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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ENRICO PESENTI, MAURIZIO D'INCALCI, DARIO
BALLINARI, and JUERGEN MOLL¹

Appeal 2015-006259
Application 13/054,646
Technology Center 1600

Before RICHARD J. SMITH, JOHN E. SCHNEIDER, and
RYAN H. FLAX, *Administrative Patent Judges*.

FLAX, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134(a) involving claims directed to a therapeutic combination of an Aurora kinase inhibitor and an antimetabolite agent for cancer treatment. Claims 1, 4, 5, 10, 12, and 15 are on appeal as rejected under 35 U.S.C. § 103(a) and on the ground of nonstatutory obviousness-type double patenting. We have jurisdiction under 35 U.S.C. § 6(b).

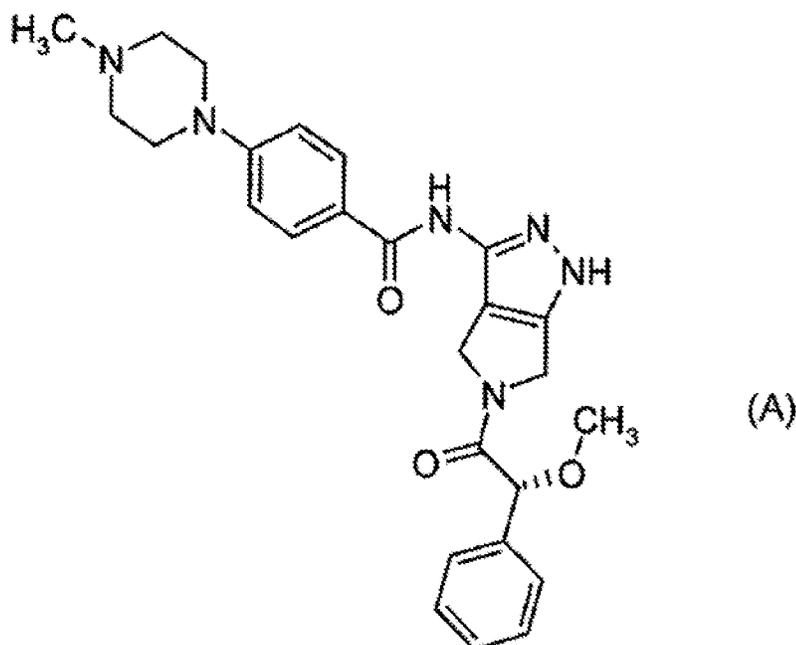
We affirm.

¹ We understand the Real Party in Interest to be Nerviano Medical Sciences, S.R.L. Br. 2.

STATEMENT OF THE CASE

The appealed claims can be found in the Claims Appendix of the Appeal Brief. Claim 1 is the sole independent claim, is representative, and reads as follows:

1. A therapeutic combination comprising (a) Compound 1 of formula (A):



, and (b)
one or more antineoplastic agents selected from the group consisting of antimetabolite agents, wherein the active ingredients of the combination are present in each case in free form or in the form of a pharmaceutically acceptable salt thereof.

Br. 10 (Claims App'x).

The following rejections are on appeal:

Claims 1, 4, 5, 10, 12, and 15 stand rejected under 35 U.S.C. § 103(a) over Fancelli 1,² Fancelli 2,³ Nair,⁴ and Kleespies.⁵ Final Action 3.

Claims 1, 4, and 5 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 1–5 of Fancelli 628⁶ and Nair and Kleespies. Final Action 6.

Claims 1, 4, 5, 12, and 15 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 1–5 of Fancelli 568⁷ and Nair and Kleespies. Final Action 7–8.

We adopt the Examiner’s findings of fact, reasoning on scope and content of the prior art, and conclusions set out in the Final Action and Answer. Any findings of fact set forth below are provided only to highlight certain evidence of record.

² International Patent Application Pub. No. WO 2005/005427 A1 (published Jan. 20, 2005) (hereinafter “Fancelli 1”).

³ Daniele Fancelli et al., *1,4,5,6-Tetrahydropyrrolo[3,4-c]pyrazoles: Identification of a Potent Aurora Kinase Inhibitor with a Favorable Antitumor Kinase Inhibition Profile*, 49 J. MED. CHEM. 7247–51 (2006) (hereinafter “Fancelli 2”).

⁴ J. S. Nair et al., *A Novel Aurora B Kinase Inhibitor with Potent Anticancer Activity Either as a Single Agent or in Combination with Chemotherapy*, 22 J. CLIN. ONCOLOGY 9568 (2004) (July 15 Supplement) (hereinafter “Nair”).

⁵ Axel Kleespies et al., *Tyrosine Kinase Inhibitors and Gemcitabine: New Treatment Options in Pancreatic Cancer?*, 9 DRUG RESISTANCE UPDATES 1–18 (2006) (hereinafter “Kleespies”).

⁶ U.S. Patent No. US 7,582,628 B2 (issued to Fancelli et al. on Sept. 1, 2009) (hereinafter “Fancelli 628”).

⁷ U.S. Patent No. US 7,141,568 B2 (issued to Fancelli et al. on Nov. 28, 2006) (hereinafter “Fancelli 568”).

DISCUSSION

Appellants contend no single reference “discloses the combination of Compound 1 of formula (A) and one or more antimetabolite agents,” but do not argue that the combination of references fails to set forth all of the limitations of the claimed invention. Br. 5. Appellants argue the combination of prior art would not be made as set forth in the final rejection because there would have been “no reasonable expectation that compound 1 of formula (A) would work in an antimetabolite’s milieu and vice versa, let alone that the combination would work together as claimed, and then to the level of efficacy shown.” *Id.* The Appellants’ final argument on the aforementioned “level of efficacy” is that the combined elements of the invention create a “synergistic effect based on the equation of Chou-Talalay” and, in relation thereto, the invention provides unexpectedly good results. *Id.* These arguments were presented by Appellants most directly regarding the obviousness rejection; however, they are referenced as the only arguments over the double patenting rejections as well and, so, we address all arguments together.

As to Appellants’ first argument, “[n]on-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. . . . [The references] must be read, not in isolation, but for what [they] fairly teach[] in combination with the prior art as a whole.” *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). Therefore, the fact that no single reference teaches the precise combination of elements as claimed is not determinative. The combined art was determined by the Examiner to disclose each element

of the claims, and this is not persuasively contested by Appellants.

Therefore, we move on to Appellants' second argument.

Appellants argue there would be no reasonable expectation of success in combining pyrrolo[3,4-c]pyrazole compounds of formula (A), for example, the claimed N-{5-[(2R)-2-methoxy-2-phenylethanoyl]-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-yl}-4-(4-methylpiperazin-1-yl)benzamide (also identified as compound 9d of Francelli 2's Table 2), disclosed by Francelli 1 and Francelli 2 to be inhibitors of Aurora-2 and/or Aurora kinases A and B, with antimetabolite agents, e.g., gemcitabine, oxaliplatin and 5-FU, as disclosed by Nair and Kleespies (as being combinable with an Aurora B kinase inhibitor or a tyrosine kinase inhibitor), such as proposed by the Examiner in finally rejecting the claims. *Compare* Br. 5–6 with Final Action 3–5 and Ans. 9–10. Appellants concede that each cited reference is directed to a treatment for cancer, but contend “[t]he Office Action’s reasoning boils down to the premise that if one compound is good at alleviating a problem, and a second compound is also good at alleviating the problem, it is obvious that their combination must be even better and will be successful.” Br. 6. Appellants’ argument is not persuasive.

“It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. . . . [T]he idea of combining them flows logically from their having been individually taught in the prior art.” *In re Kerkhoven*, 626 F.2d 846, 850 (CCPA 1980).
Further, the

case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as

there was a reasonable probability of success. . . . Indeed, a rule of law equating unpredictability to patentability . . . would mean that any new salt—including those specifically listed in the [prior art] itself—would be separately patentable, simply because the formation and properties of each salt must be verified through testing. This cannot be the proper standard since the expectation of success need only be reasonable, not absolute.

Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1364 (Fed. Cir. 2007).

The Specification identifies the claimed compound 1 of formula (A) as “an aurora kinase inhibitor” and also that Francelli 1 disclosed how to prepare this claimed compound. Spec. 1, 4–5. Nair disclosed successfully combining cancer therapies by pairing an Aurora B inhibitor with several other cancer-therapy compounds, including docetaxel, vinorelbine, gemcitabine, oxaliplatin, and 5-fluoruracil. Nair Abstract. Nair also reported “a more than additive effect” in “all [such] combinations.” *Id.* Kleespies also disclosed compound combinations for cancer therapy, specifically, “a strong case for combining gemcitabine with TKIs [tyrosine kinase inhibitors],” calling gemcitabine “the cornerstone of chemotherapy for advanced and metastatic pancreatic cancer,” and, further, “[c]ombination regimens of gemcitabine with other cytotoxic drugs have shown promising [but limited] activity in Phase II studies . . . [and n]ew conventional cytotoxic agents and other gemcitabine combinations might improve survival for patients with pancreatic cancer[,] . . . [t]herefore, novel therapeutic strategies are urgently needed.” Kleespies 1 (abstract), 2 (left col.), and 3 (paragraph spanning left and right cols.).

It is well established that an invention “composed of several elements is not proved obvious merely by demonstrating that each of its elements was,

independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). That being so, however, the “interrelated teachings of multiple [prior art references]; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all [can provide] an apparent reason to combine the known elements in the fashion claimed.” *Id.*

Here, the primary cancer-therapy compounds of the claims, that is, Aurora kinase inhibitors, were known, as was their combination with a variety of other chemotherapeutic agents, and the prior art teaching of those compounds was expressly referenced in the Specification. *See* Francelli 1 Abstract, 3:15–5:5, 16:8–17, 17 (Table 1), 17:22–18:8; Francelli 2 7247 (Abstract), 7248 (Scheme 1, Table 2), 7249 (left col.), 7250 (Figure 4). Further, the secondary cancer-therapy compounds of the claims, that is, antimetabolite agents, were also known in the art and, moreover, their combination with other cancer-therapeutics, including from the family of Aurora kinase inhibitors like recited by the claims, was expressly suggested by the cited references. *See* Nair (Abstract); Kleespies 1 (Abstract), 2–3. The references themselves provide ample reason for the skilled artisan to believe that the combination of an Aurora kinase inhibitor and an

antimetabolite would be reasonably successful, if not more successful than either component alone.

We turn now to the final argument presented by Appellants, that is, that the claimed invention provides unexpected synergism and, thereby, unexpected results.

In determining obviousness and assessing evidence of unexpected results and synergism, it is proper to consider the closest prior arts' disclosure of synergistic effects when combining therapeutic compounds similar to those claimed. *Novo Nordisk A/S v. Caraco Phama. Labs., Ltd.*, 719 F.3d 1346, 1355 (Fed. Cir. 2013) (upholding district court's finding that the closest prior art combination of similar compounds, with similar mechanism of action, yielded synergistic effects and one would expect similar synergy from claimed combination). Moreover, "[s]ynergism, in and of itself, is not conclusive of unobviousness in that synergism might be expected." *In re Kollman*, 595 F.2d 48, 55 n.6 (CCPA 1979). "[B]y definition, any superior property must be *unexpected* to be considered evidence of non-obviousness. Thus, in order to properly evaluate whether a superior property was unexpected, the [fact-finder] should have considered what properties were expected." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007).

Here, the closest prior art expressly suggests combining an Aurora kinase inhibitor, as recited by the claims, with a variety of other chemotherapeutic agents (*see* Fanceli 1 17:22–18:8; *see also* Final Action 4–5) and also discloses that combining an antimetabolite agent, e.g., the also-recited gemcitabine, with an Aurora kinase inhibitor “revealed more than

[an] additive effect,” i.e., it was synergistic in combination (*see* Nair Abstract; *see also* Final Action 4–5). Thus, the synergistic effect of combining the claimed Aurora kinase inhibitor and an antimetabolite agent, specifically the also-claimed gemcitabine, was not unexpected, but was obvious and expected based on the closest prior art.⁸

For the reasons above, we affirm the obviousness rejection and the obviousness-type double patenting rejections.

SUMMARY

The rejection of claims 1, 4, 5, 10, 12, and 15 under 35 U.S.C. § 103(a) over Fancelli 1, Fancelli 2, Nair, and Kleespies is affirmed. Claims 4, 5, 10, 12, and 15 were not argued separately and fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

The rejection of claims 1, 4, and 5 on the ground of nonstatutory obviousness-type double patenting over claims 1–5 of Fancelli 628 and Nair and Kleespies is affirmed.

The rejection of claims 1, 4, 5, 12, and 15 on the ground of nonstatutory obviousness-type double patenting over claims 1–5 of Fancelli 568 and Nair and Kleespies is affirmed.

TIME PERIOD FOR RESPONSE

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

AFFIRMED

⁸ We consider, but find unpersuasive, the mere conclusory statements of the Declaration of Enrico Pesenti under 37 C.F.R. § 1.132, dated Nov 22, 2012.