes incorporation of a UDG substrate into DNA of cancer cells, comprising:

> obtaining a sample of cancer cells from the subject;
>
> measuring the level of UDG in the cancer cells;
>
> comparing the measured levels of UDG in the cancer cells to a control level; wherein an increase in the measured levels of UDG in the cancer cells compared to a control level indicates that the cancer is less susceptible to treatment with pemetrexed;

treating the cancer in the subject with pemetrexed and methoxyamine if the measured level of UDG activity is increased relative to the control level.

Claim 8: A method of treating human non-small cell lung cancer in a subject comprising:

obtaining a sample of cancer cells from the subject;

measuring the level of UDG expression in the cancer cells;

comparing the measured levels of UDG expression in the cancer cells to a control level; and

administering pemetrexed that induces or promotes incorporation of a UDG substrate into DNA of cancer cells to the subject if the measured level of UDG expression is decreased compared to a control level or administering pemetrexed in combination with an AP endonuclease inhibitor if the measured level of UDG expression is increased compared to a control level.

OPINION

Claims 1, 5, 8, 13–16, and 23–28 stand rejected under 35 U.S.C. § 103(a) as obvious based on Theuer[2] and Weeks.[3] Ans. 4. The Examiner found that Theuer "teaches a therapy for cancers being treated with an antifolate, e.g. pemetrexed, including, human non-small cell lung cancers, comprising administering the antifolate in combination with a base excision repair inhibitor, e.g. methoxyamine." *Id*. The Examiner found that Theuer also teaches "that the combination results in synergistic efficacy, and that the combination can be administered to a patient having a cancer that is at least

[2] Theuer et al., US 2008/0234298 A1, Sept. 25, 2008.
[3] Lachelle D. Weeks et al., *Mice Deficient in Uracil DNA Glycosylase (UDG) Display Increased Sensitivity to the Antifolate Pemetrexed*, Cancer Research 71(8 Suppl.):Abstr. 5490 (2011).

partially resistant to the antifolate (pemetrexed) treatment alone to overcome the resistance." *Id*.

The Examiner also found that Theuer "teaches the measurement of UDG levels from tumor tissue samples," but "does not expressly teach comparing the UDG levels to a control level and administering the combination when UDG levels are increased relative to the control." *Id*. However, the Examiner found that "Weeks teaches that UDG expression levels in cancers are markers for sensitivity to pemetrexed and that decreased expression indicate[s] sensitivity and increased expression indicate[s] resistance." *Id*.

The Examiner concluded that it would have been obvious to measure the UDG expression level in a cancer cell sample and compare it to a control, then to administer a combination of pemetrexed and methoxyamine, as taught by Theuer, "if the levels are increased relative to the control, since Weeks teaches that UDG expression levels in cancers are markers for sensitivity to pemetrexed and that decreased expression indicates sensitivity and increased expression indicates resistance." Ans. 5. That is, the combination of pemetrexed and methoxyamine "would have [been] seen as appropriate in the treatment of cancers with high UDG expression levels, since this was known to indicate resistance to pemetrexed, and the administration of the drug with methoxyamine was known to overcome such resistance." *Id*.

Appellant argues that, while Theuer teaches that "protein levels of UDG are increased with the combination of pemetrexed and methoxyamine, . . . there is no teaching in Theuer et al. regarding the comparison of UDG

levels to control levels and/or the significance of such a comparison in the treatment of cancer." Appeal Br. 13. Appellant argues that Weeks "fails to make up for the deficiencies of Theuer," because Weeks discloses only that "gene-targeted UDG-/- mice were more sensitive to DNA damage from pemetrexed than UDG+/+ and UDG+/- mice," and "fail[s] to provide any disclosure regarding situations where UDG is increased in cancer cells compared to control levels." *Id*.

We agree with Appellant that the evidence cited by the Examiner does not support a prima facie case of obviousness. Each of independent claims 1, 8, and 23 include the active steps of measuring the level of UDG in cancer cells, comparing the measured level to a control level, and administering pemetrexed in combination with methoxyamine (or another AP endonuclease inhibitor) *if the measured level of UDG expression is increased* compared to the control.

Theuer discloses administering an antifolate compound such as pemetrexed in combination with methoxyamine "to enhance or increase the effect (i.e. potentiate activity) of the antifolate anticancer agent." Theuer ¶ 14. Theuer also discloses administering pemetrexed in combination with methoxyamine to overcome resistance of cancer cells to pemetrexed alone. *Id*. ¶¶ 17–20.

Theuer discloses that "protein levels of UDG are affected by treatment [with] a combination of pemetrexed and MX [methoxyamine]." *Id*. ¶ 61. That is, after treatment with pemetrexed and methoxyamine, UDG levels are

changed.[4] But Theuer does not disclose measuring the expression level of UDG in cancer cells before treatment with pemetrexed and methoxyamine, or comparing that level to a control, or administering pemetrexed and methoxyamine when the UDG levels are increased compared to the control.

Weeks reports on "the role of UDG expression on pemetrexed sensitivity in vivo using gene-targeted UDG-/- mice"; i.e., genetically modified mice that lack a functional UDG gene. Weeks, abstract. The UDG-/- mice were "compared to UDG+/+ and UDG+/- littermates"; i.e., mice that had either one (+/-) or two (+/+) copies of the normal, functional UDG gene. *Id*.

Weeks reports that the results "strongly suggest[ed] that UDG deficiency potentiates pemetrexed cytotoxicity in in vitro as well as in in vivo models." *Id*. Weeks also reports that the data "promote UDG as a target for improving pemetrexed efficacy." *Id*.

Thus, Weeks discloses that "UDG deficiency"—i.e., a lower level of UDG compared to a normal-level control—results in increased pemetrexed cytotoxicity, and therefore increased efficacy of pemetrexed against UDG-deficient cancer cells. However, Weeks does not disclose anything about the effect of UDG expression that is increased compared to a normal-level control, because all of the mice described by Weeks had either normal (+/+) or lower-than-normal (+/-, -/-) levels of UDG expression.

The evidence therefore does not support the Examiner's finding that Weeks teaches that increased UDG expression, compared to a control level,

[4] Theuer's Figure 7 appears to show increased UDG levels after treatment with pemetrexed and methoxyamine. Theuer, Fig. 7.

indicates pemetrexed resistance in cancer cells. *See* Ans. 5. That finding is the basis for the Examiner's conclusion that it would have been obvious to administer a combination of pemetrexed and methoxyamine to treat cancers with increased UDG expression levels. *Id*. We conclude that the rejection of claims 1, 5, 8, 13–16, and 23–28 under 35 U.S.C. § 103(a) based on Theuer and Weeks is not supported by a preponderance of the evidence, and we therefore reverse it.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 5, 8, 13–16, 23–28	103(a)	Theuer, Weeks		1, 5, 8, 13–16, 23–28

REVERSED