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

PATENT OWNERS' NOTICE OF APPEAL

via PTAB E2E
Patent Trial and Appeal Board

via Hand Carry
Director of the United States Patent and Trademark Office
c/o Office of the General Counsel, 10B20
Madison Building East
600 Dulany Street
Alexandria, VA 22314

via CM/ECF
United States Court of Appeals for the Federal Circuit

Pursuant to 37 C.F.R. § 90.2(a), notice is hereby given that Patent Owners ARCH DEVELOPMENT CORP. and DANA-FARBER CANCER INSTITUTE, INC., ("Patent Owners") hereby appeal to the United States Court of Appeals for the Federal Circuit from the Decision Denying Request for Rehearing on the Final Written Decision of the Patent Trial and Appeal Board, entered on November 28, 2017, in case IPR2016-01034, Paper 46, the Final Written Decision, entered on November 28, 2017, Paper 45 (copies of Paper 45 and Paper 46 are attached as Appendix A), and from all underlying findings, orders, decisions, rulings, and opinions. This notice is timely filed within 63 days of the November 28, 2017, denial of rehearing of the Board's Final Written Decision dated September 11, 2017, Paper 43. 37 C.F.R. § 90.3(b). In accordance with 37 C.F.R. § 90.2(a)(3)(ii), Patent Owners indicate that the issues on appeal include, but are not limited to, the Board's determinations with respect to (i) patentability of claims 1-3, 5 and 6 of U.S. Patent No. 7,838,512 over the art, (ii) denial of Patent Owners' Motion to Exclude (Paper 37) as moot, and (iii) its findings supporting or relating to the aforementioned issues.

Patent Owners also indicate that the issues on appeal include any other issues decided adversely to Patent Owners in any orders, decisions, rulings, or opinions issued in the IPR proceeding.

A copy of this Notice of Appeal is being filed with the Patent Trial and Appeal Board as well as with the Director of the United States Patent and Trademark Office in accordance with 37 C.F.R. § 90.2(a)(1). In addition, this Notice of Appeal and the required fee are being submitted to the Clerk's Office for the United States Court of Appeals for the Federal Circuit.

Dated: January 26, 2018

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Attorneys For Patent Owner

I. CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

The undersigned hereby certifies that on January 26, 2018, a true and correct copy of the above-captioned "Patent Owners' Notice of Appeal" was filed electronically through the Patent Trial and Appeal Board's E2E System and was filed with the Director of the United States Patent and Trademark office c/o the Office of General Counsel via hand delivery to the following address:

Director of the United States Patent and Trademark Office
c/o Office of the General Counsel
United States Patent and Trademark Office
Madison Building East, Room 10B20
600 Dulany Street
Alexandria, VA 22314

II. CERTIFICATE OF FILING

The undersigned hereby also certify that on January 26, 2018, a true and correct copy of the above-captioned "Patent Owners' Notice of Appeal" was filed electronically with the Clerk's Office of the United States Court of Appeals for the Federal Circuit via CM/ECF, along with copies of the Final Written Decision (Paper 45) and the Decision Denying Request for Rehearing (Paper 46).

The undersigned hereby further certifies that the above-captioned "Patent Owners' Notice of Appeal" was served in its entirety on January 26, 2018, upon the following counsel of record for the Petitioner via electronic mail:

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APPENDIX A

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Paper No. 45
Entered: November 28, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

OSI PHARMACEUTICALS, LLC
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ARCH DEVELOPMENT CORP. and
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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*.

FINAL WRITTEN DECISION
Claims 1–3, 5, and 6 Shown to Be Unpatentable
35 U.S.C. § 318(a); 37 C.F.R. § 42.73

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–3, 5, and 6 (collectively, "the challenged claims") of U.S. Patent No. 7,838,512 B1 (Ex. 1001, "the '512 patent"). We have jurisdiction under 35 U.S.C. § 6. For the reasons that follow, we determine that Petitioner has shown, by a preponderance of the evidence, that claims 1–3, 5, and 6 of the '512 patent are unpatentable.

A. Procedural History

OSI Pharmaceuticals, LLC and Genentech, Inc., ("Petitioner")[1] filed a Petition requesting an *inter partes* review of claims 1–3, 5, and 6 of the '512 patent. Paper 3 ("Pet."). Arch Development Corp. and Dana-Farber Cancer Center Institute, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp."). Based on these submissions, we instituted an *inter partes* review of claims 1–3, 5, and 6 on the following grounds of unpatentability alleged in the Petition. Paper 9 ("Inst. Dec.").

[1] Petitioner further identifies Astellas US LLC, Astellas US Holding, Inc., Astellas Pharma Inc., and Roche Holdings, Inc. as real parties in interest. Pet. 4

Ground	References	Basis
II	Honma[2], in view of the knowledge of a person of ordinary skill in the art ("POSA"), Honma 1992,[3] and McGahon[4]	§ 103
IV	Akinaga,[5] in view of the knowledge of a POSA, Seynaeve,[6] Friedman,[7] and Tam[8]	§ 103

After institution of trial, Patent Owner filed a Patent Owner Response (Paper 16, "PO Resp."), to which Petitioner filed a Reply (Paper 34, "Reply").

In support of its challenges, Petitioner relies on the Declaration of Alan Eastman, Ph.D. (Ex. 1002). Patent Owner relies on the Declaration of first named inventor, Donald W. Kufe, M.D. (Ex. 2011).

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[2] Yoshio Honma et al., *Induction of Erythroid Differentiation of K562 Human Leukemic Cells by Herbimycin A, an Inhibitor of Tyrosine Kinase Activity*, 49 CANCER RES. 331–34 (1989). EX. 1003.
[3] Yoshio Honma et al., *Herbimycin A, an Inhibitor of Tyrosine Kinase, Prolongs Survival of Mice Inoculated with Myeloid Leukemia C1 Cells with High Expression of v-abl Tyrosine Kinase*, 52 CANCER RES. 4017–20 (1992). Ex. 1022.
[4] Anne McGahon et al., *BCR-ABL Maintains Resistance of Chronic Myelogenous Leukemia Cells to Apoptotic Cell Death*, 83 BLOOD 1179–87 (1994). Ex. 1029.
[5] Shiro Akinaga et al., *Enhancement of Antitumor Activity of Mitomycin C In Vitro and In Vivo by UNC-01, a Selective Inhibitor of Protein Kinase C*, 32 CANCER CHEMOTHERAPY AND PHARMACOLOGY 183–89 (1993). Ex. 1004.
[6] 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.
[7] 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.
[8] Sun W. Tam and Robert Schlegel, *Staurosporine Overrides Checkpoints for Mitotic Onset in BHK Cells*, 3 CELL GROWTH & DIFFERENTIATION 811–17 (1992). Ex. 1012.

Patent Owner filed a Motion to Exclude. Paper 37. Petitioner filed an Opposition (Paper 38), and Patent Owner filed a Reply (Paper 40). An oral hearing was held on June 20, 2017. A transcript of the hearing has been entered into the record. Paper 42 ("Tr.").

B. Related Proceedings

The '512 Patent is at issue in *Arch Development Corp. v. Genentech, Inc.*, No. 1:15-cv-6597 (N.D. Ill.), which is currently stayed. Pet. 4; Paper 6; Paper 20, 1.

C. The '512 Patent and Relevant Background

The '512 patent is directed to the use of DNA damaging agents in combination with tyrosine kinase inhibitors (TKIs) to enhance cancer cell death. *See generally* Ex. 1001, Title, Abstract, 4:12–40, 5:28–38. According to Petitioner's expert, Dr. Eastman, tyrosine kinases are enzymes that catalyze the phosphorylation of a substrate protein by attaching a phosphoryl group to a tyrosine amino acid residue on the substrate. Ex. 1002 ¶ 31. Tyrosine kinases were known to be involved in cell signaling pathways that control cell growth, differentiation, and cell death. Pet. 7 (citing Ex. 1002 ¶¶ 31–38). Elevated tyrosine kinase activity has also been associated with cancers because it can promote abnormal cell proliferation. *Id.* (citing Ex. 1002 ¶ 37).

According to the Specification, the treatment of cancer cells with ionizing radiation or chemotherapeutic agents such as the DNA alkylating agent, mitomycin C, results in DNA damage. Ex. 1001, 1:32–35, 3:51–65, 4:41–54. "The cellular response to DNA damage includes activation of DNA repair, cell cycle arrest, and lethality (Hall, 1988)." *Id.* at 1:32–35. As explained by Petitioner:

> By 1994, it was well known that the cell cycle involves progression through four phases: G1 (growth phase); S (copying of DNA); G2 (rapid growth in preparation for mitosis/cell division); M (mitosis/cell division). (Eastman Decl. ¶¶40-41 (Ex. 1002).) The cell cycle can arrest in G1, S and G2 to allow cells with damaged DNA to repair their DNA. (*Id.* ¶42.) In part, these "checkpoints" are regulated by tyrosine kinases. (*Id.* ¶44.) Cells with damaged DNA that advance to the M phase, however, cannot properly divide and instead die. (*Id.*)

Pet. 8. Consistent with this summary, the Specification points to prior art showing that environmental conditions following exposure to DNA damaging agents can influence cell survival. Ex. 1001, 1:38–55, 2:50–63. For example,

> cell survival can be increased if the cells are arrested in the cell cycle for a protracted period of time following radiation exposure, allowing repair of DNA damage. (Hall, 1988). Thus [potentially lethal damage] is repaired and the fraction of cells surviving a given dose of x-rays is increased if . . . cells do not have to undergo mitosis while their chromosomes are damaged."

Id. at 2:56–63. The Specification further states that "available evidence suggests that G_2 arrest is necessary for repair of DNA damage before entry into mitosis." *Id.* at 1:37–44; *see also id.* at 3:43–46. In particular, "[c]ells that are irradiated or treated with DNA damaging agents halt in the cell cycle at G_2, so that an inventory of chromosome damage can be taken and repair initiated and completed before mitosis is initiated." *Id.* at 3:3–7. "By preventing delays in G_2, cells will enter mitosis before the DNA is repaired and therefore the daughter cells will likely die." *Id.* at 3:46–48.

Recognizing that DNA damaging agents result in the activation of $p56/p53^{lyn}$ tyrosine kinase, a protein implicated in cell cycle control,[9] the

[9] Example 1 of the Specification discloses that the DNA damaging agent mitomycin C activates (via autophosphorylation) the tyrosine kinase

Specification proposes that tyrosine kinase inhibitors, such as genistein or herbimycin A, could force damaged cells to override the G_2 arrest checkpoint and enter mitosis before completing DNA repairs, and thereby enhance cell killing. *Id.* at 3:38–42, 5:28–32, 19:10–27. Accordingly, the '512 patent teaches "contact[ing] the cell with a DNA damaging agent and a tyrosine kinase inhibitor in a combined amount effective to kill the cell," i.e., such that "cell death is induced." *Id*. at 3:66–4:5.

D. Challenged Claims

Claims 1–3, 5, and 6 are in independent format. Claim 1 is illustrative (paragraphing and footnote added):

> 1. A method of improving chemotherapeutic intervention in a patient, the method comprising:
>
> (a) administering a chemotherapeutic[10] DNA damaging agent to the patient;
>
> (b) administering a therapeutically effective amount of a low molecular weight tyrosine kinase inhibitor to the patient,
>
> wherein the low molecular weight inhibitor binds intracellularly to inhibit the activity of more than one tyrosine kinase protein, and
>
> wherein the agent and the inhibitor act in combination by effecting a series of intracellular events to enhance cell death, thereby improving chemotherapeutic intervention.

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p56/p53^{lyn}, which, in turn, associates with and phosphorylates the tyrosine 15 residue (Tyr 15) of the p34^{cd2} polypeptide chain. *See* generally *id.* at 9:4–14:5. The cellular protein p34^{cd2} is a serine/threonine protein kinase that controls entry of cells into mitosis. *Id.* at 1:45–55, 13:21–22. Phosphorylation of p34^{cd2} at Tyr 15 inhibits the entry of cells into mitosis and, thus, promotes G_2 arrest. *Id.* at 13:27–32.

[10] *See* Ex. 1001, Certificate of Correction dated November 23, 2010 (adding the modifier "chemotherapeutic" to all claims).

Claims 2, 3, and 5 further specify that the tyrosine kinase inhibitor intracellularly inhibits phosphorylation of downstream effector molecules (claims 2, 3, and 5), "inhibit[s] the activity of [epidermal growth factor receptor] EGFR" (claim 3), and acts in combination with the DNA damaging agent "to enhance apoptosis" (claim 5).

In contrast to claims 1–3 and 5, claim 6 does not recite the enhancement of either cell death or apoptosis, but more broadly requires that the DNA damaging agent and the low molecular weight tyrosine kinase inhibitor "act in combination to alter the cell's response to the agent."

II. DISCUSSION

A. Principles of Law

Petitioner bears the burden of proving unpatentability of the challenged claims, and the burden of persuasion never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). To prevail, Petitioner must establish the facts supporting its challenge by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of

nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). A decision on the ground of obviousness must include "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The obviousness analysis "should be made explicit" and 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*, 550 U.S. at 418.

B. Person of Ordinary Skill in the Art.

The parties agree that a person of ordinary skill in the art as of the effective filing date of the '512 patent, "would have held an M.D. or Ph.D. in molecular biology, biochemistry, pharmacology, or a related field and have had several years of experience working in cancer research." Pet. 17 (citing Ex. 1002 ¶ 19); PO Resp. 4. This level of ordinary skill is consistent with the prior art asserted in the Petition. *See Chore-Time Equip., Inc. v. Cumberland Corp.*, 713 F.2d 774, 779 n.2 (Fed. Cir. 1983) (indicating that the prior art itself may reflect the appropriate level of ordinary skill in the art). Accordingly, we adopt the parties' definition for the purpose of this Decision.

C. Claim Construction

Petitioner asserts, and Patent Owner does not contest, that the '512 patent expired as of April 8, 2015. Pet. 17; Prelim. Resp. 8–9. Although we accord claims of an unexpired patent their broadest reasonable interpretation in light of the specification, our review of claims of an expired patent is similar to that of a district court. *See In re Rambus, Inc.*, 694 F.3d 42, 46 (Fed. Cir. 2013). Specifically, claim terms are given their ordinary and

customary meaning, as would be understood by a person of ordinary skill in the art at the time of the invention in light of the language of the claims, the specification, and the prosecution history of record. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313–17 (Fed. Cir. 2005) (en banc).

i. Administering a Therapeutically Effective Amount of a Low Molecular Weight Tyrosine Kinase Inhibitor

Petitioner proposes that the term "therapeutically effective amount," as used in the claim phrase "administering a therapeutically effective amount of a low molecular weight tyrosine kinase inhibitor," be accorded its plain and ordinary meaning of "an amount that would be sufficient to have a desired therapeutic effect." Pet. 19–21 (citing, *e.g.*, Ex. 1002 ¶¶ 79–80). Patent Owner admits that Petitioners' proposed definition of the plain and ordinary meaning of the term "may be correct" (Prelim. Resp. 7), but contends that the Board should instead apply an express definition of "therapeutically effective amount" set forth in the Specification (PO Resp. 5–8).

Patent Owner points to column 4, lines 16 to 19 of the Specification, which defines a "therapeutically effective amount" as "an amount of a DNA damaging agent and tyrosine kinase inhibitor that, when administered to an animal in combination, is effective to kill cells within the animal." *Id.* at 5. The challenged claims, however, use "therapeutically effective amount" in a context different from the express definition set forth in the Specification. As noted by Petitioner, the definition at column 4, lines 16 to 19 of the Specification refers to "a *combined* amount of the DNA damaging agent and the tyrosine kinase inhibitor, while the claims require that *only* the tyrosine kinase inhibitor be administered in a 'therapeutically effective amount.'" *See* Pet. 20.

In response, Patent Owner points to the Specification's teaching that "[t]herapeutically effective combinations are thus generally combined amounts of DNA damaging agents and tyrosine kinase inhibitors that function to kill more cells than either element alone and that reduce the tumor burden" (Ex. 1001, 4:21–25), which, according to Patent Owner, indicates that "the inventors of the '512 patent expressly contemplated that both the claimed tyrosine kinase inhibitor and chemotherapeutic damaging agent are each capable of killing cells, *i.e.*, each may be administered in a 'therapeutically effective amount.'" PO Resp. 5. We do not find this argument persuasive.

First, the term "therapeutically effective combinations," as defined in the cited passage, is not found in any of the challenged claims. Second, that the tyrosine kinase inhibitor and the chemotherapeutic DNA damaging agent are each *capable* of killing cells is not dispositive as to whether the challenged claims *require* them to be present in individually cytotoxic amounts. Similarly, that the combination of agents "function to kill more cells than either element alone" does not indicate that either agent is necessarily present in an individually cytotoxic amount, particularly in light of the Specification's teaching that the combination may have synergistic effects on cell death. *See* Ex. 1001, 4:5–10*; see also id.* at 4:42–15 ("The term 'in a combined amount effective to kill the cell' means that the amount of the DNA damaging agent and inhibitor are sufficient so that, when combined within the cell, cell death is induced."). Thus, the passage relied on by Patent Owner (column 4, lines 21–25) encompasses an amount of tyrosine kinase inhibitor that is insufficient to kill cells alone, yet enhances cell killing in combination with a chemotherapeutic damaging agent.

Patent Owner also contends that its proposed definition of "a therapeutically effective amount" is "consistent with the stated aim of the claimed invention, i.e., the 'synergistic cancer cell killing effects.'" PO Resp. 6. We, however, agree with Petitioner, "[E]ven if one of the stated purposes of the invention is as Patent Owners contend . . . , this cannot overcome the ordinary meaning of the term as used in the claims." Reply 6 (citing *E-Pass Techs., Inc. v. 3Com Corp.*, 343 F.3d 1364, 1370 (Fed. Cir. 2003) ("An invention may possess a number of advantages or purposes, and there is no requirement that every claim directed to that invention be limited to encompass all of them.")).

Patent Owner further argues that we should adopt its construction to maintain internal consistency among the claims. *See* PO Resp. 7–8. As we understand the argument, Patent Owner contends that each of claims 1–3 and 5 require "cell death" or apoptosis (defined as "a series of intracellular events that lead to cell death") such that "the express 'desired therapeutic effect' is cell death." *Id.* at 8. We are not persuaded that internal consistency informs the meaning of "administering a therapeutically effective amount of a low molecular weight tyrosine kinase inhibitor" because, although claims 1–3 and 5 require that the chemotherapeutic agent and the tyrosine kinase inhibitor "act in combination to enhance cell death [or apoptosis]," claim 6 recites that "the agent and the inhibitor act in combination *to alter the cell's response to the agent*." Emphasis added. Accordingly, the "desired therapeutic effect" in claim 6 is potentially broader than that of claims 1–3 and 5.

Where the Specification reveals a special definition for a claim term, the inventors' lexicography governs. *Phillips*, 415 F.3d at 1316. Any such special definition must be set forth in the specification with reasonable

clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). On the present record, we are not convinced that the inventors' express definition of "therapeutically effective amount" applies to the tyrosine kinase inhibitor as set forth in the challenged claims, as opposed to the combination of inhibitor and DNA damaging agent referenced at column 4, lines 16 to 19 of the Specification. Accordingly, we construe "therapeutically effective amount" as used in the claim phrase, "administering a therapeutically effective amount of a low molecular weight tyrosine kinase inhibitor" according to its plain and ordinary meaning of "an amount that would be sufficient to have a desired therapeutic effect."

ii. Cell Death and Apoptosis

Claims 1–3 of the '512 Patent recite that "the [chemotherapeutic] agent and the [tyrosine kinase] inhibitor act in combination to enhance cell death"; in claim 5, the two components "act in combination to enhance apoptosis." Noting that the '512 patent expressly provides that "[t]he terms, 'killing', 'programmed cell death' and 'apoptosis' are used interchangeably" to describe "a series of intracellular events that lead to target cell death" (Ex. 1001, 5:35–38), we previously agreed with the parties' proposed construction of "apoptosis" as meaning "a series of intracellular events that lead to target cell death." *See* Dec. 11.[11] In light of the same passage in the Specification, we likewise construe "cell death" as also meaning "a series of intracellular events that lead to target cell death." It is our understanding

[11] While we recognize Patent Owner's argument that "not all cell death is apoptotic in nature" (PO Resp. 14), we rely here on the express definition in the Specification. Moreover, for purposes of this Decision, we need not distinguish apoptosis from cell death generally, as the result would be the same.

that the parties do not oppose this construction. *See* Tr. 13:9–17, 19:5–12, 22:18–20, 51:4–52:1.

The parties vigorously disagree, however, whether cell death and apoptosis should be understood as the proximal cause of a low molecular weight tyrosine kinase inhibitor acting in combination with a chemotherapeutic agent, or whether these terms further include the induction of differentiation processes, wherein cancer cells are rendered "mortal and naturally die after a limited lifespan." *See, e.g.*, Tr. 26:20–27:4; Pet. 31; PO Resp. 12–14; Reply 7–8.

Petitioner contends that the challenged claims "have no immediacy limitation," such that the terms "enhanc[ing] cell death" and "enhancing apoptosis" encompass inducing an otherwise immortal cancer cell to differentiate and, eventually, die. Reply 7; Pet. 29; *see* Ex. 1002 ¶¶ 125–128. According to Petitioner, "[d]ifferentiation is the process by which precursor cells undergo a series of changes—including intracellular events—to become a more specialized cell. When cells reach the point that they can differentiate no more, they are terminally differentiated, in which state they live out their days and die." Pet. 29 (citations and footnote omitted).

Patent Owner argues that the '512 Patent is directed to "enhancing cancer cell death," which does not include "natural cell death," i.e., "waiting for . . . differentiated cells to die naturally." PO Resp. 12–13 (citing Ex. 1001, Abstract). According to Patent Owner, "[n]ot a single embodiment disclosed in the '512 patent results in . . . cell differentiation" (PO Resp. 6), and moreover, "the Specification of the '512 patent uses the terms "cell death" or "cell killing" 30 times but only once uses the word "differentiation" (Tr. 42:15–43:5; *see* Ex. 1001, 2:26–27 ("Protein tyrosine

phosphorylation contributes to the regulation of cell growth and differentiation.")).

Consistent with Patent Owner's analysis, nowhere does the Specification suggest that the inventors contemplated the induction of a differentiation pathway. *See* Ex. 2011 ¶ 4. To the contrary, and as discussed above in Section 1(C), the Specification focuses on the use of DNA damaging agents in combination with tyrosine kinase inhibitors to force damaged cells to override the G_2 arrest checkpoint and enter mitosis before completing DNA repairs. *See, e.g.*, Ex. 1001, 3:46–48 ("By preventing delays in G_2, cells will enter mitosis before the DNA is repaired and therefore the daughter cells will likely die."). Accordingly, we agree with Patent Owner that, in light of the Specification, one of ordinary skill in the art would not understand the terms "enhanc[ing] cell death" and "enhancing apoptosis" to encompass the a process by which cancer cells are differentiated, become mortal, and, subsequently, "live out their days and die." *See* Pet. 29; Ex. 1002, ¶ 127.

In reaching this determination, we recognize Petitioner's argument that the challenged claims include no mechanism of action. Reply 8. We disagree with that assessment to the extent the plain language of the claims requires that the chemotherapeutic agent and the low molecular weight tyrosine kinase inhibitor generally "act in combination by effecting a series of intracellular events." Although Petitioner may be correct that nothing in the claims requires that "'enhance[d] cell death' must be due to the TKI 'acting as a tyrosine kinase inhibitor'" (*see id.*), our reviewing court instructs that "we strive to capture the scope of the actual invention, rather than . . . allow the claim language to become divorced from what the specification conveys is the invention." *Retractable Techs., Inc. v. Becton, Dickinson &*

Co., 653 F.3d 1296, 1305 (Fed. Cir. 2011) (citing *Phillips*, 415 F.3d at 1323–34). In the present case, we do not find that the Specification conveys to one of ordinary skill in the art that "enhanc[ing] cell death" or "enhancing apoptosis" encompasses a process involving differentiation and eventual cell death.

We also find persuasive the following passage from the prosecution history of the '512 Patent in which Applicants made clear that inducing differentiation is not the same as cell killing:

> Watanabe *et al.* appears to be concerned only with showing that inhibitors of tyrosine kinases, such as genistein, are able to induce, in combination with mitomycin C, the differentiation of mouse erythroleukemia cells. A skilled artisan, reading Watanabe, would merely conclude that such treatment is useful only for forcing cells into a terminally differentiated state. There is no teaching or suggestion that such a combination would be useful for increasing cell killing.

Ex. 1016, 6; s*ee also id.* at 8 ("[U]nlike the results shown in Watanabe wherein a protein tyrosine kinase inhibitor induced differentiation, the instant invention shows increased cell killing in combination with DNA damaging agents."). Applicants' assertion was repeatedly discussed during this proceeding. *See* PO Resp. 3; Pet. 29 n.3; Reply 6 n.4; Tr. 12:2–13:19.

Petitioner takes the position that 1) irrespective of the Applicants' statements during prosecution, "the specification is the controlling interpretation"; moreover, 2) the file history is less relevant because "the word 'killing' is not actually used in any of the challenged claims." Tr. 13:3–16. With respect to Petitioner's first argument, there is no dispute that apoptosis and cell death refer to "a series of intracellular events that lead to target cell death," as set forth in column 5, lines 35–38 of the Specification. To the extent that definition is "controlling," it provides only

the general outlines of the claim term. In order to determine whether the expressly recited definition encompasses cellular differentiation processes that render cancer cells mortal, as Petitioner contends, we consider all of the intrinsic evidence, including the prosecution history. *See Phillips*, 415 F.3d at 1317.

With respect to Petitioner's argument that "the word 'killing' is not actually used in any of the challenged claims," we note that the Specification uses interchangeably the terms "killing," "programmed cell death," and "apoptosis." The following passage of the Specification expressly sets forth this equivalency:

> To achieve cell killing, both agents are delivered to a cell in a combined amount effective to kill the cell, i.e., to induce programmed cell death or apoptosis. The terms, "killing", "programmed cell death" and "apoptosis" are used interchangeably in the present text to describe a series of intracellular events that lead to target cell death.

Ex. 1001, 5:32–38. Read in the context of the Specification, we conclude that one of ordinary skill in the art would understand "cell killing" in the prosecution history as synonymous with the claim terms "cell death" and "apoptosis." Petitioner presents no evidence to the contrary. Thus, to the extent the Specification provides a controlling, albeit general, definition of the claim terms, it does not convey to one of ordinary skill in the art that "cell death" or "apoptosis" encompasses a process involving differentiation and eventual cell death.

iii. Non-limiting Elements

The parties agree that the preamble of each challenged claim, as well as the "thereby" clause of claims 1–3 ("thereby improving chemotherapeutic intervention"), are non-limiting. Pet. 17–18, 21–22; Prelim. Resp. 5, 8; Ex. 2001, 15. On the present record, we adopt the parties' proposed

interpretation of these claim elements. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999) (instructing that only those terms that are in controversy need be construed, and only to the extent necessary to resolve the controversy).

D. Ground II: Obviousness over Honma, in view of the knowledge of a POSA, Honma 1992, and McGahon

Petitioner asserts that claims 1–3, 5, and 6 would have been obvious over the combination of Honma, in view of the knowledge of a person of ordinary skill in the art, Honma 1992, and McGahon. *See* Pet. 2, 22–41; Reply 10–17. Having considered the full trial record, we determine that Petitioner has not shown by a preponderance of evidence that claims 1–3 and 5 are unpatentable as obvious over the cited references, but we determine that Petitioner has met its burden with respect to claim 6.

Petitioner addresses the individual limitations of the challenged claims at length, including in a detailed claim chart. *See* Pet. 2, 22–41; Reply 10–17. We begin with an overview of the asserted references.

i. Overview of Asserted References

1. Honma (Ex. 1003)

Honma teaches that herbimycin A, "a selective inhibitor of intracellular tyrosine kinase," induces erythroid differentiation of K562 human leukemic cells in a dose-dependent manner, as measured by benzidine staining. Ex. 1003, Abstract, 331–332. Herbimycin A was also found "to inhibit the growth of K562 cells at concentrations higher than 6×10^{-8} M, [with] 50% inhibition of growth occurring at 9.5×10^{-8} M" and 65% inhibition of growth at 1×10^{-7} M. *Id.* at 332, Fig. 1. According to Honma, "the effective concentration [of herbimycin A] was noncytotoxic." *Id.* at 333. In investigating the mechanism for these effects, Honma determined that "[w]hen K562 cells were labeled with $^{32}P_i$ in the presence of 5×10^{-8} M herbimycin A, the level of all tyrosine-phosphorylated proteins was greatly reduced," including a reduction of approximately 55% of the tyrosine kinase $p210^{c\text{-}abl}$. *Id.* at 333.

Honma also examined the effect of herbimycin A in combination with other inducers of erythroid differentiation in K562 cells, including the DNA damaging agent Adriamycin. *Id.* at 333. Honma concludes that "a low concentration of herbimycin A increases inhibition of cell growth of K562 cells by Adriamycin," and the combination has "additive or more than additive effects on [erythroid differentiation]." *Id.*; *see id.* at Figs. 4, 5. Honma concludes that "herbimycin A and the other differentiation inducers have additive or more than additive effects on induction of benzidine-positive cells in suboptimal concentrations (Fig. 4)." *Id.*

In light of these results, Honma suggests that "tyrosine kinase activity may be critically involved in growth control mechanism of K562 cells, possibly as a result of induction of terminal differentiation." *Id.*

"Herbimycin A and its derivatives might be useful as cancer chemotherapeutic agents against some types of leukemia oncogenesis where tyrosine kinase activities are implicated." *Id.* And, "[s]ince herbimycin A can have an additive or more than additive effect with some well-known antitumor agents such as Adriamycin . . . [,] these combinations may be useful for the treatment of some types of leukemia." *Id.*

2. Honma 1992 (Ex. 1022)

According to Honma 1992:

> Chronic myelogenous leukemia and some cases of acute lymphocytic leukemia are characterized by the Philadelphia t(9;22)(q32;q11) chromosome translocation, in which the 5' sequences of the *bcr* gene become fused with the c-*abl* protooncogene. The resulting genes encode proteins with high activity as protein tyrosine kinases . . . . [and t]he transforming activity of the chimeric gene is closely associated with its tyrosine kinase activity.[12]

Ex. 1022, 4017. Honma 1992 also notes that herbimycin A "inhibits the activities of protein tyrosine kinases encoded by several oncogenes . . . . including v-*src*, v-*abl*, and *bcr-abl*." *Id.* Accordingly, Honma 1992 proposes that "a selective inhibitor of tyrosine kinase activity might be useful in chemotherapy of some leukemias with the Philadelphia chromosome." *Id.*

[12] According to Dr. Eastman, "[t]he protein c-Abl is a normal kinase with a molecular weight around 120 kDa. The protein called p210c-*abl* was originally thought to be a mutated form of c-Abl, but was later identified to be a fusion protein that includes part of the c-Abl protein and part of another protein, called Bcr. The fusion protein, originally called p210c-*abl*, became more commonly known as Bcr-Abl." Ex. 1002 ¶ 88 n.2.

With this background, Honma 1992 focuses on experiments using the viral homolog of c-*abl*.[13] In particular, Honma 1992 explains that the mouse C1 cell line comprises "megakaryoblastic cells established by coinfection with Abelson murine leukemia virus and recombinant SV40," which express high levels of v-*abl*. *Id.* (footnote omitted); *id.* at Abstract. "These cells are induced to differentiate into megakaryocytes by treatment with some inhibitors of tyrosine kinase, including herbimycin A, and inhibition of their v-*abl* tyrosine kinase activity is preceded by induction of their differentiation." *Id.*; *see also id.* at 4019 ("Herbimicyin A . . . induces differentiation of C1 cells.").

Honma 1992 teaches that, whereas nude mice inoculated with 10^6 C1 cells died of leukemia within 30 days, "[a]dministration of herbimycin A significantly enhanced the survival of mice inoculated with C1 cells." *Id.* at Abstract; *see also id.* at 4019. Honma 1992, thus, concludes that, the "differentiation-inducing and growth-inhibitory effects [of herbimycin A] are compatible with its effects in prolonging survival of mice inoculated with leukemia cells." *Id.* at 4019. According to Honma 1992, "[t]he present results suggest that herbimycin A and related compounds may be very effective for eliminating malignant cells from the bone marrow of patients with leukemias in which tyrosine kinase activity is implicated as a determinant of the oncogenic state." *Id.* at 4020.

[13] *See* Ex. 1002 ¶ 36 (explaining, with respect to v-src and its human homolog c-src, that "[t]he "v" and "c" stand for viral and cellular, respectively"); *id.* ¶¶ 199–202; Tr. 59:1–2.

3. McGahon (Ex. 1029)

McGahon teaches that K562 is a chronic myelogenous leukemia cell line (CML) expressing the Bcr-Abl fusion protein. Ex. 1029, Abstract. McGahon further teaches that K562 cells are "particularly resistant to cell death via apoptosis" (*id.* at 1185) and suggests that *bcr-abl* "acts as an anti-apoptosis gene in CML cells" and that its "effect is dependent on the *abl* kinase activity." *Id.* at Abstract; *see also id.* at 1184 (suggesting "the root cause" of CML "is an elevation in the activity of the *ABL* protein when it is produced as an *BCR-ABL* chimera"). McGahon demonstrates the use of anti-sense oligonucleotides to down-regulate Bcr-Abl protein expression and, thus, reduce Bcr-Abl tyrosine kinase activity, which rendered the treated cells susceptible to induction of apoptosis by chemotherapeutic agents. *Id.* at Abstract, 1180–1184, Figs. 1–5.

According to McGahon, "the *abl* gene was a potent suppressor of apoptosis." *Id.* at 1185. In CML, "deregulated expression of *bcr-abl* . . . may contribute to an increase in tumor cell number by inhibition of apoptosis, and this can also contribute to resistance to the induction of cell death by therapeutic agents or treatments." *Id.* But because "inhibiting expression of the BCR-ABL protein primes the cells for apoptosis induced by a second stimulus," "[b]y re-opening the apoptotic pathway, cells can be rendered susceptible to induction of apoptosis through DNA damage." *Id.* Accordingly, "[i]nhibition of *bcr-abl* to render CML cells susceptible to apoptosis can be combined with therapeutic drugs and/or treatment capable of inducing apoptosis to provide an effective strategy for elimination of these cells." *Id.* at Abstract.

ii. Analysis of Ground II: Claims 1–3 and 5

Petitioner argues that the primary reference, Honma, "teaches exactly what the '512 patent later claimed—i.e., using a low molecular weight tyrosine kinase inhibitor (herbimycin A, one of the preferred inhibitors disclosed in the '512 patent) in combination with a chemotherapeutic DNA damaging agent (Adriamycin) to treat cancer." Pet. 2; *see id.* at 23 (citing, *e.g.*, Ex. 1003, Abstract). With respect to the requirement that the DNA damaging agent and the tyrosine kinase inhibitor act in combination to enhance cell death (claims 1–3) or apoptosis (claim 5), Petitioner equates the differentiation of K562 cells in Honma with (eventual) cell death. Pet. 30 (citing Ex. 1002 ¶¶ 124–129); Reply 10–12. In particular, Petitioner argues (1) that Honma's "Adriamycin/herbimycin A combination causes immortal cells to become mortal, thereby enhancing cell death." *Id.* at 30 (citing, *e.g.*, Ex. 1002 ¶¶ 124–129). In section II(C)(ii) above, we construe cell death and apoptosis as "a series of intracellular events that lead to target cell death" that does not encompass the induction of a differentiation process, whereby cancer cells are rendered mortal and naturally die after a limited lifespan. In light of our construction, we agree with Patent Owner that Honma does not teach enhancing cell death or apoptosis. *See* PO Resp. 9–14.

In the alternative, Petitioner argues that because Adriamycin and herbimycin A, individually, were known to cause cell death, one of ordinary skill in the art would have understood that Honma's combination of these two compounds would as well. *Id.* at 31 (citing Ex. 1002 ¶131–134;

Ex. 1034;[14] Ex. 1026[15]); *see also* Reply 12–14 (arguing that Honma and other prior art references "are not inconsistent with cell death"). Petitioner does not, however, persuade us that one of ordinary skill in the art would have believed that the concentration of herbimycin A taught by Honma was cytotoxic to K562 cells, either alone or in combination with Adriamycin. To the contrary, as noted in Section II(D)(i)(1) above, Honma documents the growth inhibitory and differentiation-inducing effects of low concentrations of Adriamycin. *See, e.g.*, Ex. 1003, 333 (noting that "a low concentration of herbimycin A increases inhibition of cell growth of K562 cells by Adriamycin" and that "the effective concentration [of herbimycin A] was noncytotoxic"). Further, upon determining that Adriamycin in combination with the tyrosine kinase inhibitor herbimycin A induces erythroid differentiation of K562 human leukemic cells, rather than teaching cell death or apoptosis, Honma suggests that the combination may be clinically useful for differentiation therapy.[16]

Petitioner further cites Honma 1992 as disclosing that treatment of K562 cells with herbimycin A inhibits $p210^{c\text{-}abl}$ —a tyrosine kinase also known as Bcr-Abl. Pet. 36 (citing, *e.g.*, Ex. 1002 ¶¶ 122–123, 158). Pointing to McGahon as teaching that inhibition of Bcr-Abl tyrosine kinase expression using anti-sense oligonucleotides renders K562 cells susceptible to apoptosis caused by DNA damaging agents, Petitioner argues that one of

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[14] Andrzej Skladanowski and Jerzy Konopa, *Adriamycin and Daunomycin Induce Programmed Cell Death (Apoptosis) in Tumour Cells*, 46 BIOCHEMICAL PHARMACOLOGY 375–82 (1993).
[15] Declaration Under 37 C.F.R. § 1.132 of Ralph R. Weichselbaum.
[16] Honma 1992 refers to chemotherapeutic treatments that induce leukemia cell differentiation as "differentiation therapy." *See* Ex. 1022, 4019.

ordinary skill in the art "would have understood McGahon to demonstrate that administering Honma's combination enhances apoptosis, and would have understood enhanced apoptosis to be a likely cause of the antiproliferative effects reported in Figure 5 of Honma." Pet. 42–43 (citing Ex. 1002 ¶¶ 182–183).

Although Petitioner's expert interprets Honma Figure 5 as "consistent with an enhancement of apoptosis" (Ex. 1002 ¶ 183), we weigh this testimony against 1) the countervailing testimony of Dr. Kufe that "Honma's work is premised on the use of a non-cytotoxic dosage of the Adriamycin/ herbimycin A combination" (Ex. 2011 ¶ 12); 2) the express teaching in Honma that Figure 5 shows "[e]nhancement . . . of antiproliferative activity" (Ex. 1003, Fig. 5, legend); and 3) Honma's conclusion "that tyrosine kinase activity may be critically involved in growth control mechanism of K562 cells, possibly as a result of induction of terminal differentiation" (*id.* at 333). On balance, we are not convinced that Petitioner has shown, by a preponderance of the evidence, that Honma teaches or suggests cell death or apoptosis as opposed to antiproliferative activity and differentiation. Accordingly, we do not find Petitioner's argument persuasive.

Having considered the parties' arguments and evidence, we conclude that Petitioner has failed to satisfy its burden of demonstrating, by a preponderance of the evidence, that the subject matter of claims 1–3 and 5 of the '512 patent would have been obvious over the combination of Honma, in view of the knowledge of a person of ordinary skill in the art, Honma 1992, and McGahon.

iii. Analysis of Ground II: Claim 6

The above analysis of claims 1–3 and 5 turns on whether a DNA damaging agent and a low molecular weight tyrosine kinase inhibitor "act in combination by effecting a series of intracellular events to enhance cell death / apoptosis." This element is not found in claim 6, which instead recites that the DNA damaging agent and a low molecular weight tyrosine kinase inhibitor "act in combination to alter the cell's response to the [DNA damaging] agent."

According to Petitioner, "Honma discloses this limitation by teaching tyrosine kinase inhibition by herbimycin A." Pet. 39. In particular, Petitioner contends that Honma Figure 5

> demonstrates (1) that herbimycin A alone had almost no effect on cell number after 5 days over a dose range from 1×10^{-8} M to 5×10^{-8} M; and (2) that, at a constant concentration of Adriamycin, K562 cell numbers decreased as the concentration of herbimycin A increased. Honma teaches that these results "indicate that a low concentration of herbimycin A increases inhibition of cell growth of K562 cells by Adriamycin.

Pet. 40 (citations omitted); *see* Reply 9. Accordingly, Petitioner asserts that "[a] POSA would have understood Figure 5 and its supporting discussion to show that herbimycin A, the inhibitor, alters the cell's response to Adriamycin, the agent, as required by this limitation of claim 6." Pet. 40–41 (citing Ex. 1002 ¶ 168).

Petitioner further argues that Honma discloses all elements of claim 6 including the requirement that the low molecular weight tyrosine kinase inhibitor "bind intracellularly to alter substrate function by inhibiting substrate phosphorylation." Pet. 39–40; *see id.* at 43–45. Although, like claims 1–3 and 5, claim 6 recites "administering a therapeutically effective amount of a low molecular weight tyrosine kinase inhibitor to the patient,"

we are not persuaded by Patent Owner's argument that "a therapeutically effective amount," as used in these claims, comprises an amount of a DNA damaging agent and tyrosine kinase inhibitor that, when administered to an animal in combination, is effective to kill cells within the animal. *See supra* section II(C)(i). Patent Owner does not otherwise oppose Petitioner's arguments with respect to claim 6.

In light of our construction of "therapeutically effective amount" as "an amount that would be sufficient to have a desired therapeutic effect," we find that Honma discloses all elements of claim 6. Accordingly, we conclude that Petitioner has demonstrated, by a preponderance of the evidence, that the subject matter of claim 6 of the '512 patent would have been obvious over the combination of Honma, in view of the knowledge of a person of ordinary skill in the art, Honma 1992, and McGahon.

E. Ground IV: Obviousness over Akinaga, in view of the knowledge of a POSA, Seynaeve, Friedman, and Tam

Petitioner asserts that claims 1–3, 5, and 6 would have been obvious over the combination of Akinaga, in view of the knowledge of a person of ordinary skill in the art, Seynaeve, Friedman, and Tam. *See* Pet. 2–3, 42–67; Reply 17–26. Having considered the full trial record, we determine that Petitioner has shown by a preponderance of evidence that claims 1–3, 5, and 6 are unpatentable as obvious over the cited references.

Petitioner addresses the individual limitations of the challenged claims at length, including in a detailed claim chart. *See* Pet. 2–3, 42–67; Reply 17–26. We begin with an overview of the asserted references.

i. Overview of Asserted References

1. Akinaga

Akinaga examines the effect of UCN-01 (7-hydroxy-staurosporine) alone, and in combination with the DNA damaging agent mitomycin C ("MMC"). *See* Ex. 1004, Abstract; *see also id.* at Fig. 1 (showing chemical structures of UCN-01 and staurosporine). Noting that MMC caused delays in the S and G_2M phases of the cell cycle, whereas UCN-01 blocked the cell cycle progression at G_1, Akinaga concludes that "[t]hese findings [provide] a strong indication for combining both drugs." Ex. 1004, 188.

Akinaga reports that in *in vitro* studies using A431 human epidermoid carcinoma cells, "UCN-01 potentiated the antiproliferative activity of mitomycin C." *Id.* at Abstract. Referencing the in vitro analysis summarized in Figure 3, Akinaga reports that "Isobologram analysis revealed that the interaction of UCN-01 with MMC was synergistic in its antiproliferative activity" (*id.*), in particular, "[o]n the basis of the data in Fig. 3, we conclude that UCN-01 and MMC exert an additive cytostatic effect and a synergistic cytotoxic effect" (*id.* at 183).

In vivo studies using xenografted human epidermoid carcinoma A432 cells in nude mice similarly showed that "the combination of both drugs in a single i.v. injection exhibited greater antitumor activity than MMC and UCN-01 alone ($P<0.01$)." *Id.*; *see id.* at 187. Akinaga reports that "[t]his synergistic antitumor effect was also confirmed in two other solid tumor cell lines, i.e. human xenografted colon carcinoma Co-3 and murine sarcoma 180," as well as in a "P388 leukemia model, in which we saw an increased lifespan of mice when UCN-01 was combined with MMC." *Id.* at Abstract; *see id.* at 187–188. According to Akinaga, "[t]hese results suggest the feasibility of using UCN-01 in clinical oncology, especially with alkylating

agents such as MMC. In addition, this combination therapy might be a novel chemotherapeutic approach to MMC-insensitive tumors in clinical trials." *Id.* at 183.

Akinaga describes UCN-01 as "a potent and selective inhibitor of protein kinase C (PKC)" and "suggest[s] that the selective inhibition of PKC by UCN-01 might contribute to the enhancement of the antiproliferative activity of MMC." Ex. 1004, Abstract, 183. Akinaga also presents, in Table 1, evidence that UCN-01 inhibits other kinases, including the tyrosine kinase $pp60^{v\text{-}src}$ and "suggests that UCN-01 exhibits its antitumor activity by the inhibition of PKC *and/or other protein kinases*." *Id.* at 183, 184 (emphasis added). Akinaga concludes:

> To our knowledge this is the first report that an inhibitor of PKC and/or other protein kinases can enhance the antitumor activity of MMC in vivo as well as in vitro. Although little is known about the mechanism(s) of the combined effect of UCN-01 and MMC, the results of our in vivo studies strongly suggest that this novel combination chemotherapy may merit clinical trials in cancer patients.

Id. at 189.

2. Seynaeve

Seynaeve states that UCN-01 "has the demonstrated capacity to inhibit a number of kinases at nanomolar concentrations including PKC (IC_{50} = 4.1 nm), PKA (IC_{50} = 42 nm), and $p60^{v\text{-}src}$ protein tyrosine kinase (IC_{50} = 45 nm). Ex. 1014, 2081 (footnotes omitted); *see also id.* at Abstract ("UCN-01 . . . [has] "the capacity to inhibit a number of tyrosine and serine/threonine kinases."). Seynaeve demonstrates that UCN-01 reduces tyrosine phosphorylation of four cellular proteins of *Mr* 33,000, 57,000, 83,000, and 175,000 in MDA-MB468 breast carcinoma cells. *Id.* at 2084–85, Fig. 7. Noting that "UCN-01 . . . decreased tyrosine phosphorylation of

at least 4 proteins as arrest in G_1 becomes apparent" (*id.* at 2085), Seynaeve proposes a link between UCN–01's inhibitory effects on tyrosine kinases and its inhibitory effects on the cell cycle. In particular:

> The development of G_1 to S block correlates with the persistent inhibition of total phosphate labeling and tyrosine phosphorylation of discrete cellular phosphoproteins. . . .
>
> Most notable is the decrease of phosphorylation in the M_r 33,500 protein species, and the inhibition of tyrosine phosphorylation in the approximately M_r 83,000 protein at a time when the transition from G_1 to S is occurring in these cells."

Id. at 2085.

3. Tam

Tam teaches that "[s]taurosporine is a potent general protein kinase inhibitor that can suppress *in vitro* the activity of phospholipid Ca^{2+}-dependent and cyclic nucleotide-dependent serine/threonine protein kinases as well as the tyrosine kinases $p60^{v\text{-}src}$ and epidermal growth factor receptor [EGFR]" Ex. 1012, 811; *see also id.* at 816 ("*in vitro* IC_{50} levels for staurosporine are in the range of 3–8 nm for cyclic nucleotide- and Ca^{2+}-dependent serine/threonine kinases and for certain tyrosine kinases").

Tam further teaches that "DNA damage prolongs the G_2 phase of the cell cycle. This delay allows additional time for repair of DNA before mitotic onset and increases cell survival." *Id.* at 815 (footnotes omitted). Tam demonstrates that staurosporine "can uncouple mitosis from the completion of DNA replication and override DNA damage-induced G_2 delay." *Id.* at Abstract; *see id.* at 815. Thus, in suppressing G_2 delay in cells that have suffered DNA damage, "staurosporine bypasses normal checkpoints for mitotic onset" and "induces premature mitosis in cells that contain incompletely replicated genomes." *Id.* at 811.

4. Friedman

Friedman discloses that "[s]taurosporine is a potent microbial inhibitor of a number of protein kinases, including protein kinase C, cyclic AMP-dependent kinase, and the tyrosine kinase $pp60^{src}$. Ex. 1031, Abstract. The IC_{50} for the inhibition of these kinases by staurosporine "are within the same order of magnitude, ranging from 3 to 30 nm." *Id.* at 533; *see also id.* at 536 (stating that "staurosporine is a kinase inhibitor with a wide specificity that extends to certain tyrosine kinases").

Friedman further discloses that "[s]taurosporine is an effective inhibitor of the EGF-stimulated receptor tyrosine kinase *in vitro*" (*id.* at Abstract) and similarly states that "staurosporine is an effective inhibitor of the EGF receptor tyrosine kinase and could block stimulation of the kinases in vivo" (*id.* at 536). Friedman suggests that staurosporine inhibits EGFR tyrosine kinase activity by "interacting with the ATP-binding domains of the EGF receptor." *Id.* at 538.

ii. Analysis of Ground IV

With respect to Ground IV, we adopt Petitioner's claim chart showing where each limitation is taught or suggested in the prior art. *See* Pet. 64–67. We address below Patent Owner's arguments that the cited references are deficient and that Petitioner has not established sufficient motivation to combine Akinaga with Seynaeve, Tam, and Friedman. We initially focus our analysis on claim 1, but also address arguments made by Patent Owner as to the other claims in the analysis.

1. Akinaga

In summarizing the basis for Ground IV, Petitioner asserts that "Akinaga discloses that . . . the combination of a tyrosine kinase inhibitor

(UCN-01) and a DNA damaging agent (MMC), has a synergistic cytotoxic effect on human cancer cells." Reply 17. In particular,

> Akinaga teaches that the combination of the chemotherapeutic DNA damaging agent (mitomycin C ("MMC")[)] . . . and a low molecular weight tyrosine kinase inhibitor (UCN-01) produces cell killing effects *in vitro* and *in vivo*. Akinaga discloses *in vivo* tests in mice and proposes clinical trials using this combination to treat human cancer patients.

Pet. 3. Petitioner further argues that Akinaga teaches that MMC and UCN-01 result in cell cycle arrest in different phases of the cell cycle, thus providing "a strong indication for combining both drugs." *Id.* at 46–47 (quoting Ex. 1004, 188). Petitioner further argues that "Akinaga even ties the synergistic cytotoxic effect to particular cell cycle events that were dramatically altered by the combination of UCN-01 and MMC . . . ." Reply 17–18 (citing Pet. 61; Ex. 1002 ¶ 239).

According to Dr. Eastman, one of ordinary skill in the art would have understood from Akinaga that UCN-01 would enhance the cell death (apoptosis) resulting from the chemotherapeutic DNA damaging effects of MMC. *See* Pet. 58–59 (citing, *e.g.*, Ex. 1002 ¶ 229). In particular, Dr. Eastman states that

> UCN-01 "potentiates the lethality," (Lau at abst. (Ex. 1013)), of the DNA damage caused by MMC, which would otherwise be repaired during G_2, and instead induces the damaged cells to undergo premature mitosis, thereby causing the cell to undergo micronucleation and die. (Tam at 812 & fig. 1C (Ex. 1012); Lau at abst. (Ex. 1013).) Akinaga's combination of UCN-01 and MMC therefore enhances a series of intracellular events that lead to target cell death of cancer cells.

Ex. 1002 ¶ 229.

As an initial matter, Akinaga was distinguished during prosecution on the basis that the Examiner did not establish that Akinaga taught a tyrosine

kinase inhibitor. *See* Pet. 14, 46; *see* Ex. 1017,[17] 6 ("On this record, the examiner failed to provide the factual evidence necessary to establish a nexus between protein tyrosine kinase inhibitors and the teachings of . . . Akinaga."). On the present record, however, we credit Dr. Eastman's testimony that "Akinaga explicitly discloses that UCN-01 inhibits 'pp60$^{v\text{-}src}$,' which is identified as 'v-src tyrosine kinase' in Table 1." Ex. 1002 ¶ 96.

Patent Owner concedes that Akinaga discloses v-src (Tr. 58:18–21), but argues that of the kinases listed in Akinaga's Table 1, "only pp60$^{v\text{-}src}$ is a tyrosine kinase, and is expressed only in chicken cells infected with Rous sarcoma virus," such that "any observed cytostatic or cytotoxic effect on a human or murine cell line [in Akinaga] would not have been the result of the inhibition of pp60$^{v\text{-}src}$ found only in chickens." PO Resp. 22. Patent Owner takes the position that, despite knowing that UCN-01 inhibits v-src, one of ordinary skill in the art would have no reason to believe that UCN-01 would inhibit its cellular homolog of c-src because "C-src is more difficult to inhibit." *See* Tr. 58:11–61:5. In support of this position, Patent Owner relies on paragraphs 14 and 15 of Dr. Kufe's Declaration (Ex. 2011) and the following passage from his deposition:

> Q: What does it mean that C-SRC is the cellular homologue of V-SRC?
>
> A: V-SRC is a mutant kinase. It is mutated in the C terminal domain and it's constitutively active as a results of that. There's a mutation at a tyrosine residue in V-SRC.

[17] Decision on Appeal from Application No. 08/309,315, dated Sept. 19, 2001.

> As a result, V-SRC functions very differently from C-SRC. V-SRC is activated all the time. It's not subject to this down-regulation whereas C-SRC is.
>
> So the structures are different, and so they're not the same.

Ex. 1043, 78:7–18. Dr. Kufe's testimony that there are differences in structure and function between the two molecules is not persuasive evidence that one of ordinary skill in the art would believe "c-src is more difficult to inhibit," as Patent Owner argues. *See* Tr. 59:6. To the contrary, we credit the well-supported testimony of Petitioner's expert:

> Because 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. For example, by 1993, it was known that staurosporine, a molecule very similar to UCN-01, inhibited both v-Src and c-Src. (*See, e.g.*, Robinson et al., *Enzyme, Whole Cell and In vivo Tumor-Models to Identify and Assess Inhibitors of pp60(c-src)*, 2 Int'l J. Oncology 253, 255 (1993) (Ex. 1036).) Thus, a person of ordinary skill in the art would have recognized that UCN-01 would inhibit tyrosine kinases in both animals and humans.

Ex. 1002 ¶ 202 (footnote omitted); *see also* Ex. 2010, 43:19–44:6, 56:21–57:12 (testifying that human epidermoid carcinoma, sarcoma 180, and murine lymphocytic P388 tumor cell lines express c-src). Accordingly, we find that one of ordinary skill in the art would understand from Akinaga that UCN-01 would inhibit the c-src tyrosine kinase in humans and animals, and is, thus, a tyrosine kinase inhibitor.

Patent Owner further attempts to distinguish Akinaga by arguing that the reference "does not attribute any cytotoxic or even cytostatic effect to tyrosine kinase inhibition" but, instead, characterizes UCN-01 as "a potent and selective inhibitor ***of protein kinase C.***" *See* PO Resp. 21–24; *see also*

id. at 28–29 (arguing that "the Seynaeve, Tam, and Friedman references, either alone or in combination, do not teach cytotoxicity resulting from tyrosine kinase inhibition"). Although Patent Owner correctly identifies Akinaga's focus on protein kinase C, the plain language of the challenged claims requires that chemotherapeutic agent and the low molecular weight tyrosine kinase inhibitor "act in combination" to produce the desired effect, and does not, as Petitioner points out, specify that "tyrosine kinase inhibition itself causes any particular effect." *See* Reply 19. Accordingly, it is sufficient that Akinaga shows that the DNA damaging agent MMC acts in combination with UCN-01 to produce "a synergistic cytotoxic effect," and that the art (Akinaga and Seynaeve) identifies UCN-01 as a tyrosine kinase. *See* Ex. 1004, 183.

With respect to claim 5, Patent Owner contends that Akinaga did not report on particular hallmarks of apoptosis discussed in McGahon. PO Resp. 24–25. We do not find this argument persuasive in light of our construction of "apoptosis," as meaning "a series of intracellular events that lead to target cell death" (*see supra* Section II(C)(ii)), and the '512 Patent's express definition of "apoptosis" as equivalent to the generic term "killing" (Ex. 1001, 5:35–38). We further note that neither Akinaga nor McGahon suggest that the cytostatic or cytotoxic effects of UCN-01 are the result of differentiation.

2. Seynaeve

Petitioner further relies on Seynaeve as showing that UCN-01 inhibits the activity of more than one tyrosine kinase protein as required by the challenged claims. Pet. 52, 61–62, 65; Reply 21; *see* Ex. 1002 ¶¶ 208, 236, 224. Patent Owner argues that Seynaeve's disclosure that UCN-01 results in decreased phosphorylation of certain proteins could be due to enhanced

phosphatase activity rather than tyrosine kinase inhibition. PO Resp. 25; Tr. 64:15–66:10. We do not find Patent Owner's arguments persuasive.

As Petitioner points out, Dr. Kufe and Dr. Eastman agree that one of ordinary skill in the art would have understood that kinase inhibition was commonly demonstrated as a decrease in the phosphorylation of the kinase's substrate. *See* Reply 21–22 (citing Ex. 1043, 67:15–18; Ex. 2010, 19:15–21). In accord with this testimony, Seynaeve describes UCN-01 as "an inhibitor of protein kinases, [which] caused . . . decreased tyrosine phosphorylation of at least 4 proteins as arrest in G1 became apparent." Ex. 1014, 2085. Thus, for the reasons set forth at pages 21–22 of the Reply, which we adopt, we agree with Petitioner that one of ordinary skill in the art reading Seynaeve "would have concluded that the decreased tyrosine phosphorylation in the presence of UCN-01 resulted from tyrosine kinase inhibition." Reply 22.

3. Tam and Friedman

In discussing the requirement of claim 3, "wherein the low molecular weight inhibitor binds intracellularly to inhibit the activity of EGFR and at least one other tyrosine kinase," Petitioner points to the knowledge of one of ordinary skill in the art and to the teachings of Tam and Friedman. Pet. 56 (citing, *e.g.*, Ex. 1035[18], 4889–90, Fig. 2); Ex. 1002 ¶¶ 223–25. With respect to Tam, Petitioner relies on Dr. Eastman's testimony regarding the similarity between staurosporine and its 7-hydroxy derivative, UCN-01, and Tam's disclosure that staurosporine "can suppress in vitro the activity of . . .

[18] 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).

tyrosine kinases $p60^{vsrc}$ and epidermal growth factor receptor." Pet. 56 (citing Tam 811; Ex. 1002 ¶ 224).

In attempting to distinguish Tam, Patent Owner argues that there is no indication that the cell lines used in Tam expressed EGFR. *See* PO Resp. 26–27. We do not find Patent Owner's argument persuasive in light of Tam's express disclosure that "[s]taurosporine is a potent general protein kinase inhibitor that can suppress *in vitro* the activity of . . . epidermal growth factor receptor [EGFR]" Ex. 1012, 811; *see also* Ex. 1002 ¶ 251 ("Friedman discloses that staurosporine inhibits EGFR and suggests that it does so by interfering with ATP binding at the ATP binding domain of EGFR. (Friedman at 537 & fig. 7 (Ex. 1031).)").

Petitioner similarly relies on Friedman as disclosing that staurosporine, "a close structural analog of UCN-01," inhibits tyrosine kinases by competing with ATP at a kinase's ATP binding domain. Pet. 56 (citing Ex. 1031, 537–538, Fig. 8; Ex. 1002 ¶ 224). "Based on this mechanism of action," Petitioner concludes that "a POSA would have logically predicted that UCN-01 would also inhibit the tyrosine kinase activity of EGFR." *Id.* at 57 (citing Ex. 1002 ¶ 225). Patent Owner argues that "[t]he method of interaction reported in Friedman . . . does not equate to staurosporine being a tyrosine kinase inhibitor." Patent Owner, however, does not point us to any evidence to support that argument, and we are not persuaded by Patent Owner's unsupported assertion. *Meitzner v. Mindick*, 549 F.2d 775, 782 (C.C.P.A. 1977) ("Argument of counsel cannot take the place of evidence lacking in the record.").

4. Reason to Combine

Petitioner argues that one of ordinary skill in the art would have had reason to combine Akinaga with Seynaeve, Tam, and Friedman "because

they involve administration of the same tyrosine kinase inhibitor (UCN-01) or its close structural analog [staurosporine], which has substantially similar effects on the cell cycle." Pet. 61. We are persuaded by Petitioner's argument and credit the testimony of its expert, Dr. Eastman, as evidence for a reason to combine:

> Dr. Eastman stated in his declaration that "staurosporine and UCN-01 were understood to be very similar compounds with UCN-01 differing only by the addition of one hydroxyl group," that both compounds had been known to inhibit Src and enhance cell killing, and that the two compounds were known to have a similar mechanism of action. (Eastman Decl. ¶224 (Ex. 1002).) Dr. Eastman reiterated during cross-examination that it was the "common ground" disclosures in the references relating to staurosporine and UCN-01, as well as the "abrogation of cell cycle [ar]rest that is shown in these papers," that would have led a POSA in 1994 to combine the references. (Eastman Dep. 97:9-15 (Ex. 2010).)

Reply 25; *see also* Tr. 35:5–8 ("[T]he motivation to combine rests on the similarities in both structure and mechanism of action of UCN-01 and staurosporine."); *id.* at 37:7–39:10.

Patent Owner argues that Petitioner has not established sufficient motivation to combine Akinaga with Seynaeve, Tam, and Friedman. PO Resp. 28–30. In particular, Patent Owner argues that there is no motivation to combine the cited references because "in the context of Akinaga's teachings, UCN-01 is not acting as a tyrosine kinase inhibitor." *Id.* We do not find Patent Owner's argument persuasive. Akinaga suggests combining the chemotherapeutic agent MMC with UCN-01 because the two compounds cause delays in different stages of the cell cycle. *See supra* Section II(E)(i). Akinaga concludes that, in combination, MMC and UCN-01, together, "exert . . . a synergistic cytotoxic effect" in vitro and

"synergistic antitumor effects" in mouse models. *Id.* Although Akinaga suggests that the anti-tumor effect of the combination may relate to UCN-01's inhibition of PKC, Akinaga (and Seynaeve), nevertheless, indicate that UCN-01 is also a tyrosine kinase inhibitor. *Id.* Thus, Akinaga teaches or suggests a therapeutically effective amount of the tyrosine kinase inhibitor UCN-01, which, in this case, encompasses an amount sufficient to provide a synergistic cytotoxic effect when administered in combination with MMC.[19] Accordingly, we find sufficient Petitioner's statement of reasons to combine, and find it irrelevant that Akinaga attributes UCN-01's antitumor activity to the "inhibition of PKC and/or other protein kinases." *See id.*

Except as addressed above, Patent Owner does not separately address challenged claims 2, 3, 5, and 6. We have reviewed Petitioner's claim chart, arguments, and evidence as to those claims, and determine that Petitioner has established by a preponderance of the evidence that the combination of Akinaga, in view of the knowledge of a person of ordinary skill in the art, Seynaeve, Tam, and Friedman renders those claims obvious as well. *See, e.g.*, Pet. 64–67. Accordingly, in view of the above, we conclude that Petitioner has demonstrated, by a preponderance of the evidence, that the subject matter of claims 1–3, 5, and 6 of the '512 patent would have been obvious over the combination of Akinaga, in view of the knowledge of a person of ordinary skill in the art, Seynaeve, Tam, and Friedman.

[19] Our analysis of Ground IV would be essentially unchanged under Patent Owner's proposed definition of "therapeutically effective amount."

III. PATENT OWNER'S MOTION TO EXCLUDE

Patent Owner seeks to exclude Exhibits 1041, 1042, and 1044. Paper 37. Because we do not rely on any of these exhibits to reach the final decision, we dismiss Patent Owner's Motion to Exclude as moot.

IV. ORDER

For the reasons given, it is

ORDERED that claims 1–3, 5, and 6 of the '512 patent are held unpatentable;

ORDERED that Patent Owner's Motion to Exclude is denied as moot; and

FURTHER ORDERED that this is a Final Written Decision; therefore, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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Paper No. 46
Entered: November 28, 2017

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 Tam[4] (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.

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[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

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[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$^{c\text{-}src}$. *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

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[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$^{v\text{-}src}$ 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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