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OBLON, MCCLELLAND, MAIER & NEUSTADT, L.L.P.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER
ANDERSON, JAMES D

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iahmadi@oblon.com
patentdocket@oblon.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte SHIGEKAZU KURIHARA and
TAKASHI TSUCHIYA[1]

Appeal 2020-001258
Application 15/008,865
Technology Center 1600

Before FRANCISCO C. PRATS, JOHN G. NEW, and DAVID COTTA, *Administrative Patent Judges*.

NEW, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] We use the term "Appellant" to refer to the "applicant" as defined in 37 C.F.R. § 1.142. Appellant identifies Ajinomoto Co., Inc. of Tokyo, Japan as the real party-in-interest. App. Br. 1.

SUMMARY

Appellant files this appeal under 35 U.S.C. § 134(a) from the Examiner's Final Rejection of claims 5–8, 12–23 and 26–29 as unpatentable under 35 U.S.C. § 103 as being obvious over the combination of Shibahara (US 7,767,714 B2, August 3, 2010) ("Shibihara"), S. Kurihara et al., *Enhancement of Antigen-Specific Immunoglobulin G Production in Mice by Co-Administration of L-Cystine and L-Theanine*, 69(12) J. VET. MED. SCI. 1263–70 (2007) ("Kurihara"), S. Yoshida et al., *Effects of Glutamine Supplements and Radiochemotherapy on Systemic Immune and Gut Barrier Function in Patients with Advanced Esophageal Cancer*, 227(4) ANNS. SURG. 485–91 (1998) ("Yoshida"), S. Kojima et al., *Protective Effects of Glutathione on 5-Fluorouracil-induced Myelosuppression in Mice*, 77 ARCH. TOXICOL. 285–90 (2003) ("Kojima"), and J.F. Smyth et al., *Glutathione Reduces the Toxicity and Improves Quality of Life of Women Diagnosed with Ovarian Cancer Treated with cisplatin: Results of a Double-Blind, Randomised Trial*, 8 ANNS. ONCOL. 569–73 (1997) ("Smyth").[2]

We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

[2] Claims 14–16 and 18–28 were also rejected as unpatentable under 35 U.S.C. § 112(b) as being indefinite. Final Act. 5. The Examiner has withdrawn this rejection. Ans. 16.

NATURE OF THE CLAIMED INVENTION

Appellant's claimed invention is directed to agents containing (A) cysteine, or a derivative thereof, and (B) theanine, in combination, that are useful for reducing side effects of cancer chemotherapy. Abstr.

REPRESENTATIVE CLAIM

Claim 5 is representative of the claims on appeal and recites:

> 5. A therapeutic drug for cancer, comprising:
>
> cystine or a derivative thereof;
>
> theanine; and
>
> at least one anticancer agent selected from the group consisting of a platinum preparation, an alkylating agent, an antimetabolite, a plant alkaloid, an agent for molecular targeted therapy, and a hormonal agent,
>
> wherein the cystine or a derivative thereof and the theanine are included in amounts sufficient to reduce a side effect of the at least one anticancer agent, and
>
> the derivative of cystine comprises at least one selected from the group consisting of glutathione, glutathione disulfide, glutathione alkyl ester, oxidized glutathione dialkyl ester, cysteine, cysteine alkyl ester, 3-[(carboxymethyl)thio]alanine, N-acylcysteine, N-acylcysteine alkyl ester, N-acylcystine, N-acylcystine alkyl ester, N, N′-diacylcystine, N, N′-diacylcystine dialkyl ester, and S-alkylcysteine sulfoxide.

App. Br. 14.

ISSUES AND ANALYSES

We adopt the Examiner's findings, reasoning, and conclusion that the claims on appeal are *prima facie* obvious over the combined cited prior art. We address the arguments raised by Appellant below.

A. Rejection of Claim 6[3]

Issue

Appellant argues that the Examiner erred because a person of ordinary skill in the art would not have been led to combine the teachings of the references with a reasonable expectation of success. App. Br. 4.

Analysis

The Examiner finds that Shibahara teaches a tablet containing 175 mg of L-cystine and 70 mg of L-theanine (i.e., a cystine:theanine ratio of 2.5: 1). Final Act. 7 (citing Shibihara Ex. 4, col. 7, ll. 17–37).

The Examiner finds that Kurihara teaches that administration of both cystine and glutamic acid increases the synthesis of glutathione (GSH), which has a marked effect on immune cell function, as compared with supplementation with either amino acid alone in human macrophages *in vitro*. Final Act. 8. The Examiner finds that Kurihara teaches that, as ingested glutamic acid is metabolized during intestinal transport, oral

[3] Appellant makes no arguments with respect to claims 7, 8, 12–16, 18–23, and 27–29. We therefore consider these claims as argued together with, and standing or falling with, claims 5, 6, 17, and 26.

administration of L-theanine (γ-glutamylethylamide), which is metabolized to glutamic acid mainly in the liver, may act as a glutamic acid donor *in vivo*. *Id.* The Examiner further finds that Kurihara teaches that co-administration of L-cystine (200 mg/kg) and L-theanine (80 mg/kg) for 11 days prior to immunization significantly increased the levels of total glutathione ("GSH") in the liver six hours after immunization compared to levels in control mice, and that Kurihara thus demonstrates that it was known in the art at the time of Appellant's invention that administration of L-cystine and L-theanine increases levels of liver GSH. *Id.* (citing Kurihara Abstr.).

The Examiner finds that Yoshida teaches that glutamine supplements improved protein metabolism in tumor-bearing rats undergoing chemotherapy, and reduced the toxicity of chemotherapy through an enhancement of glutathione production. App. Br. 9 (citing Yoshida Abstr.).

The Examiner particularly points to Yoshida's citation of K. Rouse et al., *Glutamine Enhances Selectivity of Chemotherapy through Changes in Glutathione Metabolism*, 221 Anns. Surg. 420–426 (1995) ("Rouse"), which teaches that glutamine supplements reduced the toxicity of chemotherapy because of enhanced glutathione synthesis in tumor bearing rats. *Id.* (citing Yoshida 485–86).

The Examiner finds that Kojima teaches that GSH is important in the detoxification of a variety of toxic xenobiotics, such as in acetaminophen-induced liver injury, aflatoxin B1-induced liver tumors, alcoholic liver toxicity, bromobenzene-induced liver necrosis, p-dichlorobenzene-induced hepatotoxicity, eugenol-induced hepatotoxicity, pulmonary toxicity induced by a metabolite of 4-ipomeanol, 5-fluorouracil-induced teratogenicity, and

thiabendazole-induced nephrotoxicity, in various animal models. Final Act. 10 (citing Kojima 285). The Examiner finds that Kojima teaches that GSH exerts a protective effect on 5-fluorouracil-induced myelosuppression in mice. *Id.* (citing Kojima Abstr., 286).

The Examiner finds that Smyth teaches that GSH provides protection from the toxic effects of cisplatin. Final Act. 11. The Examiner finds that Smyth teaches that co-administering GSH and the chemotherapeutic agent cisplatin ("CDDP") allows more cycles of CDDP treatment to be administered because less toxicity is observed and the patient's quality of life improved. *Id.* (citing Smyth Abstr.).

The Examiner concludes that a person of ordinary skill in the art would have found it obvious to increase GSH levels to reduce the side effects of cancer chemotherapeutic agents, such as 5-fluorouracil or cisplatin, as taught by the combination of Yoshida, Kojima, and Smyth. Furthermore, the Examiner reasons, because cystine and theanine were known in the art to increase GSH levels when administered, as taught by Kurihara, a skilled artisan would expect that administration of cystine and theanine in combination with an anticancer agent, would reduce the toxicity of chemotherapeutic agents such as cisplatin or 5-fluorouracil by increasing GSH levels. Final Act. 15.

Appellant argues that Shibahara and Kurihara are directed to administering L-cystine and L-theanine to healthy subjects, whereas Yoshida, Kojima, and Smyth are directed to administering chemicals other than L-cystine and L-theanine to cancer patients. App. Br. 5. Appellant therefore contends that there is no overlap between the subject groups and the chemicals described in these references. *Id.*

Moreover, argues Appellant, even if Shibahara and Kurihara are combined with Yoshida, Kojima, and Smyth, a person of ordinary skill in the art would not have had a reasonable expectation that administration of L-cystine and L-theanine to a cancer patient would result in reducing a side effect of cancer chemotherapy performed by administering certain anticancer agent(s). App. Br. 6. Appellant contends that Kurihara teaches that oral administration of L-cystine and L-theanine increases the glutathione (GSH) levels in the liver. *Id.* (citing Kurihara 1264, 1265). Furthermore argues Appellant, Yoshida (citing Rouse) describes reducing toxicity of chemotherapy because of enhanced glutathione synthesis after administration of glutamine. *Id.* Appellant asserts that Rouse teaches oral administration of glutamine and methotrexate ("MTX," a chemotherapeutic agent) to tumor-bearing rats, and demonstrates that GSH level decreased in the tumor cells and increased in the host tissues. *Id.* (citing Rouse 421, 422). According to Appellant, these references show that administration of GSH precursors increases GSH levels in healthy subjects or tissues due to synthesis of GSH *in vivo*. *Id.* at 7.

However, Appellant argues, unlike Kurihara and Yoshida (and Rouse), Kojima and Smyth teach the direct administration of GSH and an anticancer agent to a cancer patient. App. Br. 7. Appellant contends that Kojima and Smyth neither teach nor suggest that GSH synthesized *in vivo* can also be used to alleviate possible side effects of the anticancer agent. *Id.*

Appellant therefore argues that a person of ordinary skill in the art would not have had a reasonable expectation that GSH, synthesized *in vivo* as described in Kurihara, Yoshida, and Rouse, would act like directly administered GSH, as described in Kojima and Smyth. App. Br. 7. Rather,

Appellant asserts, a skilled artisan would have understood that administration of GSH itself, as described in Kojima and Smyth, does not necessarily increase metabolic GSH levels. *Id.* In fact, Appellant argues, it was known in the prior art at the time of invention that oral administration of GSH was unlikely to cause increases in metabolic GSH levels, because GSH can be hydrolyzed and decomposed by the activity of γ-glutamyl transferase. *Id.*

In support of this argument, Appellant points to the prior art teachings of A. Witschi et al., *The Systemic Availability of Oral Glutathione*, 43(6) EUR. J. CLIN. PHARMACOL. 667–69 (1992) ("Witschi") and J. Allen et al., *Effects of Oral Glutathione Supplementation on Systemic Oxidative Stress Biomarkers in Human Volunteers*, 17(9) J. ALT. COMP. MED. 827–33 (2011) ("Allen"). App. Br. 7. Appellant argues that Witschi teaches that orally-administered GSH is hydrolyzed by intestinal and hepatic γ-glutamyltranserase and therefore does not increase the amount of circulating GSH. *Id.* (citing Witschi Abstr.). Similarly, argues Appellant, Allen teaches that orally administered GSH did not increase GSH levels in healthy humans. *Id.* (citing Allen Abstr., 829–30). Appellant therefore contends that, because oral administration of GSH does not necessarily increase metabolic GSH levels, as taught by Witschi and Allen, a skilled artisan would have understood that the reduction of toxicity of the anticancer agents taught by Kojima and Smyth must be caused by mechanisms other than increases in metabolic GSH levels, and that there is no correlation between metabolic GSH levels *in situ* and toxicity of an anticancer agent. *Id.* at 8. Appellant asserts that a person of ordinary skill in the art, aiming to reduce toxicity of the claimed anticancer agents, would not have been led to

administer precursors of GSH, such as L-cystine and L-theanine, as a means of increasing GSH level in a subject. *Id.*

We are not persuaded by Appellant's arguments. We acknowledge Appellant's argument that the teachings of Witschi and Allen, at first glance, may seem to contradict the teachings of Kojima that oral administration of GSH can increase levels of circulating GSH. Indeed, we agree with Appellant that Witschi teaches that GSH may be hydrolysed "by intestinal and hepatic [γ]-glutamyltransferase" and that "*dietary* glutathione is not a major determinant of circulating glutathione." Witschi (Abstr., emphasis added). However, in reaching this conclusion, Witschi expressly teaches only that "oral administration of a single dose of 3g of glutathione" is insufficient to achieve a "clinically beneficial" increase in circulating GSH. *Id.*

Similarly, Allen teaches that "oral GSH supplementation (500 mg twice daily) was given to the volunteers" and that: "No significant changes were observed in biomarkers of oxidative stress, including glutathione status, in this clinical trial of oral glutathione supplementation in healthy adults." Allen Abstr.

In contrast, Kojima teaches oral administration of GSH in mice at "at a dose of 800 mg/kg … for 21 consecutive days." Kojima Abstr. This is the equivalent of a daily dosage in humans of approximately 50g over an interval of three weeks.[4] Although, direct comparisons between the

[4] The average mass of a human, measured globally, is approximately 62 kg. *See* S.C. Walpole et al., *The Weight of Nations: an estimation of Adult Human Biomass*, 12 BMC PUBLIC HEALTH 439 (2012) ("Walpole") *available at*: https://doi.org/10.1186/1471–2458–12–439.

metabolic capabilities of mice and humans is difficult, it is nevertheless evident that Kojima teaches administration of a significantly more massive equivalent dosage: more than 10 times that of Witschi and 50 times that of Allen. This may have some bearing upon the differences between the teachings of Witschi and Allen, on the one hand, and Kojima on the other. Nevertheless, we acknowledge that Witschi teaches that it was known in the contemporaneous art that GSH is hydrolysed in the gut and liver by γ-glutamyl transferase and that this may prevent low dosages of GSH from elevating circulating levels of GSH. *See also* Allen Abstr.

However, we find the teachings of Witschi and Allen with respect to oral administration of GSH to be entirely irrelevant to the teachings of Smyth. Smyth expressly teaches *intravenous* co-administration of GSH and CDDP. *See* Smyth 570 ("A total of 151 women with ovarian cancer stage I-IV (mean age 57 years, range 21–76) received *i.v.* CDDP 100 mg/m^2 + GSH 3 g/m^2 (placebo controlled) every three weeks for six courses") (emphasis added). We find that a person of ordinary skill in the art would have understood that intravenous administration largely bypasses the enteric and hepatic systems (and hence, hydrolysis of GSH by γ-glutamyl transferase) and would directly increase circulating levels of GSH.

Nevertheless, we find that Appellant makes an important point, although not, perhaps, the intended one, *viz.*, that it was known in the art at the time of invention that orally administered GSH can be hydrolyzed in the gut and liver by γ-glutamyl transferase, and that this may prevent an increase in circulating levels of GSH. However, it was also known in the contemporaneous art that oral administration of GSH precursors, including L-cystine and L-theanine, (and its derivatives, glutamine and glutamate) can

increase circulating levels of GSH. *See* Kurihara Abstr. ("Supplementation with both cystine and glutamic acid increases the synthesis of glutathione (GSH)"). Similarly, Yoshida teaches that oral administration of another rate-limiting precursor of glutathione, glutamine, can also increase GSH levels, and that the concomitant increase in GSH levels following glutamine administration can decrease anticancer agent toxicity *in vivo*.[5] *See* Yoshida 489–90; Rouse Abstr., 422–23.

Given these teachings of the prior art, we agree with the Examiner that a person of ordinary skill in the art would have found it obvious to combine the teachings of the cited prior art references (and those of Witschi and Allen) and to administer precursors to GSH known to elevate circulating levels of GSH, and to co-administer these precursors with an anticancer agent, because Yoshida, Kojima, and Smyth (and Rouse) teach that elevating levels of circulating GSH can reduce the side effects (including toxicity) of anticancer agents. We consequently affirm the Examiner's rejection of claim 6. Furthermore, Appellant makes the same arguments with respect to claim 5. App. Br. 12. For the reasons we have explained, we similarly affirm the Examiner's rejection of claim 5.

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[5] Both glutamine and L-theanine are metabolized to glutamic acid, which is one of the three peptides constituting GSH. *See* Kurihara 1263; Yoshida 489–90. Orally-administered glutamate is metabolized in the intestine and consequently does not reach GSH-producing organs. *See* Kurihara 1263. L-theanine and glutamine are thus precursors to glutamate, an essential and rate-limiting precursor in GSH synthesis. *See* Yoshida 489–90. We conclude that it would therefore have been obvious to a skilled artisan, seeking to increasing metabolic GSH levels, to administer either of these metabolic precursors to glutamate and GSH.

B. Rejection of Claim 17

Issue

Appellant argues that the Examiner erred in finding that the combined cited prior art teaches or suggests the limitation of dependent claim 17 reciting: "wherein the side effect of cancer chemotherapy is at least one selected from the group consisting of anorexia, nausea, vomiting, diarrhea, stomatitis, malaise, and exanthema." App. Br. 10.

Analysis

Appellant argues that Kojima teaches only some side effects of 5-FU, such as myelosuppression, and in particular thrombocytopenia, leukopenia, erythrocytopenia, granulocytopenia, and reticulocytopenia. App. Br. 10 (citing Kojima 28–89). Appellant asserts that Kojima is silent about reducing the specific side effects recited in claim 17, and that there is no evidence of record showing that patients suffering myelosuppression also necessarily suffer from the side effects recited in the claims. *Id.*

Appellant also contends that Smyth appears to mention nausea and/or vomiting as a possible toxic effect of cisplatin administration, but Smyth neither teaches nor suggests that its subjects suffer from nausea and/or vomiting and the administration of cisplatin and GSH alleviate cisplatine-induced nausea and/or vomiting. App. Br. 10.

We are not persuaded. Smyth teaches:

> Each question in the Rotterdam Symptoms Checklist was analysed separately. Forty-five of the 47 questions had the better observed mean response in the glutathione group, when the responses were scored from 1 to 4.
>
> Eight of these differences were statistically significant at the 5% level. These comprised the questions on nausea, vomiting,

> tingling hands/feet, loss of hair, short of breath, difficulty concentrating, housekeeping and shopping. The overall finding is one of improved mood in the GSH group.

Smyth 571, *see also* Table 4. Smyth thus teaches that the subjects of its study reported that co-administration of GSH with cisplatin/CDDP alleviated symptoms of nausea and vomiting as compared to administration of cisplatin/CDDP alone. Smyth also teaches that fewer patients discontinued treatment with cisplatin/CDDP when co-administered with GSH (n=2) than those administered cisplatin alone (n=7). *See id.* Table 3.

We therefore agree with the Examiner that Smyth teaches that co-administration of GSH with cisplatin/CDDP reduces the side effects of cancer chemotherapy including nausea and vomiting, and we consequently affirm the Examiner's rejection of claim 17. Furthermore, Appellant makes the same arguments with respect to claim 26. App. Br. 11–12. For the reasons we have explained, we similarly affirm the Examiner's rejection of that claim.

CONCLUSION

The Examiner's rejection of claims 5–8, 12–23, and 26–29 under 35 U.S.C. § 103 is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1).

AFFIRMED

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
5–8, 12–23, 26–29	103	Shibihara, Kurihara, Yoshida, Kojima, Smyth	5–8, 12–23, 26–29	