

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

OSI PHARMACEUTICALS, LLC
and GENENTECH, INC.,

Petitioner,

v.

ARCH DEVELOPMENT CORP. and
DANA-FARBER CANCER INSTITUTE, INC.,

Patent Owner.

Case IPR2016-01034
Patent 7,838,512 B1

Before LORA M. GREEN, TINA E. HULSE, and
ROBERT A. POLLOCK, *Administrative Patent Judges*.

POLLOCK, *Administrative Patent Judge*.

DECISION
Denying Request for Rehearing
37 C.F.R. §42.71

I. INTRODUCTION

A. *Background*

In our Final Written Decision (Paper 43, “Dec.”), we held that claims 1–3, 5, and 6 (collectively, “the challenged claims”) of U.S. Patent No. 7,838,512 B1 (Ex. 1001, “the ’512 patent”) were unpatentable over Akinaga,¹ in view of the knowledge of a person of ordinary skill in the art, Seynaeve,² Friedman,³ and Tam⁴ (Ground IV). *See* Dec. 38–39.⁵ Patent Owner timely filed a Request for Rehearing requesting that we vacate the portion of our Decision relating to that Ground. Paper 44 (“Reh’g Req.”).⁶ We did not authorize any response to the Request for Rehearing.

For the reasons that follow, we deny Patent Owner’s Request for Rehearing.

¹ Shiro Akinaga et al., *Enhancement of Antitumor Activity of Mitomycin C In Vitro and In Vivo by UCN-01, a Selective Inhibitor of Protein Kinase C*, 32 CANCER CHEMOTHERAPY AND PHARMACOLOGY 183–89 (1993). Ex. 1004.

² Caroline M. Seynaeve et al., *Cell Cycle Arrest and Growth Inhibition by the Protein Kinase Antagonist UCN-01 in Human Breast Carcinoma Cells*, 53 CANCER RES. 2081–86 (1993). Ex. 1014.

³ BethAnn Friedman et al., *Regulation of the Epidermal Growth Factor Receptor by Growth-Modulating Agents: Effects of Staurosporine, a Protein Kinase Inhibitor*, 50 CANCER RES. 533–38 (1990). Ex. 1031.

⁴ Sun W. Tam and Robert Schlegel, *Staurosporine Overrides Checkpoints for Mitotic Onset in BHK Cells*, 3 CELL GROWTH & DIFFERENTIATION 811–17 (1992). Ex. 1012.

⁵ We note that Paper 43, the Final Written Decision, issued September 11, 2017, contains font changes introduced during the uploading process. Paper 43 is hereby republished to eliminate the unintended font changes.

⁶ We further found claim 6 invalid for reasons not at issue here.

B. Standard for Reconsideration

The applicable standard for a request for rehearing is set forth in 37 C.F.R. § 42.71(d), which provides in relevant part:

A party dissatisfied with a decision may file a request for rehearing, without prior authorization from the Board. The burden of showing a decision should be modified lies with the party challenging the decision. The request must specifically identify all matters the party believes the Board misapprehended or overlooked, and the place where each matter was previously addressed in a motion, an opposition, or a reply.

II. ANALYSIS

Patent Owner argues that we should grant its Request for Rehearing because our conclusion is based on findings that 1) staurosporine was known to inhibit the tyrosine kinase c-src in human and animal cells; and 2) that staurosporine has a structure and mechanism of action similar to UCN-01, such that one of ordinary skill in the art would expect UCN-01 to likewise inhibit tyrosine kinases such as c-src. *See* Reh’g Req. 1–2. As an initial matter, we reject the premise of Patent Owner’s argument that our Decision stands or falls on whether one of ordinary skill in the art would have understood that UCN-01 inhibits the tyrosine kinase c-src in human and animal cells.

As illustrated in claim 1, the challenged claims are generally directed to administering a chemotherapeutic DNA damaging agent in combination with a low molecular weight tyrosine kinase inhibitor.⁷ According to the Specification, this combination is beneficial because treatment with a DNA damaging agent promotes cell cycle arrest, during which time cells attempt

⁷ Patent Owner concedes that claim 1 is representative and does not argue claims 2, 3, 5, and 6 separately. *See, e.g.*, PO Resp. 3.

to repair DNA damage before undergoing mitosis and subsequent cell division. *See* Dec. 4–6. Tyrosine kinase inhibitors, however, force cells to override the cell cycle arrest checkpoint and enter mitosis before repairs are complete, thereby enhancing the cytotoxic effects of the DNA damaging agents. *Id.*

As discussed in our Decision, Akinaga examines the effect of UCN-01 alone, and in combination with the DNA damaging agent mitomycin C. *See* Dec. 27–28; Ex. 1004. Noting that the two compounds had 1) complementary effects in delaying cell cycle progression; and 2) synergistic cytotoxic and antitumor effects, Akinaga expressly suggests the combination of UCN-01 and DNA-damaging agents for cancer chemotherapy. *Id.* Seynaeve establishes that UCN-01 inhibits multiple tyrosine kinases in human breast cancer cells coincident with promoting cell cycle arrest. Dec. 28–29, 34–35; Ex. 1014. Accordingly, “Seynaeve proposes a link between UCN-01’s inhibitory effects on tyrosine kinases and its inhibitory effects on the cell cycle.” Dec. 29.⁸

Akinaga further suggests combining a chemotherapeutic DNA damaging agent with UCN-01 because the two compounds cause delays in different stages of the cell cycle and result in synergistic cytotoxic and antitumor effects, whereas Seynaeve examines the effects of UCN-01 on the cell cycle of human carcinoma cells and shows that UCN-01 is a tyrosine kinase inhibitor. *See* Dec. 37–38. Because both references

⁸ Considering Seynaeve teachings with respect to UCN-01, we reject Patent Owner’s contention that “there is no evidence from which one can reasonably find that Petitioner carried its burden of proving that people of ordinary skill in the art considered either staurosporine or UCN-01 to be tyrosine kinase inhibitors.” *See* Reh’g. Req. 6.

investigate the effect of UCN-01 on cell cycle arrest in human tumor cells, one of ordinary skill in the art would have found reason to combine their teachings. *See id.*

Accordingly, our Decision holding claims 1–3, 5, and 6 unpatentable under Ground IV is supported by substantial evidence irrespective of whether one of ordinary skill in the art would have understood that UCN-01 inhibits c-src in human and animal cells. We, nonetheless, address the specifics of Patent Owner’s arguments.

A. *Robinson*

In our Decision, we rejected Patent Owner’s contention that although Akinaga teaches that UCN-01 inhibits v-src (as does Seynaeve), one of ordinary skill in the art would have no reason to believe that UCN-01 would inhibit its cellular homolog c-src because v-src is “found only in chickens” and “is more difficult to inhibit.” Dec. 28, 32. We instead credited the testimony of Petitioner’s expert, Dr. Eastman that “[b]ecause v-Src and c-Src have similar structures, compounds that inhibit the tyrosine kinase activity of v-Src generally inhibit c-Src as well. Thus, a person of ordinary skill would have understood that an inhibitor of v-Src would also inhibit the c-Src protein present in A431 cells and other human tumors.” *Id.* at 33 (quoting Ex. 1002 ¶ 202). Dr. Eastman testified that Robinson, for example, showed “that staurosporine, a molecule very similar to UCN-01, inhibited both v-Src and c-Src. . . . Thus, a person of ordinary skill in the art would have recognized that UCN-01 would inhibit tyrosine kinases in both animals and humans.” *Id.*

According to Robinson, “[t]he elevation in the tyrosine-specific kinase activity of *pp60 c-src* in human carcinoma . . . is suggestive that appropriate tyrosine kinase inhibitors may represent a new class of cancer

therapeutics.” Ex. 1036, 256. Accordingly, Robinson screened a large number of compounds for tyrosine kinase inhibitory activity against isolated c-src protein, also known as pp60^{c-src}. *Id.* at 255, Table 1.

Consistent with Dr. Eastman’s testimony, Robinson reports that “[t]he most potent inhibitory effects [were] produced with staurosporine,” a “broad spectrum protein kinase inhibitor[.]” *Id.* at 255, 257. Robinson emphasizes that, “[c]onsistent with previous reports, staurosporine was a potent inhibitor of pp60^{src}.” *Id.* at 257.

Robinson further reports that staurosporine inhibited the colony formation of activated c-src transformed cells in soft agar with “IC50 values . . . in the same range as IC50 values for the isolated c-src enzyme.” *Id.* at 255. Robinson further determined that, although staurosporine and other agents inhibited colony formation of c-src transformed cells, they also inhibited the colony formation induced by different oncogenes “suggesting no selective inhibition of the src mediated transformation was being produced.” *Id.*, Abstract. In view of these results, Robinson posits that:

The lack of whole cell selectivity observed for staurosporine, quercetin, genistein and herbimycin A on oncogene transformed NIH3T3 cells perhaps reflects the multiple actions attributed to each of these agents. For example the broad spectrum of kinase inhibitory activity for staurosporine and the indication that protein kinase C may be more sensitive than pp60^{src} to its inhibitory effects may be partially responsible for the equipotent effects produced on colony formation of the variety of NIH3T3 transformants examined. Protein kinase C inhibition may also

be involved with the toxicity produced before any meaningful antitumor activity when tested *in vivo*.

Id. at 257 (internal citations omitted). Robinson concludes that “the compounds examined do not show appropriate whole cell effects to warrant development efforts.” *Id.* at 258.

Patent Owner now argues that because Robinson did not consider staurosporine a candidate for drug development as a tyrosine kinase inhibitor, one of ordinary skill in the art would not understand that staurosporine inhibits c-src in human or animal cells. See Reh’g Req. 5–6. Patent Owner’s argument is unsupported by expert testimony or a plain reading of Robinson.

Robinson expressly identifies staurosporine as an inhibitor of c-src tyrosine kinase but posits that staurosporine’s effects in cellular assays may be due to “multiple actions.” See Ex. 1036, 257.⁹ In this respect, Robinson raises the possibility that “protein kinase C may be more sensitive” to staurosporine than the tyrosine kinase c-src. *Id.* Contrary to Patent Owner’s urging, we do not equate Robinson’s failure to observe an effect attributable to tyrosine kinase inhibition in some assays with a conclusion that staurosporine is not a “low molecular weight tyrosine kinase inhibitor,” as required by claim 1.

We further note that Robinson evaluates the use of tyrosine kinase inhibitors such as staurosporine as *individual* antitumor agents. That

⁹ Consistent with Robinson, “Tam teaches that ‘[s]taurosporine is a potent general protein kinase inhibitor that can suppress *in vitro* the activity of phospholipid Ca²⁺-dependent and cyclic nucleotide-dependent serine/threonine protein kinases *as well as the tyrosine kinases p60^{v-src} and epidermal growth factor receptor [EGFR].*’” Dec. 29 (quoting Ex. 1012, 811) (emphasis added).

Robinson determined that these compounds, administered alone, did not warrant further development is not dispositive in light of Akinaga's teaching that a chemotherapeutic DNA damaging agent *in combination with* the tyrosine kinase inhibitor UCN-01 (as taught by Seynaeve) produces synergistic cytotoxic and antitumor effects.

For the reasons set forth above, we did not overlook or misapprehend the evidence relating to Robinson.

B. Akinaga 1991

In our Decision, we were persuaded by Petitioner's argument that one of ordinary skill in the art would have had a reason to combine Akinaga with Seynaeve, Tam, and Friedman "because they involve administration of the same tyrosine kinase inhibit (UCN-01) or its close structural analog [staurosporine], which has substantially similar effects on the cell cycle." Dec. 37–38. In its Rehearing Request, Patent Owner argues that we misapprehended the evidence supporting Petitioner's argument that "a person of ordinary skill would understand that a compound that inhibits v-src also would inhibit c-src" in light of Akinaga 1991.¹⁰ Reh'g Req. 7. According to Patent Owner, Akinaga 1991 demonstrated "significant differences in activity, selectivity, and potency" between "UCN-01 and staurosporine," which is "compelling evidence that the mechanisms of action between UCN-01 and staurosporine are indeed different." *Id.* at 8–9; *see, e.g.*, Ex. 1035, Abstract (indicating that while staurosporine was 9 to 90 times more potent at inhibiting growth of tumor lines *in vitro*, only UCN-01

¹⁰ Shiro Akinaga et al., *Antitumor Activity of UCN-01, a Selective Inhibitor of Protein Kinase C, in Murine and Human Tumor Models*, 51 CANCER RES. 4888–92 (1991). Ex. 1035.

showed antitumor effects in xenograft models). Patent Owner further argues that Akinaga 1991 ascribes these functional differences between the two molecules as the result of “a hydroxyl at the C-7 position of the indolocarbazole moiety of staurosporine.” Reh’g Req. 10.

According to Patent Owner, Akinaga 1991 “shows that UCN-01 and staurosporine differ in a material way in mechanism of action and in structure, and thus people of ordinary skill in the art would not assume that UCN-01 and staurosporine have the same inhibitory behavior.” *Id.* at 2. Patent Owner, again, cites no expert testimony supporting its view of the understanding of one of ordinary skill in the art. In contrast, Dr. Eastman provided evidence that both molecules had similar effects on EGFR binding and were known to compete with ATP binding in the same way. Ex. 1002 ¶¶ 223–225. Because neither Dr. Eastman’s testimony, nor Petitioner’s arguments, demand that UCN-01 and staurosporine exhibit the same “activity, selectivity or potency,” as Patent Owner appears to suggest (*see* Reh’g Req. at 8–9), we credit Dr. Eastman’s testimony that: “As both staurosporine and UCN-01 were known to have this mechanism of action, a person of ordinary skill in the art would have logically predicted that UCN-01 would also inhibit EGF-stimulated tyrosine kinase activity.” *Id.* ¶ 224.

Finally, Patent Owner asserts that Dr. Eastman’s reasons for combining the asserted references are “conclusory and refuted by record evidence,” because Akinaga 1993 and Tam showed that UCN-01 and staurosporine, respectively, showed different effects on cell cycle progression in different model systems. *See* Reh’g Req. 10–11.¹¹ In

¹¹ Patent Owner also contends that at the Oral Hearing, we described Dr. Eastman’s reasons for combining the cited references as “pretty cryptic.”

particular, Patent Owner notes that Akinaga showed that UCN-01, administered alone “arrested the cell cycle transiently at the G1 phase,” whereas Tam showed that staurosporine was able to override G2 arrest induced by DNA damage. *See id.* at 11. Patent Owner presents no persuasive evidence regarding how one of ordinary skill in the art would have viewed a comparison carried out under such diverse conditions. Nor does Patent Owner address Akinaga’s finding that in combination with a DNA damaging agent—conditions more akin to those of Tam—UCN-01 resulted in a prolongation of the S (DNA synthesis) stage of the cell cycle. *See Ex. 1004, 187* (“In contrast, the combination of both drugs caused a S phase prolongation of 48 h (Fig. 4D).”). Accordingly, based on the totality of the record, we accept Dr. Eastman’s testimony that one of ordinary skill in the art would have had reason to combine the cited references. *See Dec. 37.*

In view of the above, we did not overlook or misapprehend the evidence relating to Akinaga 1991.

III. ORDER

For the reasons given, it is

ORDERED that Patent Owner’s Request for Rehearing is denied;

FURTHER ORDERED that our Final Written Decision of September 11, 2017, is republished solely to eliminate unintended font changes; Paper 43 is expunged.

Reh’g Req 10. We disagree with Patent Owner’s interpretation as the transcript clearly shows that we were referring to Petitioner’s demonstrative slides 39 and 40. *See Ex. 42, 38:10–16.*

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