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Paper 39
Entered: October 27, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PHIGENIX, INC,
Petitioner,

v.

IMMUNOGEN, INC.,
Patent Owner.

Case IPR2014-00676
Patent 8,337,856 B2

Before FRANCISCO C. PRATS, JACQUELINE WRIGHT BONILLA, and ZHENYU YANG, *Administrative Patent Judges*.

BONILLA, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Phigenix Inc. ("Petitioner") filed a Petition requesting *inter partes* review of claims 1–8 of U.S. Patent No. 8,337,856 ("the '856 patent"). Paper 5 ("Pet."). Immunogen, Inc. ("Patent Owner") filed a Preliminary Response. Paper 10 ("Prelim. Resp."). Thereafter, we determined that the information presented in the Petition demonstrated that there was a reasonable likelihood that Petitioner would prevail in showing claims 1–8 as unpatentable. Paper 11 ("Dec. to Inst."), 2, 23. Pursuant to 35 U.S.C. § 314, we instituted this proceeding on October 29, 2014, to review whether claims 1–8 of the '856 patent would have been obvious under 35 U.S.C. § 103 over Chari 1992[1] in view of the HERCEPTIN® Label,[2] further in view of Rosenblum 1999[3] and Pegram 1999.[4] *Id.* at 23.

After institution of trial, Patent Owner filed a Patent Owner Response. Paper 18 ("PO Resp."), and Petitioner filed a Reply to the Response. Paper

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[1] Chari et al., *Immunoconjugates Containing Novel Maytansinoids: Promising Anticancer Drugs*, 52 CANCER RES.127–131 (1992) ("Chari 1992") (Ex. 1012).

[2] HERCEPTIN® (Trastuzumab) Label, dated September 1998 ("the HERCEPTIN® Label") (Ex. 1008).

[3] Rosenblum et al., *Recombinant Immunotoxins Directed against the* c-erbB-2/HER2/neu *Oncogene Product:* In Vitro *Cytotoxicity, Pharmacokinetics, and* In Vivo *Efficacy Studies in Xenograft Models*, 5 CLIN. CANCER RES. 865–874 (1999) ("Rosenblum 1999") (Ex. 1018).

[4] Pegram et al., *Inhibitory effects of combinations of HER-2/*neu *antibody and chemotherapeutic agents used for treatment of human breast cancers*, 18 ONCOGENE 2241–2251 (1999) ("Pegram 1999") (Ex. 1020).

24 ("Reply"). Petitioner also filed a Motion to Exclude certain evidence submitted by Patent Owner. Paper 28. Patent Owner responded by filing an Opposition to the Motion to Exclude (Paper 29), as well as an unopposed Motion to Seal two exhibits filed by Patent Owner in connection with the Opposition (Paper 31, 1). Petitioner filed a Reply to the Opposition to the Motion to Exclude. Paper 35.

An oral hearing was held on July 9, 2015. A transcript of the hearing has been entered into the record. Paper 38 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons that follow, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–8 of the '856 patent are unpatentable. We deny Petitioner's Motion to Exclude Evidence, and we grant Patent Owner's Motion to Seal.

A. Related Proceeding

About a month after filing the current Petition, Petitioner filed a Petition requesting *inter partes* review of claims 1–20 and 25–27 of U.S. Patent No. 7,575,748 ("the '748 patent") in Case No. IPR2014-00842. Patent Owner of the '748 patent, Genentech, Inc., a real party-in-interest in the current proceeding, filed a Preliminary Response. IPR2014-00842, Paper 9. On December 9, 2014, we declined to institute review in that case. *Phigenix, Inc. v. Genentech, Inc. and ImmunoGen, Inc.*, Case IPR2014-00842 (PTAB Dec. 9, 2014) (Paper 10).

The '748 patent, at issue in that case, is a continuation application of U.S. Patent No. 7,097,840 ("the '840 patent"). IPR2014-00842, Ex. 1001. The '856 patent, at issue here, is a divisional application of a continuation application of the '840 patent. Ex. 1001.

B. The '856 Patent (Ex. 1001)

The '856 patent relates to immunoconjugates comprising an anti-ErbB antibody, such as the humanized anti-ErbB2 antibody known as HERCEPTIN® (huMAb4D5-8), linked to a maytansinoid toxin. Ex. 1001, 1:20–52, 35:47–36:39; *see also id.* at 3:6–16 (discussing HERCEPTIN®), 6:50–67 (defining "ErbB2"), 10:40–52 (defining "humanized"), 16:23–28 (defining "epitope 4D5").

The term "ErbB2" is synonymous with "HER2," "p185^{neu}", or "*neu*," and refers to a member of the ErbB family of receptor tyrosine kinases, which mediate cell growth, differentiation, and survival. *Id.* at 1:45–60, 6:50–58. Overexpression of ErbB2 on cell surfaces can lead to cancer in humans, such as certain breast and ovarian cancers. *Id.* at 1:54–66, 8:55–60.

The specification teaches that maytansinoids, such as DM1, are highly cytotoxic, i.e., inhibit or prevent cell function and/or destroy cells, but induce "severe systemic side-effects primarily attributed to their poor selectivity for tumors" when administered alone. *Id.* at 1:38–44, 17:45–52; *see also id.* at 5:7–13 (referring to Figure 3, showing the structure of the maytansinoid designated "DM1"). The specification describes making anti-ErbB antibody-maytansinoid conjugates using "a variety of bifunctional protein coupling agents," i.e., linkers, such as N-succinimidyl-3-(2-

pyridyldithio)propionate ("SPDP"), N-succinimidyl-4-(2-pyridylthio)pentanoate ("SPP"), and succinimidyl-4-(N-maleimidomethyl)-cyclohexane-1-carboxylate ("SMCC"). *Id.* at 36:13–31.

The specification states that the "present invention is based on results obtained in a novel murine HER2-transgenic tumor model in which HERCEPTIN® or the murine antibody 4D5 from which HERCEPTIN® was derived, had little effect on tumor growth." *Id.* at 21:65–22:1. In this context, the specification states that "it was surprisingly found that while the transplanted tumor obtained from such transgenic mice responded poorly to HERCEPTIN® treatment, the HERCEPTIN®-maytansinoid conjugates were highly efficacious." *Id.* at 22:2–7.

C. The Challenged Claims

Petitioner challenges claims 1–8 of the '856 patent. Of those, only claim 1 is independent, which recites:

> 1. An immunoconjugate comprising an anti-ErbB2 antibody conjugated to a maytansinoid, wherein the antibody is huMAb4D5-8.

Id. at 81:28–31. Dependent claim 2 recites that the maytansinoid is DM1 having a specific structure, where the antibody is linked to the maytansinoid via a disulfide or thioether group at "R" shown in the structure. *Id.* at 81:31–53. Dependent claim 3 requires that the immunoconjugate "comprises from 3 to 5 maytansinoid molecules per antibody molecule." *Id.* at 82:27–30. Dependent claim 5 recites a pharmaceutical composition comprising the immunoconjugate and a pharmaceutically acceptable carrier. *Id.* at 82:37–39. Claims 4 and 6–8, which ultimately depend on claim 1 or 2, recite that

the antibody and maytansinoid are conjugated by specific chemical linkers, i.e., SPDP, SPP, or SMCC. *Id.* at 82:30–36, 39–51.

II. ANALYSIS

A. Claim Construction

For *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable interpretation in light of the patent specification. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278–79 (Fed. Cir. 2015). Claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

As noted in our Decision to Institute, Petitioner offers claim construction of the phrase "pharmaceutically-acceptable carrier," recited in dependent claim 5, as "including 'bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution.'" Dec. to Inst. 6–7 (citing Pet. 7 (citing Ex. 1001, 42:4–9)). Patent Owner does not dispute this claim construction, nor offer construction of other claims terms. Based on the record currently available, Petitioner's proposed construction is the broadest reasonable construction of the phrase. We construe other claim terms as carrying their ordinary meaning, consistent with their use in the specification.

B. Obviousness over Chari 1992 in view of HERCEPTIN® Label, further in view of Rosenblum 1999 and Pegram 1999

Petitioner contends that claims 1–8 would have been obvious over Chari 1992 in view of the HERCEPTIN® Label, further in view of Rosenblum 1999 and Pegram 1999, relying on a Declaration by Michael G. Rosenblum, Ph.D. (Ex. 1016). Pet. 8–22. Patent Owner contends otherwise, relying on a Declaration by Geoffrey A. Pietersz, Ph.D. (Ex. 2134), as well as Declarations by Linda T. Vahdat, M.D. (Ex. 2103), Joyce O'Shaughnessy, M.D. (Ex. 2105), and John C. Jarosz (Ex. 2131) in relation to objective indicia of non-obviousness. PO Resp. 2–60.

1. Chari 1992 (Ex. 1012)

Chari 1992 describes immunoconjugates comprising an anti-ErbB2 mouse monoclonal antibody, TA.1, chemically coupled to the maytansinoid toxin, DM1, using SPDP or SMCC as a linker. Ex. 1012, 128–129; *id.* at Fig. 2 (*see* maytansinoid 3 and figure legend). As stated in Chari 1992, the TA.1 antibody binds HER-2/*neu* oncogene protein (i.e., ErbB2), which is expressed at high levels on human breast tumor cells. *Id.* at 129, 1st col., 1st ¶. The reference discloses conjugates having a range of one to six maytansinoid molecules per antibody molecule, such as four maytansinoid molecules per antibody molecule. *Id.*, *see also id.* at 2nd col., Table 2.

Chari 1992 teaches that the conjugates, called "TA.1(-SS-May)$_n$," were cytotoxic when tested *in vitro* on the human breast cancer cell line, SK-BR-2. *Id.* at 129, 1st col., 2nd ¶, 2nd col. Fig. 3. In addition, the reference teaches that conjugate TA.1(-SS-May)$_4$ was at least 1000-fold less cytotoxic

toward *neu*-negative KB cells in tissue culture. *Id.* It teaches that cytotoxicity can be increased by linking more maytansinoid molecules per antibody molecule, "and it reached its maximum value at $n = 4$ (Table 2)." *Id.* at 1st col., 3rd ¶. The reference also discloses that conjugate A7(-SS-May)$_6$, where A7 is an antibody directed against a human colon cancer cell line antigen, shows similar cytotoxicity results and is not toxic in mice. *Id.* at 1st col., 3rd ¶ – 2nd col., 2nd ¶.

Chari 1992 states that the "high specific cytotoxicity of maytansinoid conjugates toward tumor cell lines in conjunction with their low systemic toxicity indicates that these potent conjugates may possess a therapeutic index sufficient for the effective treatment of human cancer." *Id.* at 130, 1st col., 2nd ¶; *see also id.* at 127, Abstract (stating that the immunoconjugates "show high antigen-specific cytotoxicity for cultured human cancer cells . . . , low systemic toxicity in mice, and good pharmacokinetic behavior"). It also states that the "development of 'humanized' antibodies will offer an opportunity to produce drug conjugates that would be less immunogenic than similar conjugates of murine antibodies." *Id.* at 130, 1st col., 3rd ¶.

2. HERCEPTIN® Label (Ex. 1008)

The HERCEPTIN® Label describes HERCEPTIN®, also known as Trastuzumab or huMAB4D5-8, as a humanized form of the mouse monoclonal antibody 4D5, which binds HER2/ErbB2. Ex. 1008, 1, 1st col. The Label describes intravenous injection administration of HERCEPTIN® after reconstitution with "Bacteriostatic Water for Injection (BWFI)," among other components. *Id.* at 1st col.

The Label describes HERCEPTIN® as being indicated for "the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease." *Id.* at 2nd col. In addition, the Label describes HERCEPTIN® in combination with paclitaxel as being "indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for their metastatic disease." *Id.*

Table 1 in the Label shows clinical trial data regarding "Phase III Clinical Efficacy in First-Line Treatment" in patients treated with chemotherapy alone or chemotherapy combined with HERCEPTIN®. *Id.* at 1st col. The Label states that "[c]ompared with patients randomized to chemotherapy alone, the patients randomized to HERCEPTIN and chemotherapy experienced a significantly longer time to disease progression, a higher overall response rate (ORR), a longer median duration of response, and a higher one-year survival rate." *Id.* (citing Table 1).

3. Rosenblum 1999 (Ex. 1018)

Rosenblum 1999 discloses an immunoconjugate comprising an anti-ErbB2 human chimeric antibody ("BACH-250") chemically coupled to a ribosomal-inhibiting plant toxin gelonin ("rGel"), using SPDP as a linker. Ex. 1018, 865, Abstract, 866, 2nd col. Immunoconjugates, antibodies alone, and toxin alone, were tested *in vitro* against human tumor cells expressing various levels of HER2, and *in vivo* against human tumor xenograft models (athymic mice bearing s.c. or i.p. SKOV-3 tumors). *Id.* at Abstract.

The reference states that although "binding of both BACH-250 and BACH-250/rGel conjugate to target cells was essentially equivalent," in SKOV-3 cells "the IC_{50} of BACH-250/rGel [conjugate] was 97 pM (17 ng/ml), whereas BACH-250 and rGel alone showed no cytotoxic effects." *Id.* The reference also states there "was a clear correlation between expression levels of HER-2/neu and cytoimmunotoxin." *Id.*; *see also id.* at 869, 1st col. (stating that cytotoxic effects of TAB-250/rGel (mouse antibody conjugate) was greatest against the SKBR-3 cell line having the highest number of cell surface HER2, as compared to other cell lines expressing lower levels).

In *in vivo* xenograft studies in mice using BACH-250 conjugates, "immunotoxin treatment slowed tumor growth by 99 and 94% at days 35 and 49 after implantation, respectively, and lengthened the median survival by 40% (from 30 to 50 days) in mice bearing lethal i.p. tumors." *Id.* at Abstract, 871–872 (describing "impressive antitumor effects" as compared to tumor growth in control groups). Rosenblum 1999 concluded "that clinical development of BACH-250/rGel may be warranted in patients with HER2/neu-expressing malignancies." *Id.* at Abstract.

4. Pegram 1999 (Ex.1020)

Pegram 1999 states that "[p]revious studies have demonstrated a synergistic interaction between rhuMAb HER2 and the cytotoxic drug cisplatin in human breast and ovarian cancer cells." Ex. 1020, 2241, Abstract. Pegram 1999 conducted studies in "preclinical models *in vitro* and *in vivo*" using rhuMAb HER2 in combination with other cytotoxic drugs.

Id., *see also id.* at 2241, 2nd col., 2242, 2nd col. The reference describes observing "[s]ynergistic interactions at clinically relevant drug concentrations" for rhuMAb HER2 in combination with cisplatin, thiotepa, or etoposide, and "[a]dditive cytotoxic effects" with rhuMAb HER2 plus doxorubicin, paclitaxel, methotrexate, or vinblastine. *Id.* at Abstract.

The reference indicates that "rhuMAb HER2" is a recombinant, humanized form of 4D5. *Id.* at 2241, 2nd col. It states that when "compared to murine 4D5, rhuMAb HER2 exhibits a stronger binding affinity for $p185^{HER\text{-}2/neu}$ but has similar specific antiproliferative activity against HER-2/*neu*-overexpressing cell lines and xenografts." *Id.* The reference also states that in *in vivo* studies using human breast cancer xenografts in athymic mice, vinblastine ("VBL"), a microtubule inhibitor, combined with rhuMAb HER2 "significantly reduced MCF7/HER-2 xenograft volume compared to treatment with VBL alone or single agent rhuMAb HER2 (Figure 6b)." *Id.* at 2245, 2nd col.; *see also id.* at 2248, ¶ spanning 1st and 2nd col. (describing "significantly superior anti-tumor efficacy" of rhuMAb HER2 when combined with different chemotherapy drugs, such as VBL, as compared to effects of each drug alone).

5. Petitioner's Contentions

Petitioner contends that Chari 1992 teaches all limitations recited in claims 1–8 of the '856 patent, except that it does not disclose huMAB4D5-8 (as recited in independent claim 1) or a pharmaceutically acceptable carrier (as recited in claim 5). Pet. 13; *see id.* at 9–13. For example, Petitioner contends that Chari 1992 discloses an immunoconjugate comprising an anti-

ErbB2 antibody conjugated to a maytansinoid, such as DMI having the structure recited in claim 2, where the immunoconjugate comprises four maytansinoid molecules per antibody molecule (as recited in claim 3), and where the antibody and maytansinoid are conjugated by chemical linkers, such as SPDP or SMCC (as recited in claims 4 and 6–8). Pet. 9–12 (citing Ex. 1012).

Petitioner also contends that the HERCEPTIN® Label describes the use of huMAB4D5-8 (i.e., HERCEPTIN®) for the treatment of patients with metastatic breast cancer, as well as the combination of HERCEPTIN® with a pharmaceutically acceptable carrier, i.e., Bacteriostatic Water for Injection. Pet. 13 (citing Ex. 1008, 1). Most relevant to our analysis, Petitioner further contends, relying on the Rosenblum Declaration (Ex. 1016), that it would have been obvious to the ordinarily skilled artisan, at the time the '856 patent was filed, to substitute the mouse monoclonal TA.1 antibody in the immunoconjugate of Chari 1992 with the humanized mAb huMAB4D5-8 to produce the claim-recited immunoconjugates "based on the teachings of Chari 1992 and HERCEPTIN® Label, as well as the general knowledge in the art at that time." Pet. 13–14.

Specifically, Petitioner contends that an ordinary artisan would have been motivated to do such a substitution because it was known that: (1) humanized mAbs, such as huMAB4D5-8, were preferred over their mouse-derived counterparts for clinical applications, as indicated in Chari 1992 (Ex. 1012, 130, 1st col.); (2) huMAB4D5-8 selectively bound with high affinity to HER2 and had been approved for use to treat breast tumors

in humans, as indicated in the HERCEPTIN® Label; and (3) clinical studies indicated that huMAB4D5-8 worked well in combination with microtubule-directed chemotherapy agents for the treatment of breast cancer, as indicated in the HERCEPTIN® Label (Ex. 1008, 1, 1st col.). Pet. 13–15.

In addition, Petitioner contends that an ordinary artisan would have had a reasonable expectation of success regarding the recited immunoconjugates because it was known that: (1) huMAB4D5-8 was more effective in treating breast cancer when used in combination with the microtubule targeting drug paclitaxel, as described in the HERCEPTIN® Label; (2) Chari 1992's maytansinoid conjugates targeted the same cells as huMAB4D5-8; and (3) an immunoconjugate containing a humanized antibody was less immunogenic, and therefore more effective in humans, than an immunoconjugate containing a mouse antibody. *Id.* at 16.

Petitioner also contends that other prior art references, such as Rosenblum 1999 and Pegram 1999, provided additional reasons to use the humanized antibody disclosed in the HERCEPTIN® Label in the immunoconjugate of Chari 1992, with a reasonable expectation of success. *Id.* at 19–22. Petitioner refers to, for example, the *in vivo* efficacy data of a similar immunoconjugate, as taught in Rosenblum 1999. *Id.* at 20 (citing Ex.1018, Figs. 12 and 13; Ex. 1016 ¶ 18). Petitioner also notes that Pegram 1999 states that "'[t]he synergistic interaction of rhuMab HER2 with alkylating agents . . . as well as the additive interaction with taxanes, . . . in HER-2/neu-overexpressing breast cancer cells demonstrates that **these are rational combinations to test in human clinical trials**' (emphasis added)."

Id. at 22 (quoting Ex. 1020, Abstract). Petitioner contends that Pegram 1999 indicates a reasonable expectation of success because it suggested that HERCEPTIN® and maytansinoid may act independently and have an additive effort in inhibiting the growth of breast tumor cells. *Id.* (citing Ex. 1016 ¶ 21).

Petitioner also refers to teachings in prior art references, such as in Pegram 1999 and the HERCEPTIN® Label, which disclose synergistic or additive effects between HERCEPTIN® and other chemotherapeutic agents, such as the antimicrotubule agent paclitaxel. *Id.* at 49. Petitioner also contends that Chari 1992 taught that "maytansinoid immunoconjugates were demonstrated to be substantially free of toxicity, based on the same kinds of assays described in the '856 patent." *Id.* at 54–55 (citing Ex. 1012, Abstract, 129, 1st col., 130 1st col.). Petitioner further cites Liu (Ex. 1023)[5] and Chari 1998 (Ex. 1015)[6] to rebut the position that one would have expected "unacceptable cytotoxic side effects for such an immunoconjugate," and that nothing before the '856 patent addressed "the unpredictability in the art" in relation to a reasonable expectation of success. Pet. 55–57 (citing Ex. 1028 ¶ 14).

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[5] Liu et al., *Eradication of large colon tumor xenografts by targeted delivery of maytansinoids*, 93 PROC. NATL. ACAD. SCI., USA 8618–8623 (1996) (Ex. 1023).

[6] Chari, *Targeted delivery of chemotherapeutics: tumor-activated prodrug therapy*, 31 ADV. DRUG DEL. REV. 89–104 (1998) (Ex. 1015).

6. Analysis regarding claims 1–8

In response to the Petition, Patent Owner argues that Petitioner has not established a prima facie case that claims 1–8 would have been obvious over the cited art. PO Resp. 2–26. Patent Owner contends that an ordinary artisan would not have had a reason to substitute the mouse monoclonal TA.1 antibody in the immunoconjugate of Chari 1992 with the humanized mAb huMAB4D5-8, i.e., Herceptin®. *Id.* at 1–3.

As noted above, Petitioner argues that an ordinary artisan would have had reason to substitute the mouse monoclonal TA.1 antibody in the immunoconjugate of Chari 1992 with huMAB4D5-8 (HERCEPTIN®) in particular because it was known that (1) humanized antibodies were preferred over mouse counterparts for clinical applications, (2) huMAB4D5-8 had been FDA approved for use to treat breast tumors in humans, and (3) clinical studies indicated that huMAB4D5-8 worked well in combination with microtubule-directed chemotherapy agents for the treatment of breast cancer. Pet. 14–15 (citing Ex. 1012, 130; Ex. 1008, 1); *see also id.* at 19–20 (stating that "Rosenblum 1999 teaches the use, efficacy and safety of an immunotoxin having humanized ErbB2 extracellular domain-targeted monoclonal antibody chemically linked to a cytotoxic moiety"); *id.* at 22 (stating that Pegram 1999 suggested that HERCEPTIN® and maytansinoid had "an additive effort in inhibiting the growth of breast tumor cells"). Petitioner also relies on different prior art references when arguing that one would have had an expectation of success in using the immunoconjugate to treat breast cancer in humans. *Id.* at 16–17; Ex. 1016 ¶ 16.

In other words, when asserting that an ordinary artisan would have had a reason to combine certain teachings in the cited references and, therefore, prepare a HERCEPTIN®-maytansinoid immunoconjugate, Petitioner relies on the position that an ordinary artisan would have expected such an immunoconjugate to work clinically to treat tumors in humans upon reading the cited references.

Patent Owner provides persuasive evidence, however, that in March 2000, at the time the '856 patent was filed, prior art indicated that HERCEPTIN®-maytansinoid immunoconjugates would have been expected to exhibit unacceptable levels of antigen-dependent toxicity in normal human liver tissue in patients. PO Resp. 1–13. For example, Patent Owner points to Pai-Scherf 1999 (Ex. 2029),[7] which describes a Phase I clinical study of human patients receiving an immunoconjugate (erb-38) comprising a portion of the anti-HER2 monoclonal antibody e23 fused to a truncated form of *Pseudomonas* exotoxin A. As stated by Patent Owner, although the Pai-Scherf group "initiated the study in humans based on 'excellent antitumor activity and acceptable animal toxicities,'" it nonetheless observed unacceptable hepatotoxicity in all patients in the treatment group. PO Resp. 4 (citing Ex. 2029, 2311, 2nd col., Abstract).

Pai-Scherf 1999 indicates that, in a clinical study, human patients experienced "hepatic injury" when exposed to erb-38. Ex. 2029, 2313–14.

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[7] Pai-Scherf et al., *Hepatotoxicity in Cancer Patients Receiving erb-38, a Recombinant Immunotoxin That Targets the erbB2 Receptor*, 5 CLINICAL CANCER RESEARCH 2311–15 (1999) (Ex. 2029).

Pai-Scherf 1999 discloses that the "toxicity of erb-38 is most likely due to the presence of erbB2 on hepatocytes, not detected by immunohistochemical staining in earlier publications." *Id.* at 2314, 1st col., 2315, 1st col. The reference further discloses that "[d]espite the fact that there is a very large difference in the amount of erbB2 on the surface of cancer cells relative to the small amount present on liver cells, liver toxicity was the first biological effect seen in this study." *Id.* at 2314, 2nd col. Pai-Scherf 1999 explains that a factor contributing to this finding is that "hepatocytes [normal liver cells] are more rapidly exposed to agents injected into the circulation than tumor cells," because "mixing within tumors is solely by diffusion and, therefore, very slow," and "tumors are often poorly vascularized." *Id.*

Pai-Scherf 1999 also discusses HERCEPTIN® in particular, noting that the "antibody alone has been found to produce objective responses in breast cancer and when combined with chemotherapy results in an increased response rate." *Id.* Pai-Scherf 1999 states that "[i]t is likely that the antitumor activity of the antibody in this setting is dependent on genetic perturbations that alter the configuration of downstream signaling events," where "the mechanism of killing depends on a genetic abnormality present in the cancer cells." *Id.* at 2314, 2nd col. – 2315, 1st col. By contrast, according to Pai-Scherf 1999, "if the antibody is used to deliver a cytotoxic agent, such as a bacterial toxin or radioisotope, the death of the target cell will be principally dependent on the amount of agent delivered to the cell." *Id.* at 2315, 1st col. Thus, Pai-Scherf 1999 indicates that the mechanism of cytotoxicity of the antibody alone differs from that of the antibody

conjugated to a toxin. In this context, Pai-Scherf 1999 concludes that "the toxicity observed with erb-38 is most likely due to the presence of erbB2 on hepatocytes," and the "targeting of tumors with antibodies to erbB2 that are armed with . . . toxic agents may result in unexpected organ toxicities due to erbB2 expression on normal tissues." *Id.* at 2315, 2nd col.

Patent Owner further cites evidence indicating that HERCEPTIN® and maytansinoids each caused toxicity to normal human cells, including liver cells, on their own. PO Resp. 7–13; Ex 1008, 1, 2nd col., 2, 2nd col. (observing heart toxicity generally, and "hepatic failure" in at least one patient); PO Resp. 7–8 (citing a number of exhibit references discussing hepatic toxicity and injury upon administering maytansinoids to patients).

In response, Petitioner contends that Pai-Scherf 1999 is not relevant to our analysis because it describes the use of a "fusion protein," not an antibody-drug conjugate. Reply 4–6. We disagree that Pai-Scherf 1999 is not relevant. Although the reference discloses clinical studies using a "single-chain" immunoconjugate comprising a portion of an anti-HER2/erbB2 antibody and a truncated form of a toxin, Pai-Scherf 1999 discusses generally the "targeting of tumors with antibodies to erbB2 armed with radioisotopes or other toxic agents." Ex. 2029, 2311, Abstract, 2315, 2nd col. As noted above, the reference also expressly states that the "toxicity of erb-38 is most likely due to the presence of erbB2 on hepatocytes," i.e., normal liver cells that "are more rapidly exposed to agents injected into the circulation than tumor cells" (Ex. 2029, 2314, 1st and 2nd col.)—a situation equally applicable when using a full-length anti-HER2

antibody linked to a toxin, i.e., "an antibody-drug conjugate," as Petitioner calls it. Reply 5; PO Resp. 20 (citing Ex. 2111, 8987, 2nd col. (stating that "treatment of solid tumors presents a potential problem because full-length antibodies must diffuse into the tumor against a hydrostatic pressure gradient and into disordered vasculature")).

Patent Owner persuades us that one would have considered the teachings of Pai-Scherf 1999 when reading Chari 1992, the HERCEPTIN® Label, as well as other references cited by Petitioner, such as Rosenblum 1999 and Pegram 1999. Chari 1992 states generally, based on clearance/degradation studies in mice and *in vitro* cytotoxicity studies on human cells in tissue culture, that maytansinoid conjugates "may possess a therapeutic index sufficient for the effective treatment of human cancer," and "development of 'humanized' antibodies will offer an opportunity to produce drug conjugates." Ex. 1012, 130. Petitioner does not establish by a preponderance of the evidence that those general statements in Chari 1992, in view of teachings years later in the HERCEPTIN® Label, Pai-Scherf 1999, and other references regarding liver toxicities, would have motivated an ordinary artisan to substitute the mouse TA.1 antibody in the immunoconjugate of Chari 1992 with HERCEPTIN® on the basis that one would have expected that modified immunoconjugate to work to treat human tumors. Pet. 14–15 (citing Ex. 1016 ¶¶ 12–15); PO Resp. 5–6, 19; Ex. 2134 ¶¶ 29, 52–57.

Petitioner's citation to Rosenblum 1999 and Pegram 1999, which disclose the testing of other anti-HER2-toxin immunoconjugates or

combinations of antibodies and toxins (using different anti-HER2 antibodies and different toxins) in *in vitro* tissue culture, and *in vivo* in mice expressing human tumors (mouse xenograft models), does not persuade us otherwise.[8] Pet. 17–22; Reply 6–8, 11–12. Patent Owner persuades us that an ordinary artisan would have understood that such studies would not have provided adequate information regarding toxicities to normal human cells *in vivo*. PO Resp. 12–13, 23–24; Ex. 2134 ¶¶ 22–27, 51. By contrast, the human clinical study in Pai-Scherf 1999 provided such information and observed hepatotoxicity when using a relevant immunoconjugate and suggested "unexpected organ toxicities due to erbB2 [HER2 expression] on normal cells" in relation to all anti-HER2 antibodies linked to toxins. Ex. 2029, Abstract.

To establish that the challenged claims would have been obvious, Petitioner must show that "a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable

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[8] In its Petition, Petitioner also relies on Hudziak 1998 (Ex. 1017), Baselga 1998 (Ex. 1019), Liu (Ex. 1023), and Chari 1998 (Ex. 1015), which likewise disclose studies conducted in tissue culture *in vitro* and/or in xenograft mice expressing human tumor cells using different antibodies and toxins. Pet. 17–21, 55–56; Hudziak, et al., U.S. Patent No. 5,770,195, issued June 23, 1998, 18:51–19:48 (Ex. 1017); Baselga et al., *Recombinant Humanized Anti-HER2 Antibody (HerceptinTM) Enhances the Antitumor Activity of Paclitaxel and Doxorubicin against HER2/neu Overexpressing Human Breast Cancer Xenografts*, 58 CANCER RES. 2825–2831 (1998) (Ex. 1019); Ex. 1023, 8618–22; Ex. 1015, 97–102.

expectation of success from doing so." *Par Pharm. Inc. v. TWI Pharms. Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014). As noted above, Petitioner's rationale for substituting HERCEPTIN® for the antibody used in the immunoconjugate of Chari 1992 was to make an immunoconjugate useful in treating tumors in human patients. Patent Owner, however, advances persuasive evidence that ordinary artisans would not have had a reasonable expectation that any immunoconjugate, much less the claimed Herceptin®-maytansinoid immunoconjugate in particular, would be useful to treat solid tumors in humans. PO Resp. 18–22 (describing prior failures in developing immunoconjugates for treating solid tumors), 47–51 (discussing long-felt need). As noted by Patent Owner, "[r]esearchers had targeted tumors with immunoconjugates for about 40 years before the '856 patent" without success. *Id.* at 21–22 (citing numerous exhibits). Patent Owner sufficiently points to evidence of record indicating that preparing *any* antibody-toxin immunoconjugate for use in the treatment of human tumors was difficult and unpredictable. PO Resp. 22; Ex. 2006, 385–89; Ex. 2007, 67, 72–86. Thus, viewing the record as a whole, Petitioner does not persuade us that a preponderance of the evidence establishes that a skilled artisan would have had a reasonable expectation of success in 2000 that a Herceptin®-maytansinoid immunoconjugate would be useful in the treatment of breast tumors in humans, as Petitioner asserts. Pet. 16–17, 20, 22; PO Resp. 22–23 (citing Ex. 2134 ¶¶ 101–113 (citing numerous exhibits)).

For the reasons given above, and in light of the record before us, Petitioner does not establish by a preponderance of the evidence that claims

1–8 of the '856 patent would have been obvious over Chari 1992 in view of the HERCEPTIN® Label, further in view of Rosenblum 1999 and Pegram 1999.

7. Additional analysis regarding claims 6 and 8

Dependent claims 6 and 8 of the '856 patent differ from other challenged claims in that they further recite a specific non-cleavable linker, succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate ("SMCC"). Ex. 1001, 82:39–51; PO Resp. 26. Claim 8 additionally requires that the maytansinoid be DM1, and is directed specifically to the commercial product "T-DM1," marketed under the name Kadcyla®. PO Resp. 35.

As noted by Patent Owner, evidence of record indicates that the prior art emphasized the importance of releasing a drug, such as a maytansinoid, from an immunoconjugate for biologic activity, such as via cleavable linkers. PO Resp. 27–28 (citing Ex. 2006, 385; Ex. 1015, 97; Ex. 1014, 169–170). For example, Chari 1992 states, that "to exploit the cytotoxic potential of maytansine in the conjugate, . . . it is necessary to release the drug at the target cell in fully active form." Ex. 1012, 128, 1st col.; PO Resp. 27. Consistently, in its *in vitro* tissue culture studies, Chari 1992 found that a monoclonal antibody TA.1-maytansinoid immunoconjugate comprising a non-cleavable linker "was 200-fold less potent under the same conditions (Fig. 3c)," as compared to a similar conjugate comprising a cleavable linker. Ex. 1012, 129, 1st col.; PO Resp. 26, 29–34.

Petitioner responds that although Chari 1992, Fig. 3c, may indicate that the immunoconjugate with a non-cleavable linker works less well, the

immunoconjugate still exhibits cytotoxic effects in the tested cells in tissue culture. Reply 12–17.

When considering evidence of record as a whole, we are persuaded that evidence cited by Patent Owner, including Chari 1992 and other prior art references, provided reasons not to use a non-cleavable linker in an immunoconjugate, such as one comprising an anti-HER2 antibody and maytansinoid, in particular. *See* Ex. 2006, 385 (stating that "unfavorable pharmacokinetics and pharmacodynamics observed in animals with such conjugates discouraged further development," when using conjugates linking drugs "directly to antibodies via noncleavable bonds").[9] In addition to evidence discussed in the previous section, such evidence further bolsters our conclusion that Petitioner has not established by a preponderance of the evidence that a skilled artisan would have had reason to combine the teaching of the cited references to make the immunoconjugates of claim 6 and 8.

Although failure to establish a reason to combine the cited teachings is sufficient, by itself, to conclude non-obviousness, Patent Owner cites substantial evidence of objective indicia of non-obviousness in relation to claim 8, which is directed to the T-DM1/Kadcyla® commercial product. PO Resp. 34–60 (citing evidence regarding T-DM1 and unexpected superior

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[9] Blättler et al., "Immunoconjugates," in *Cancer Therapeutics: Experimental and Clinical Agents*, Chapter 17, 371–394 (1996) (Ex. 2006).

results as compared to closest prior art compositions, fulfilling a long-felt and unmet need, praise in the field, and commercial success).

For example, Patent Owner provides evidence that T-DM1 fulfilled a long-felt, unmet need for an immunoconjugate capable of targeting a solid tumor in patients without excessive toxicity. *Id.* at 46–57 (citing, for example, Ex. 2103 ¶¶ 24–48; *see id.* at ¶¶ 26–28 (citing exhibits including Ex. 2062) (discussing numerous clinical trials testing ability of immunoconjugates to treat solid tumors before March 2000, where "none of these immunoconjugates proved safe and effective for treating solid tumors"); Ex. 2134 ¶ 106 (citing exhibits). Patent Owner also provides evidence regarding the commercial success of T-DM1/Kadcyla®. PO. Resp. 57–60 (citing, for example, Ex. 2131 (testimony by Mr. Jarosz, analyzing sales and prescription data, and marketing and promotional efforts relating to Kadcyla®)).

In view of the specific components recited in claim 8, i.e., a specific antibody, linker, and toxin, which are the same as those in T-DM1/Kadcyla® (PO. Resp. 35 (citing Ex. 2025, 14), we are persuaded that Patent Owner establishes a sufficient nexus in relation to the cited objective evidence of nonobviousness. *See, e.g.*, *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995) (stating that for objective evidence to be accorded substantial weight, the record "must establish a nexus between the evidence and the merits of the claimed invention"); *In re Kao*, 639 F.3d 1057, 1068–69 (Fed. Cir. 2011) (unexpected results); *Rambus Inc. v. Rea*, 731 F.3d 1248, 1256 (Fed. Cir. 2013) (long-felt need); *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318,

1328 (Fed. Cir. 2008) (praise); *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996) (commercial success).

Petitioner's contentions do not persuade us that results obtained using T-DM1/Kadcyla® were expected in view of cited prior art references, for the reasons discussed in the section above. *See supra* § II.B.6; Reply 18–19. We also are not persuaded by Petitioner's position that the alleged unexpected results are not commensurate in scope with claim 8, or that a lack of nexus exists between the asserted industry praise and commercial success. *Id.* at 19–23. Claim 8 is directed to a very specific immunotoxin comprising the humanized antibody huMAb4D5-8 (HERCEPTIN®) conjugated to the maytansinoid DM1 toxin via the SMCC linker. The specification of the '856 patent discloses, and claim 8 recites, the very components that led to the unexpected results, praise and commercial success. *See, e.g.*, *GPAC*, 57 F.3d at 1580 (stating, in relation to commercial success, that the evidence must show "that the thing (product or method) that is commercially successful is the invention disclosed and claimed in the patent") (quoting *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988))).

Patent Owner sufficiently establishes that it is the exact combination of those components recited in claim 8, rather than different components previously combined in the prior art, that provided the unexpected results at issue, and led to praise and commercial success. PO Resp. 35–46 (citing evidence in support). For example, Patent Owner provides evidence that T-DM1/Kadcyla® provides unexpectedly superior results in patients, as

compared to HERCEPTIN® plus a chemotherapy agent, in HERCEPTIN®-resistant patients. *Id.* at 35–46 (citing, for example, Ex. 2105 ¶¶ 24–35; Ex. 2012).

For the additional reasons given above, Petitioner does not establish by a preponderance of the evidence that claims 6 or 8 of the '856 patent would have been obvious over Chari 1992 in view of the HERCEPTIN® Label, further in view of Rosenblum 1999 and Pegram 1999.

C. Petitioner's Motion to Exclude

In its Motion to Exclude, Petitioner seeks to exclude Exhibits 2240–44, 2256, 2319, and 2320, as well as certain paragraphs in the Jarosz Declaration (Ex. 2131) relying on those exhibits. Paper 28. Patent Owner cites those exhibits and paragraphs in relation to assertions regarding commercial success of T-DM1/Kadcyla®. PO Resp. 57–59. Petitioner contends that Exhibits 2240–44, 2256, 2319, and 2320 lack foundation under Federal Rule Evidence ("Fed. R. Evid.") 901, and are inadmissible hearsay under Fed. R. Evid. 801, 802 as "out-of-court statements by another that are relied upon for the truth of the matter asserted therein." Paper 28, 7–8. Petitioner also contends that those exhibits are not qualified to be the basis for an expert opinion under Fed. R. Evid. 703, and that paragraphs in the Jarosz Declaration relying on those exhibits are hearsay and lack foundation. *Id.* at 8–9.

As stated in his Declaration, Mr. Jarosz is an economist and Managing Principal of Analysis Group, Inc., "an economic, financial, and strategy consulting firm." Ex. 2131 ¶¶ 6–7. Mr. Jarosz testifies that "Exhibits 2240–

2244, 2256, 2319–2320 provide a summary of voluminous IMS [Health] revenue and prescription data, as well as marketing and promotional efforts relating to Kadcyla." *Id.* ¶ 12. He also testifies that "I and others working under my direction prepared these exhibits." *Id.*

As an initial matter, we note that Petitioner does not establish sufficiently that the challenged claims would have been obvious, even if we do not consider any evidence of commercial success of T-DM1/ Kadcyla® cited by Patent Owner. For the reasons discussed above, Petitioner does not establish a prima facie case of obviousness of claims 1–8 of the '856 patent by a preponderance of the evidence in the first instance—meaning we come to our determination even in the absence of evidence of objective indicia of non-obviousness. In any event, as also discussed above regarding claim 8, Patent Owner provides persuasive evidence of unexpected results, fulfilling a long-felt and unmet need, and praise in the field, even if we ignore all evidence relating to commercial success. Thus, even if we excluded Exhibits 2240–44, 2256, 2319, and 2320, and paragraphs in the Jarosz Declaration citing those exhibits, it would not impact our decision in this case.

In any event, Mr. Jarosz testifies in his Declaration, as an expert, that he personally "considered information from a variety of sources," and opines "that Kadcyla has achieved substantial commercial success in the United States," and that a nexus exists between that success and the claims of the '856 patent. Ex. 2131 ¶¶ 2, 10–16. Mr. Jarosz considered various other clinical treatments on the market and the relevant marketplace. *Id.* ¶¶ 23–

36. In providing details of the basis of his opinion, he cites information, including that summarized in the exhibits at issue in the Motion to Exclude. *Id.* ¶¶ 37–109.

Federal Rule of Evidence 703 states the following.

> An expert may base an opinion on facts or data in the case that the expert has been made aware of or personally observed. If experts in the particular field would reasonably rely on those kinds of facts or data in forming an opinion on the subject, they need not be admissible for the opinion to be admitted. But if the facts or data would otherwise be inadmissible, the proponent of the opinion may disclose them to the jury only if their probative value in helping the jury evaluate the opinion substantially outweighs their prejudicial effect.

Fed. R. Evid. 703, "Bases of an Expert's Opinion Testimony." Although our proceedings do not involve juries, Fed. R. Evid. 703 is informative in our analysis regarding Petitioner's assertion of hearsay.

In his Declaration, Mr. Jarosz provided his expert opinion by direct testimony based on facts or data of which he was made aware or that he personally observed. *See* 37 C.F.R. § 42.53(a) ("Uncompelled direct testimony must be submitted in the form of an affidavit."); Fed. R. Evid. 703. Because that Declaration corresponds to Mr. Jarosz's direct testimony in this trial, we are not persuaded that any part of his Declaration constitutes an "out-of-court statement" or hearsay, as Petitioner contends.

In addition, in relation to the other exhibits at issue (cited in Mr. Jarosz's Declaration and in the Patent Owner Response when citing that Declaration), we are persuaded that the summaries of "voluminous" data and marketing efforts, as prepared by Mr. Jarosz personally or by others working

under his direction, provide probative value that substantially outweighs any possible prejudice to Petitioner. Fed. R. Evid. 703.

For the reasons discussed above, we deny Petitioner's Motion to Exclude Exhibits 2240–44, 2256, 2319, and 2320, and certain paragraphs in the Jarosz Declaration (Ex. 2131) relying on those exhibits.

D. Patent Owner's Motion to Seal

Patent Owner has filed an unopposed Motion to Seal requesting to seal Exhibits 2347 and 2348 filed by Patent Owner in connection with its Opposition to Petitioner's Motion to Exclude. Paper 31, 1.

There is a strong public policy in favor of making information filed in an *inter partes* review open to the public, especially because the proceeding determines the patentability of claims in an issued patent and, therefore, affects the rights of the public. Thus, the standard for granting a motion to seal is "for good cause." 37 C.F.R. § 42.54(a). The party moving to seal bears the burden of proof in showing entitlement to the requested relief, and must explain why the information sought to be sealed constitutes confidential information. 37 C.F.R. § 42.20(c).

We do not rely on Exhibits 2347 and 2348 in making our decision regarding the obviousness challenge of claims 1–8 of the '856 patent, or when deciding Petitioner's Motion to Exclude. We have reviewed Exhibits 2347 and 2348 for the purpose of addressing the Motion to Seal, and are persuaded that good cause exists to have these documents remain under seal. Those exhibits contain confidential information regarding Patent Owner's non-public marketing and sales-related proprietary information. Patent

Owner persuades us that Exhibits 2240–44, 2256, 2319, and 2320, which are unsealed, will fulfill adequately the needs of the public to maintain a complete and understandable record in this case.

For the above-mentioned reasons, we grant Patent Owner's unopposed Motion to Seal Exhibits 2347 and 2348.

III. CONCLUSION

For the foregoing reasons, Petitioner has not demonstrated by a preponderance of the evidence that claims 1–8 of the '856 patent would have been obvious over Chari 1992 in view of the HERCEPTIN® Label, further in view of Rosenblum 1999 and Pegram 1999.

IV. ORDER

For the reasons given, it is

ORDERED that claims 1–8 of the '856 patent are not held unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude is denied;

FURTHER ORDERED that Patent Owner's Motion to Seal is granted;

FURTHER ORDERED that, because this is a Final Written Decision, the 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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Patent 8,337,856 B2

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