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Paper No. 43
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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*.

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: G_1 (growth phase); S (copying of DNA); G_2 (rapid growth in preparation for mitosis/cell division); M (mitosis/cell division). (Eastman Decl. ¶¶40-41 (Ex. 1002).) The cell cycle can arrest in G_1, S and G_2 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

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

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