**UNITED STATES PATENT AND TRADEMARK OFFICE**

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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ELI LILLY AND COMPANY,
Petitioner

v.

THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA,
Patent Owner

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Case No. IPR2016-00458
Patent No. 7,625,558

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# PATENT OWNER'S NOTICE OF APPEAL

Pursuant to 35 U.S.C. §§ 141(c), 142, and 319, 37 C.F.R. §§ 90.2(a) and 90.3(a), and 28 U.S.C. § 1295(a)(4)(A), Patent Owner University of Pennsylvania ("Patent Owner") hereby appeals to the United States Court of Appeals for the Federal Circuit from the Final Written Decision (Paper 90, attached) entered by the Patent Trial and Appeal Board on July 13, 2017.

For the limited purpose of 37 C.F.R. § 90.2(a)(3)(ii) ("sufficient information to allow the Director to determine whether to exercise the right to intervene in the appeal"), Patent Owner identifies the following issues on appeal:

- The Board's judgment that Claims 1–7, 9–12, 14, 16, 17, and 19–31 of U.S. Patent No. 7,625,558 are unpatentable;
- The Board's claim construction; and
- Any Board finding, determination, judgment, or order supporting or related to the Final Written Decision and decided adversely to Patent Owner.

Patent Owner is concurrently filing this Notice of Appeal, together with the requisite filing fee with the Clerk's Office of the United States Court of Appeals for the Federal Circuit. In addition, a copy of this Notice of Appeal is being filed with the Patent Trial and Appeal Board and served on counsel of record for Petitioner Eli Lilly.

Dated: August 3, 2017

Respectfully submitted,

By: /Bonnie Weiss McLeod/
Bonnie Weiss McLeod
Reg. No. 43,255
**Cooley LLP**
Counsel for Patent Owner

**CERTIFICATION OF SERVICE UNDER 37 C.F.R. § 42.6(e)**

I hereby certify that on the date indicated below, the foregoing Patent Owner's Notice of Appeal was served electronically via email on the following counsel for the Petitioner, as consented to by said counsel:

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Date: August 3, 2017

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## CERTIFICATE OF FILING

I hereby certify that, in addition to being filed electronically through the Patent Trial and Appeal Board's End to End system, a true and correct copy of Petitioner's Notice of Appeal was mailed by Federal Express Overnight Delivery on August 3, 2017, with the Director of the United States Patent and Trademark Office, at 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, Virginia 22314

Date: August 3, 2017

BY: _/Bonnie Weiss McLeod/_
Bonnie Weiss McLeod
Reg. No. 43,255
Counsel for Patent Owner

## CERTIFICATE OF FILING

I hereby certify that a true and accurate copy of the foregoing Petitioner's Notice of Appeal was filed electronically by CM/ECF on August 3, 2017, with the Clerk's Office of the United States Court of Appeals for the Federal Circuit.

Pursuant to 37 C.F.R. §§ 90.2(a) and Federal Circuit Rule 15(a)(1), I certify that on August 3, 2017, the requisite $500.00 fee for appeal of the foregoing Petitioner's Notice of Appeal was paid through Pay.gov to the United States Court of Appeals for the Federal Circuit.

Date: August 3, 2017

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Paper: 90
Entered: July 13, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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ELI LILLY AND COMPANY,
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THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA,
Patent Owner.

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Case IPR2016-00458
Patent 7,625,558

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Before GRACE KARAFFA OBERMANN, RAMA G. ELLURU, and BRIAN P. MURPHY, *Administrative Patent Judges*.

ELLURU, *Administrative Patent Judge*.

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

# I. INTRODUCTION

## *A. Background*

Eli Lilly and Company ("Petitioner") filed a Petition to institute an *inter partes* review of claims 1–7, 9–12, 14, 16, 17, and 19–31 of U.S. Patent No. 7,625,558 (Ex. 1001, the "'558 patent"). Paper 1, 3 ("Pet."). The Trustees of the University of Pennsylvania ("Patent Owner") filed a Preliminary Response. Paper 6 ("Prelim. Resp."). On July 14, 2016, we instituted this trial as to claims 1–7, 9–12, 14, 16, 17, and 19–31 on one ground of unpatentability. Paper 7, 22 ("Dec.").

In our Decision on Institution, we concluded that the arguments and evidence advanced by Petitioner demonstrated a reasonable likelihood that claims 1–7, 9–12, 14, 16, 17, and 19–31 were unpatentable as having been obvious over the combination of Saleh, DeNardo, and Balaban. Dec.22. We must now determine whether Petitioner has established by a preponderance of the evidence that the specified claims are unpatentable over the cited prior art. 35 U.S.C. § 316(e). We previously instructed Patent Owner that "any arguments for patentability not raised in the [Patent Owner Response], or any evidence not referred to, are deemed waived." Paper 8, 3; *see also* 37 C.F.R. § 42.23(a) ("Any material fact not specifically denied may be considered admitted."). Additionally, the Board's Trial Practice Guide states that the Patent Owner Response "should identify all the involved claims that are believed to be patentable and state the basis for that belief." Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,766 (Aug. 14, 2012).

Subsequent to institution, Patent Owner filed a Patent Owner's Response (Paper 20, "PO Resp."), a Contingent Motion to Amend (Paper 19,

"Mot."), and a Reply in support of its to Contingent Motion to Amend (Paper 62, "PO Reply ISO Mot."). Petitioner filed a Reply in support of its Petition (Paper 58, "Pet. Reply") and an Opposition to Patent Owner's Contingent Motion to Amend (Paper 57, "Opp.").

Petitioner relies on the Declarations of Dr. David J. Riese II (Ex. 1042 (in support of Petition), 1065 (in support of Pet. Reply)) and Dr. Robert L. Hong (Ex. 1044 (in support of Petition), 1064 (in support of Pet. Reply)). Patent Owner relies on the Declaration of Dr. Rolf Craven (Ex. 2040) and Dr. Susan Knox (Ex. 2093) (both in support of Patent Owner's Response)).

An oral hearing for this proceeding was held on March 29, 2017, and a transcript of the hearing is included in the record. Paper 89 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

In connection with the arguments and evidence advanced by Petitioner to support its positions that Patent Owner chose not to address in its Patent Owner Response, the record now contains persuasive, unrebutted arguments and evidence presented by Petitioner regarding the manner in which the asserted prior art teaches corresponding elements of the claims against which that prior art is asserted. Based on the preponderance of the evidence before us, we conclude that the prior art identified by Petitioner describes all limitations of the reviewed claims, except for those that Patent Owner contested in the Patent Owner Response, which we address below.

For the reasons that follow, we determine that Petitioner has shown by a preponderance of the evidence that claims 1–7, 9–12, 14, 16, 17, and 19–31 of the '558 patent are unpatentable. We further deny Patent Owner's Contingent Motion to Amend.

### *B. Related Proceedings*

The ’558 patent is asserted in *Trustees of the Univ. of Pa. v. Eli Lilly & Co.*, 2:15-cv-06133-WB (E.D. Pa.). Pet. 1; Paper 5, 2.

### *C. The ’558 Patent (Ex. 1001)*

Application serial No. 10/100,952, which issued as the ’558 patent, was filed March 19, 2002 as a continuation of application serial No. 09/111,681, filed July 8, 1998, now U.S Pat. No. 6,417,168, which claims priority to U.S. provisional application No. 60/076,788, filed Mar. 4, 1998[1].

The ’558 patent claims methods of treating an individual who has an erbB protein mediated tumor. Ex. 1001, Abstract, 13:10–17. Each of the challenged claims comprises two steps: (a) administering to individuals with an erbB protein mediated tumor/contacting such tumor cells with an antibody; and (b) thereafter exposing the individuals/tumor cells to anti-cancer or gamma radiation. The remaining limitations of the challenged claims relate to properties of the tumor/cells, the administered antibody, or the time after which the radiation is administered.

### *D. Illustrative Claim*

We instituted a review of claims 1–7, 9–12, 14, 16, 17, and 19–31. Claims 1, 5–7, 11, 26, and 27 are independent claims. For purposes of this

[1] Petitioner argues that the claims of the ’558 Patent are not entitled to the March 4, 1998 provisional filing date. Pet. 8–9. But we need not resolve this dispute for purposes of this Decision because the asserted references predate the provisional filing date and we determine that they render the challenged claims unpatentable.

Decision, claim 1 is illustrative of the challenged claims and is reproduced below:

> 1. A method of treating an individual who has an erbB protein mediated tumor which method comprises steps of:
>
> (a) administering to said individual an antibody which inhibits formation of erbB protein dimers that produce elevated tyrosine kinase activity in a tumor cell, said inhibition having a cytostatic effect on the tumor cell; and
>
> (b) thereafter exposing said individual to a therapeutically effective amount of anti-cancer radiation.

*E. Grounds of Unpatentability Instituted for Trial*

We instituted trial based on the following asserted references.

| Reference | Patent/Publication | Date | Exhibit |
|---|---|---|---|
| Saleh | Saleh et al., *In vitro and in vivo evaluation of the cytotoxicity of radiation combined with chimeric monoclonal antibody to the epidermal growth factor receptor*, 37 Proc. Am. Assoc. Cancer Res. 612: Abstract No. 4197 (1996) | 1996 | Ex. 1003 |
| DeNardo | DeNardo et al., *The Importance of Time Dose Relationships in Enhancement Strategies for RIT of Breast Cancer*, 2(3) Tumor Targeting: J. Int. Soc. Tumor Targeting 148–49 (1996) | 1996 | Ex. 1004 |
| Balaban | Balaban et al., *The effect of ionizing radiation on signal transduction: antibodies to EGF receptor sensitize A431 cells to radiation*, 1314 Biochim. Biophys. Acta 147–156 (1996) | 1996 | Ex. 1016 |

We instituted review of claims 1–7, 9–12, 14, 16, 17, and 19–31 based on the following ground.

| References | Basis | Claims Challenged |
|---|---|---|
| Saleh, DeNardo, and Balaban | § 103 | 1–7, 9–12, 14, 16, 17, and 19–31 |

Dec. 22.

## II. ANALYSIS

### *A. Claim Interpretation*

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *see Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2146 (2016). Under the broadest reasonable construction standard, claim terms are presumed to have 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 Paulson*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). For purposes of this decision, we analyze Patent Owner's proposed claim constructions of the following claim terms: "anti-cancer radiation" and "gamma radiation," "cytostatic effect," and "multimeric receptor ensembles."

#### "*anti-cancer radiation" and "gamma radiation*"

Each of independent claims 1, 7, 11, 26, and 27 recites exposing the individual/tumor cell to "anti-cancer radiation," while independent claims 5 and 6 recite exposure to "gamma radiation." In our Decision on Institution,

we construed "anti-cancer radiation" and "gamma radiation" to mean "any of the protocols and parameters regarding the administration of therapeutic radiation to treat tumors described in the *Perez & Brady* textbook, which includes RIT." Dec. 7.

Petitioner does not propose constructions for these terms, but rather argues that a skilled artisan would conclude that radio immunotherapy ("RIT")[2] and external beam radiation are within the scope of "anti-cancer radiation" and "gamma radiation," as those terms are used in the claims of the '558 Patent. Pet. 15 (citing Ex. 1044 ¶¶ 30, 32). Patent Owner disagrees, arguing that "anti-cancer radiation" "refers to conventional external beam radiation and excludes RIT." PO Resp. 24. According to Patent Owner, a skilled artisan "reading the patent specification and patent office record would not interpret 'anti-cancer radiation' as including RIT, because (1) it was not conventional at the time of filing, and (2) it was known to operate through a different mechanism than mitotic cell death." *Id*. at 24.

In support, Patent Owner avers that the '558 patent specification is "replete with statements that make clear that the Patent Owner was referring to conventional external beam radiation that had long been used to treat cancer patients." *Id*. at 24–26. Patent Owner points to disclosure in the specification referring to "*conventional* cytotoxic agents such as gamma irradiation," "[g]amma radiation . . . delivered according to *standard* radiotherapeutic protocols," "therapeutic adjuvant *in combination with preexisting treatments*," and "cancer cells more sensitive to concurrent

[2] Radio immunotherapy uses antibodies labeled with a radionuclide to deliver cytotoxic radiation to a target cell. Ex. 1035, 447.

treatment *with preexisting agents*." PO Resp. 25 (citations omitted) (emphases in original). In addition, according to Patent Owner, "the only anti-cancer radiation described in the '558 Patent Examples is external beam radiation." *Id*. at 26 (citing Ex. 1001, 49:60–63, 65:27–30). Patent Owner's expert, Dr. Knox, supports Patent Owner's proposed construction. Ex. 2093 ¶ 29; *see id*. at ¶¶ 26–28.

Patent Owner also argues that RIT was "neither standard nor conventional in the art at the time of the invention." *Id*. at 27. Dr. Knox opines that a skilled artisan would have known that RIT was "still being investigated for its mechanism of action, utility, limitations and safety." Ex. 2093 ¶ 33. Patent Owner further contends that excluding RIT from the scope of "anti-cancer radiation" is consistent with Federal Circuit law on the scope of incorporation by reference. PO Resp. 28 (citing *Zenon Envtl., Inc. v. U.S. Filter Corp*., 506 F.3d 1370, 1379 (Fed. Cir. 2007)).

Lastly, Patent Owner argues, with supporting opinion testimony from Dr. Knox, that because the cellular mechanisms involved in tumor cell death in response to RIT and external beam therapy are different, a skilled artisan would not construe "anti-cancer radiation" as encompassing RIT. *Id*. at 28–29 (citations omitted). In particular, Patent Owner contends that RIT and external beam therapy deliver radiation to tumor cells at different dose rates. *Id*. at 29–30. According to Patent Owner, RIT delivers low dose rate radiation to cancer cells resulting in the mechanisms of cell death towards apoptosis (i.e., a process that, at the time, was thought to not involve dividing cells) and external beam radiation delivers higher dose rates, resulting in a relatively more radiation-induced mitotic death (i.e., selectively killing more dividing cells). *Id*. According to Dr. Knox, a

skilled artisan reading the '558 patent and prosecution history would have known that "anti-cancer radiation" was referring to radiation that selectively kills dividing cells (i.e., mitotic death) and not RIT. Ex. 2093 ¶¶ 38, 42.

With respect to the term "gamma radiation," Patent Owner proposes the construction "gamma radiation delivered by conventional external beam radiation" for the reasons discussed above with respect to "anti-cancer radiation." PO Resp. 30. Patent Owner additionally argues that the challenged claims require that the gamma radiation have a therapeutic effect, with claims 5 and 6 reciting, "exposing the individual to a therapeutic amount of gamma radiation." *Id*. at 31. Specifically, Patent Owner disagrees with Petitioner that Yttrium-90 ("Y-90" or "$^{90}$Y")[3], the radionuclide disclosed in one of the asserted references, qualifies as gamma radiation within the meaning of the claims of the '558 patent. *Id*. While acknowledging that $^{90}$Y emits gamma radiation, Patent Owner argues that $^{90}$Y does not have therapeutic applicability. *Id*. Thus, concludes Patent Owner, a skilled artisan reviewing the challenged claims seeking to administer "gamma radiation" to treat a cancer patient would not have considered using RIT employing a radionuclide-labeled antibody, and would have understood the claims to require "exposing the individual to gamma radiation via conventional, established external beam gamma beam radiation therapies used at the time of the filing to treat cancer patients."[4] *Id*. at 31–32 (citing Ex. 2093 ¶¶ 54, 56).

[3] $^{90}$Y is an RIT agent. Ex. 1004, 149.

[4] Patent Owner states that its arguments also apply to dependent claims 7 and 11, which recite that the anti-cancer radiation is present in an "effective amount." PO Resp. 32, n.4.

We agree with Petitioner that Patent Owner's proposed constructions of "anti-cancer radiation" and "gamma radiation" that excluding RIT are not the broadest reasonable interpretations of those terms in light of the specification. Pet. Reply 10. Specifically, Patent Owner's proposed constructions are inconsistent with the ordinary meaning of these terms and their use in the specification, and there is no disavowal of the ordinary meanings of these terms. *See id*. at 9; *see* Ex.1001, 18:13–19 (quoted below).

As Petitioner points out (*id*. at 2), Patent Owner's expert, Dr. Knox, admitted that "anti-cancer radiation" would encompass RIT outside the context of the '558 patent. Ex. 1066, 100:11–102:4. Dr. Knox testified that "in the broadest possible definition, including things that were still very investigational [RIT] would fall under that umbrella ["anti-cancer radiation"], but we're not talking about the patent, we're not talking about my interpretation of the language in the patent. We're talking in very general terms apart from the patent what is the broadest definition that one could use." *Id*. at 101:19–102:4. Dr. Knox explains that in "general terms," "anti-cancer radiation" "would be any form of radiation that can kill tumor cells." Ex. 1066, 100:11–18. Moreover, Patent Owner's attempts to exclude RIT from the scope of "anti-cancer radiation" and "gamma radiation" are not persuasive.

The challenged claims do not exclude RIT. In addition, the '558 patent specification incorporates by reference a text on the treatment of cancer patients with radiation that features an entire chapter devoted to RIT. The '558 patent specification expressly states:

> Those skilled in the art can readily formulate an appropriate radiotherapeutic regimen. Carlos A Perez & Luther W Brady: Principles and Practice of Radiation Oncology, 2nd Ed. JB Lippincott Co, Phila, 1992, which is incorporated herein by reference describes radiation therapy protocols and parameters which can be used in the present invention.

Ex. 1001, 18:13–19. Chapter 17 of the *Perez & Brady* textbook (*Radioimmunoglobulins in Cancer Therapy*) discloses the use of radiolabeled antibodies to treat cancer, *i.e.*, RIT. Ex. 1035, 453; *see also* Ex. 1044 ¶¶ 27–29. The *Perez & Brady* textbook also states that "[r]adiolabeled antibodies have had demonstrable efficacy in clinical applications," and specifically refers to the radioisotope $^{90}$Y, a gamma emitter (Ex. 1052, 47–48), conjugated to antibodies for use in RIT. Ex. 1035, 450; Ex. 1044, ¶ 27. We agree with Petitioner that a skilled artisan would understand this specification passage to mean that the protocols and parameters regarding the administration of therapeutic radiation described in the *Perez & Brady* textbook (Ex. 1035) can be used to practice the methods claimed in the '558 patent. Pet. 14 (citing Ex. 1044 ¶¶ 25–26). In light of the incorporation of *Perez & Brady* in the specification of the '558 patent, and the express statement that the "radiation therapy protocols and parameters [described therein] *can be used* in the present invention," Ex. 1001, 18:18–20 (emphasis added), including RIT within the scope of "anti-cancer radiation" and "gamma radiation" is both reasonable and consistent with the specification. *See* Pet. Reply 13.

Patent Owner's reliance on references in the specification to "conventional" and "standard" as limiting "anti-cancer radiation" and "gamma radiation" to external beam radiation is unavailing. *See* PO Resp. 25–26. As Petitioner points out (Pet. Reply 11), for example, Dr. Knox

admits that brachytherapy, a form of radiation where a sealed radiation source is placed next to a cancer tumor, was a conventional and established radiation therapy as of 1998. Ex. 1066, 202:8–203:20. Brachytherapy, however, is not external beam radiation. Ex. 1066, 203:18–20. Thus, Patent Owner's proposed claim constructions of "anti-cancer radiation" and "gamma radiation" would exclude brachytherapy, a conventional and well established anti-cancer radiation method as of 1998, because brachytherapy is not external beam radiation. *See* Pet. Reply 11.

Patent Owner's reliance on the disclosed examples in the '558 patent also is unavailing. See PO Resp. 26. As Petitioner further points out, only two of the examples in the specification refer to radiation, one example employing a device not suitable for treating human patients and one which does not provide any detail to specify that external beam radiation was used. Ex. 1064 ¶¶ 10–16. Furthermore, Patent Owner has not sufficiently persuaded us that we should limit the broadest reasonable construction of the claim terms to the disclosed examples. *See Glaxo Wellcome, Inc. v. Andrx Pharm., Inc.*, 344 F.3d 1226, 1233 (Fed. Cir. 2003) ("When a claim term has an accepted scientific meaning, that meaning is generally not subject to restriction to the specific examples in the specification.").

In addition, there was no prosecution history disavowal of RIT. Patent Owner does not argue that the applicant during prosecution disavowed RIT from the scope of these terms. Tr. 58:3–4 ("[t]here was no expressed disavowal of the RIT chapter of Perez & Brady"). In order for the prosecution history to limit the scope of the claim terms, "the alleged disavowing actions or statements made during prosecution be both clear and unmistakable." *SAS Institute, Inc. v. ComplementSoft, LLC*, 825 F.3d 1341,

1349 (Fed. Cir. 2016), *cert. granted sub nom.*, *SAS Institute Inc. v. Lee*, No. 2016-696, 2017 WL 468440 (U.S. May 22, 2017). "Where the alleged disavowal is ambiguous, or even amenable to multiple reasonable interpretations," disclaimer does not apply. *Id.* The record does not contain sufficient evidence to support prosecution history disavowal of RIT.

Patent Owner's argument that the cellular mechanisms involved in tumor cell death in response to RIT is apoptosis versus mitotic cell death also is unavailing. PO Resp. 28–29. The claims do not require a particular method of cell death. Ex. 1066, 124:2–12 (Dr. Knox admits, the '558 patent claims do not specify a particular mechanism of cell death). Dr. Hong, Petitioner's expert, agrees with Dr. Knox that, regardless of the mechanism of cancer cell death, the radiation from RIT kills cancer cells. Ex. 1064 ¶ 16 ("[r]egardless of the mechanism of cancer cell death, Dr. Knox and I agree that radiation from RIT kills cancer cells").

Thus, we are not persuaded that RIT is excluded from the scope of the claim terms "anti-cancer radiation" and "gamma radiation." Further, for purposes of this Decision, we need not expressly construe these terms.

"*cytostatic effect*"

Independent claim 1 recites "administering . . . an antibody which inhibits formation of erbB protein dimers that produce elevated tyrosine kinase activity in a tumor cell, said inhibition having a *cytostatic effect* on the tumor cell." Independent claims 5, 6, 7, and 11 include similar language. For example, claim 6 recites, "administering . . . an antibody that disrupts kinase activity mediated by EGFR, said disruption having a *cytostatic effect* on the tumor cells."

Petitioner does not propose a construction for the claim term

"cytostatic effect" and argues that the asserted prior art "discloses a cytostatic antibody in combination with radiation, even under Patent Owner's narrow claim construction of 'cytostatic effect.'" Pet. Reply 1.

Patent Owner argues that the term "cytostatic effect" means "an inhibition of tumor cell growth by accumulation of tumor cells in the $G_1$ (also known as $G_0/G_1$)[5] phase of the cell cycle." PO Resp. 32 (citing Ex. 2040 ¶¶ 24-28). Patent Owner further argues that "when the inhibitory agent is removed, growth resumes." *Id*. (citing Ex. 1002, 217 ¶ 16 (Dr. Jeffrey A. Drebin, M.D., Ph.D. ("Dr. Drebin") stating that "[t]he term 'cytostatic' is used in oncology to describe therapeutic agents that inhibit or suppress cell growth and multiplication. This is distinguished from other therapies that actually kill the cancer cells, and are therefore said to be 'cytotoxic.' Unlike cytotoxic agents, cytostatic agents do not kill cancer cells.")); *see also* 1002, 217 ¶ 17 (Dr. Drebin stating, "[t]he claims specify, however, that the antibody does not kill the cancer cells. Rather, the antibody stops the cancer cells from multiplying, by inhibiting the formation of erbB-protein dimers, thereby disrupting their tyrosine kinase activity.").

According to Patent Owner, the specification explains that growth inhibition arises via accumulation of the cells in the $G_0/G_1$ phase of the cell cycle. PO Resp. 33 (citing Ex. 1001, 24:6-9 (noting that "[d]isruption of tyrosine kinase activity, such as by inhibiting dimer formation between monomeric components, results in a cytostatic effect on the tumor cells.")); Ex. 1001, 51:6-9 ("U87/T691 cells exhibited a higher $G_0/G_1$ fraction, and reduced S and $G_2$/M populations when compared to parental glioblastoma

[5] Patent Owner provides an explanation of the different phases of dividing cells. PO Resp. 6–8.

cells when grown asynchronously in culture either with or without radiation treatment, and the largest difference was in the $G_0/G_1$ population."). Patent Owner concludes that this interpretation is consistent with what was known to a skilled artisan at the time of the invention, i.e., that inhibiting the signaling pathways activated by growth factors led cells to accumulate in the $G_0/G_1$ phase of the cell cycle. PO Resp. 33 (citing Ex. 2040 ¶¶ 24-28).

Although Petitioner does not propose a construction, Petitioner contends that Dr. Drebin's testimony on the meaning of "cytostatic effect" conflicts with Patent Owner's proposed construction. Pet. Reply 6, n.1. Petitioner notes that Dr. Drebin testified that a "cytostatic effect" does not "require arresting the cells in a certain phase of the cell cycle." *Id*. (citing Ex. 1076, 30:20–31:2). Petitioner further notes that Dr. Drebin also testified that the arresting of cells in any phase of the cell cycle, not just the $G_0/G_1$ phase, would be considered a cytostatic effect. *Id*. (citing Ex. 1076, 31:9–32:13). Furthermore, Dr. Drebin explained that "marked *reduction, suppression or inhibition of growth that isn't complete* [] would still be considered cytostatic." Ex. 1076, 27:6–16 (emphasis added). Consistent with this testimony, Dr. Craven, Patent Owner's expert, opines that a skilled artisan, in the context of the '558 patent, "would understand that cytostatic effect generally refers to a result whereby tumor growth is inhibited but tumor cells are not killed, such that once the inhibitory agent is removed tumor growth resumes." Ex. 2040 ¶¶ 24–28. Dr. Craven, however, does not provide support from the specification for the requirement that growth resumes once the inhibitory agent is removed. *Id*.

We determine that although the specification does not provide an express construction for the term "cytostatic effect," the specification

discloses a mechanism that results in a "cytostatic effect" on tumor cells. Because the specification expressly states that "[d]isruption of tyrosine kinase activity, such as by inhibiting dimer formation between monomeric components, results in a cytostatic effect on the tumor cells" (Ex.1001, 24:6–9), we need not determine whether a "cytostatic effect" means "an inhibition of tumor cell growth by accumulation of tumor cells in the $G_1$ (also known as $G_0/G_1$) phase of the cell cycle," as proposed by Patent Owner. A showing in the prior art of an antibody that disrupts tyrosine kinase activity, such as by inhibiting dimer formation, is sufficient to satisfy the claimed inhibition having a "cytostatic effect."

"*multimeric receptor ensembles*"

Independent claim 5 recites that the tumor cells have "multimeric receptor ensembles which provide tyrosine kinase activity associated with a transformed phenotype." Petitioner contends that the term "multimeric receptor ensembles" includes "EGFR homodimers and/or EGFR-p185 heterodimers because EGFR and p185 are erbB family members that dimerize." Pet. 16 (citing Ex. 1042 ¶ 40; Ex. 1001, 23:27–35).

Patent Owner agrees with the Petitioner's proposed definition of "Multimeric Receptor Ensembles" "as referring to homodimers and heterodimers of the erbB family members, including EGFR (erbB1) homodimers, p185 (erbB2) homodimers, and EGFR-p185 (erbB2) heterodimers." PO Resp. 33 (citing Ex. 1001 at 1:45–55, 23:27–35). Patent Owner, however, contends that "the remainder of claim 5" limits the claim to specific types of multimeric receptor ensembles included in this genus. *Id*. Specifically, Patent Owner contends that claim 5 is "limited to the treatment of tumor cells having multimeric receptor ensembles comprising

(i) erbB homodimers that are mutant EGFR homodimers or p185 homodimers; or (ii) erbB heterodimers that are *p185/EGFR heterodimers*, p185/mutant EGFR heterodimers, p185/erbB3 heterodimers, p185/erbB4 heterodimers or EGFR/mutant EGFR heterodimers." *Id*. at 33–34 (emphasis added).

We need not construe the claim term "multimeric receptor ensembles" because both parties agree that the scope of this claimed element includes EGFR-p185 heterodimers.

### *B. Level of Ordinary Skill in the Art*

According to Petitioner's expert, Dr. Riese, with respect to the aspects of the '558 Patent pertaining to the characteristics of the antibody and its effects on tumor cells, a person of ordinary skill in the art at the time of the invention "would have [had] a Ph.D. or M.D., with at least five years of specialized research experience in the biochemistry and physiology of the Epidermal Growth Factor family of peptide hormones and their receptors, the erbB receptor tyrosine kinases." Ex. 1042 ¶ 15. According to Petitioner's expert, Dr. Hong, with respect to the aspects of the '558 Patent pertaining to administering a therapeutically effective amount or therapeutic amount of radiation, a person of ordinary skill in the art at the time of the invention "would have had at least an M.D., with at least five years of specialized clinical experience in the treatment of tumors, such as those caused by cancer, using radiation in combination with other therapies." Ex. 1044 ¶ 24.

According to Patent Owner's expert, Dr. Craven, with respect to the aspects of the '558 Patent pertaining to the characteristics of the anti-erbB antibody and its effects on tumor cells, a person of ordinary skill in the art at

the time of the invention "would have had several years of specialized research experience in the biology of erbB receptor tyrosine kinases. . . . acquired by education, training, work experience, or some combination thereof, or by other means." Ex. 2040 ¶ 21. According to Patent Owner's Expert, Dr. Knox, with respect to the aspects of the '558 Patent relating to anti-cancer radiation and gamma radiation, a person of ordinary skill in the art at the time of the invention "typically would have had several years of specialized clinical experience in the treatment of tumors using radiation therapy. . . . acquired by education, training, work experience, or some combination thereof, or by other means," would have been "conversant with current medical treatments and the standard of care at the time," "would have understood how to identify, assess and/or apply contemporary radiation therapies in a clinical setting," and "would have been familiar with the scientific literature relating to anti-cancer radiation and radiotherapy at the time of the effective filing date of the '558 Patent." Ex. 2093 ¶¶ 21, 23.

The parties' formulations as to the level of ordinary skill in the art are similar, and neither side identifies with specificity an error in the opposing side's formulation. *See* PO Resp. 18–20. On the record presented, we determine that the cited prior art is representative of the level of ordinary skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the level of ordinary skill in the art may be evidenced by the cited references themselves). Specifically, the references are consistent with the parties' formulations and demonstrate the level of skill in the art. Our determinations regarding the patentability of the challenged claims would remain the same under either side's proposed formulation.

### *C. Scope of Petitioner's and Patent Owner's Replies*

We authorized each party to file papers identifying with particularity each new argument or evidence in the opposing party's reply paper that the party believes is beyond the scope of a proper reply, as an alternative to authorizing the filing of motions to strike. Exhibit 1114, Papers 72, 74, 81, 82.

#### *1. Petitioner's Position Regarding Patent Owner's Reply In Support of Contingent Motion to Amend*

Petitioner contends that Patent Owner's Reply in support of its contingent Motion to Amend presents new arguments and evidence. Paper 72. Specifically, Petitioner challenges Paper 62, 3–4 and Exhibits 2111–2116 as new arguments and evidence relating to alleged support in the original disclosure for the claimed antibodies. Paper 72, 1–2. Petitioner also challenges: Paper 62, 11–12, discussing the alleged statistical insignificance results of DeNardo 1997; and Paper 62, 12, discussing March 1998 experimental work by Dr. Park in support of conception and due diligence to antedate certain references. Paper 72, 2–3.

Patent Owner persuasively contends that the challenged arguments and evidence, Paper 62, 3–4 and Exhibits 2111–2116, were submitted to rebut Petitioner's argument raised in its Opposition that the '681 application does not provide adequate support for the claimed antibodies and to refute Petitioner's alleged mischaracterization of the disclosure of the '681 application. Paper 81, 1–2. Patent Owner also persuasively contends that the challenged arguments presented at Paper 62, 11–12 were submitted to rebut Petitioner's argument that Patent Owner failed to distinguish DeNardo 1997 in its contingent motion to amend. Paper 81, 2. Lastly, Patent Owner persuasively contends that arguments submitted at Paper 62, 12 were not

newly submitted because Petitioner was already on notice of the relevant antedating time period and respond to Petitioner's opposition to its motion by noting that evidence already of record is allegedly sufficient to antedate these three references. Paper 81, 2–3. Patent Owner also points out that Dr. Park's Notebook (Ex. 2080) and his Declaration (Ex. 2087), discussed in the motion to amend, describe Dr. Park's March 1998 experiments. *Id*. at 3.

We have reviewed Patent Owner's Reply in support of its motion to amend and determine that the arguments and evidence submitted are within the scope of a proper reply to Petitioner's opposition to the motion. *See* 37 C.F.R. § 42.23(b) (a reply may only respond to arguments raised in the corresponding opposition, and cannot cure deficiencies in the original motion). Specifically, the arguments and evidence at Paper 62, 3–4 and Exhibits 2111–2116 support Patent Owner's position, and rebut Petitioner's argument to contrary, that the '681 application provides adequate support for the claimed antibodies. The challenged arguments presented at Paper 62, 11–12 rebut Petitioner's argument that Patent Owner failed to distinguish DeNardo 1997 in its contingent motion to amend. The arguments submitted at Paper 62, 12 were within the scope of a proper reply because Petitioner was already on notice of the relevant antedating time period. These arguments respond to Petitioner's opposition by identifying evidence already of record that is allegedly sufficient to antedate Petitioner's asserted references.

2. *Patent Owner's Position Regarding Petitioner's Reply In Support of Petition*

Patent Owner contends that Petitioner's Reply (Paper 58, 16) relating to the Wollman reference, presents new substantive arguments. Paper 74, 1. Specifically, Patent Owner contends that this proceeding was instituted on

one single ground (the combination of Saleh, DeNardo, and Balaban), the Petition referenced Wollman in a single sentence, and the Petition did not rely on Wollman for any of Petitioner's § 103 arguments. *Id*.

Petitioner persuasively contends that the challenged argument(s) relating to the Wollman reference was submitted to rebut Patent Owner's argument raised in its Patent Owner response that Balaban teaches away from the claimed treatment method by relying on the same portion of Wollman cited in the Petition. Paper 82, 1–3; *compare* Pet. 11, *with* Pet. Reply 16.

We have reviewed Petitioner's reply in support of its Petition and determine that the argument(s) submitted are within the scope of a proper reply to Petitioner's opposition to the motion. *See* 37 C.F.R. § 42.23(b). Specifically, the challenged argument(s) relating to the Wollman reference rebut Patent Owner's argument that Balaban teaches away from the claimed treatment method by relying on the same portion of Wollman cited in the Petition.

### *D. Petitioner's Experts*

Patent Owner disputes the credibility of Petitioner's experts, specifically arguing that Petitioner's experts lack both the knowledge required to opine as a skilled artisan under Petitioner's own definition of "person of ordinary skill in the art," and further lacked "the candor mandated by these proceedings." PO Resp. 19–21, 46–52. With respect to a "person of ordinary skill in the art," Patent Owner contends that Petitioner's experts, Drs. Reise and Hong, are not qualified to provide opinions from the "view of a POSA," and thus, their declarations are entitled to "little weight." *Id*. at 19–21. We are not persuaded by Patent Owner's arguments.

As Petitioner argues (Pet. Reply 21), a "person of ordinary skill in the art" is a "'theoretical construct' and is 'not descriptive of some particular individual[,]'" *Norgren Inc. v. Int'l Trade Comm'n*, 699 F.3d 1317, 1325 (Fed. Cir. 2012) (citation omitted). Patent Owner does not provide any legal authority for the proposition than an expert witness must fall under the scope of a "person of ordinary skill in the art." *See* PO Resp. 20–21.

Patent Owner also disputes the credibility of Dr. Reise's and Dr. Hong's declarations, contending that they lacked candor. *Id*. at 46–52. Patent Owner, for example, contends that Dr. Reise acknowledged that he does not understand "inherency" as used in patent law. *Id*. at 46. Patent Owner, however, does not cite any legal authority indicating that understanding patent law terms of art is a requirement for qualifying a scientific or technical expert. Fed. R. Evid. 702. Patent Owner's remaining assertions are a disagreement with Dr. Reise's opinions. For example, Patent Owner contends that (i) "Dr. Riese's testimony is inconsistent with the statements in his declaration and establishes that the C225 antibody does not inherently have a cytostatic effect in A431 cells" (PO Resp. 46–47), (ii) Dr. Reise and Petitioner mischaracterized the Goldstein reference (*id*. at 47), and (iii) Dr. Reise's Declaration is deficient for allegedly not making various acknowledgements (*id*. at 47). Similarly, Patent Owner contends that Dr. Hong's testimony is "classic hindsight reconstruction" (*id*. at 47), his conclusions were "based on information taken from the patent" (*id*. at 47–48), and Dr. Hong was "purposefully evasive and nonresponsive throughout his deposition" (*id*. at 48–50). Patent Owner concludes that "neither of Petitioner's Declarations supplies the Board with substantial, reliable evidence sufficient to support the proposed ultimate conclusion of

obviousness." PO Resp. 52. Patent Owner has not provided sufficient reasons for us to disregard Petitioner's experts' opinions.

Disagreement with Petitioner's experts' opinions goes to the merits of Petitioner's obviousness arguments. We have considered the credibility of each witness's testimony and have given their opinions appropriate weight based on our consideration of the entire record. In addition, Patent Owner's contention (PO Resp. 52) that neither of Petitioner's experts analyzed the challenged claims "as a whole" is misplaced. As Petitioner points out (PO Reply 21–22), the ultimate question of obviousness from the perspective of a skilled artisan is a question of law and we may rely on expert testimony in determining what a skilled artisan would have understood at the time of the invention. Therefore, we are not sufficiently persuaded that Petitioner's expert opinions and testimony should not be given any weight.

### *E. Obviousness of Challenged Claims Over Saleh, Balaban and DeNardo*

Petitioner contends that claims 1–7, 9–12, 14, 16, 17, and 19–31 are obvious over the combination of Saleh, DeNardo, and Balaban. Pet. 24–58. We determine that Petitioner has proven by a preponderance of evidence that each of claims 1–7, 9–12, 14, 16, 17, and 19–31 is unpatentable over the combination of Saleh, Balaban, and DeNardo.

The challenged claims are directed generally to treating "erbB protein mediated tumors," as recited in claim 1, and "tumor cells that comprise EGFR," as recited in claim 6. The erbB family of receptors includes erbB1 (also known as EGFR), erbB2 (also known as p185), erbB3 and erbB4. Ex. 1001, 1:45–46; Ex. 1042 ¶ 14. As noted above, Saleh discloses the treatment of A431 tumor cells *in vitro* and in mice with anti-"EGFR Mab

C225 alone or in combination with [radiation therapy]." Ex. 1003, p. 612. Dr. Riese opines that A431 cells, the same cells used in Saleh's mouse xenograft model, are EGFR-associated tumors because they overexpress EGFR, resulting in erbB-mediated transformation. Ex. 1042 ¶¶ 132–134. In addition, Dr. Riese opines that a skilled artisan would further understand that the A431 cells used to form tumor xenografts in Saleh are an accurate model of an erbB protein mediated tumor. Ex. 1042 ¶ 134.

*1. Asserted Prior Art References*

a) *Saleh*

Saleh discloses the treatment of A431 tumor cells *in vitro* and in mice with "the chimeric anti-EGFR Mab [monoclonal antibody] C225 alone or in combination with RT [radiation therapy]." Ex. 1003, 612. A431 cells exposed to C225 and radiation therapy *in vitro* "showed increased cell kill compared to either treatment alone." *Id.* Mice with A431 tumors treated with C225 and radiation had "better tumor control [than mice treated with C225 alone] and there was a RT [radiation therapy] dose dependent increase in anti-tumor effect with combined Mab treatment." *Id.*

b) *Balaban*

Balaban discloses that "monoclonal antibodies to the EGF receptor (EGFR) sensitize [A431] cells to radiation by facilitating radiation-induced apoptosis." Ex. 1016, 147; *see also id.* at 155. Balaban reported that "[a] pronounced increase in radiation induced apoptosis was observed only when cells were pretreated with LA22." *Id.* at 153, Fig. 5; Ex. 1042 ¶ 49. LA22 is an anti-EGFR antibody. Ex. 1042 ¶ 49. Balaban concludes that "*pretreatment with monoclonal antibodies to the EGFR* may be

advantageous as a combined therapy with radiation in human epidermoid carcinoma." Ex. 1016, 155 (emphasis added); Ex. 1042 ¶ 50.

c) *DeNardo*

DeNardo reports that mice bearing HBT (human breast cancer) xenografts were given C225 before or after injection of Yi-90-ChL6, an RIT agent. Ex. 1004, 149. DeNardo found that when "MoAb c225 was given *prior to RIT*, the results showed increase in therapeutic response . . . compared to RIT or MoAb c225 alone but moderate increase in toxicity." *Id*. (emphasis added). DeNardo explains that C225 is anti-EGFR. *Id*. at 148. DeNardo further found that there was no therapeutic enhancement "if c225 followed RIT." *Id*. at 149.

*2. Law of Obviousness*

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed subject matter 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 such subject matter pertains." 35 U.S.C. § 103(a)[6]. The question of obviousness under 35 U.S.C. § 103 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 skill in the art; and (4) objective evidence of nonobviousness, i.e., secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

[6] We refer to the pre-AIA version of 35 U.S.C. § 103.

3. *Patent Owner's Background Information on Cell Division*

Patent Owner explains that dividing cells traverse through several stages referred to collectively as "the cell cycle." PO Resp. 6 (citing Ex. 2005, 4–5). Patent Owner provides the following explanation of the cell cycle of dividing cells:

> The cell cycle is traditionally divided into several distinct phases, of which the most dramatic is the M phase, wherein the cell undergoes mitosis and cytokinesis, the process of nuclear division followed by the cell dividing in two. The interval between the completion of mitosis and the beginning of DNA synthesis is called the $G_1$ phase (G =gap). Replication of DNA occurs during S phase (S=synthesis). Finally, the interval between the end of DNA synthesis and the beginning of mitosis is $G_2$ phase. Cells in $G_1$ can pause in their progress around the cycle and enter a resting state, often called $G_0$ (G zero), where they can remain up to years before resuming progress round the cell cycle at the $G_1$ phase.

*Id*. at 6–7. According to Patent Owner, at the time of the invention of the '558 patent, "it was well known that tumor cells are killed by ionizing radiation through a process involving mitotic division and DNA disrepair." *Id*. at 4. Patent Owner explains that another mechanism that results in cell death is "apoptosis," "'a process of active cell death . . . . [that] consists of sequential stages of nuclear condensation, fragmentation, phagocytosis, and degradation.'" *Id*. at 5 (citing Ex. 2002, 1). Patent Owner asserts that apoptotic programmed cell death does not involve cell division. *Id*. (citing Ex. 2003, 7).

In Patent Owner's view, "dividing cells are more sensitive [to radiation] because the most radio-sensitive part of the cell cycle is the $G_2$ phase." *Id*. at 7. At the time of the invention, according to Patent Owner, "a skilled artisan would have understood that 'radiation induced damage occurs

in the $G_2$ phase of the cell cycle.'" *Id*. (citing Ex. 2006, 8). Patent Owner argues that "it was long recognized that cells that were not cycling through the $G_2$ phase—or were delayed entering $G_2$—were more radioresistant and thus would be less responsive to radiation therapy." *Id*. According to Patent Owner, "the art recognized that deterring cell division would be counter-productive prior to radiation, because if an agent 'causes $G_0/G_1$ arrest, this would prevent cells from progressing to the $G_2$ phase, therefore becoming less sensitive to the effect of radiation.'" *Id*. at 8 (citing Ex. 2006, 8; Ex. 1002, 213–232, ¶ 27). Patent Owner concludes that, at the time of the invention, a skilled artisan "would have administered anti-cancer radiation to tumor cells that were dividing because cells traversing the cell cycle and able to enter $G_2$ phase were the known target for exerting a therapeutic effect" and "would have also known that an agent that induced growth arrest earlier in the cell cycle rendered the cells more resistant to radiation." *Id*. Patent Owner also avers that "it was known that cell killing through conventional radiation resulted from a process of DNA damage and misrepair during cell division, and while apoptosis in radiation was observed in rare cases and was less well understood, the art was actively seeking ways to understand and enhance the apoptosis pathway to enhance tumor cell killing." *Id*. at 8–9.

4. *Prosecution History*

During prosecution of the '558 patent application, Patent Owner submitted a Declaration from Dr. Drebin. Ex. 1002, 213–32. Dr. Drebin's declaration refers to Wazer (Ex. 2008), which describes experiments that investigated the effect of the chemotherapeutic agent tamoxifen on the radiosensitivity of cancer cells. *Id.* at 220 (¶ 27). According to Dr. Drebin,

"[l]ike anti-erbB antibodies investigated in the Drebin publication, tamoxifen has a cytostatic rather than a cytotoxic effect on cancer cells." *Id*. Relying on Wazer, Dr. Drebin further states that treating cancer cells with tamoxifen, arrests growth "'with near complete segregation (>90%) into $G_0/G_1$,'" phase, and that "'when proliferation is inhibited by tamoxifen, there is a marked reduction in radiosensitivity.'" *Id*. at 220 (citations omitted). Based on Wazer, Dr. Drebin concludes that a skilled artisan "would not have expected a cancer therapy combining anti-cancer radiation with the administration of a cytostatic, anti-erbB antibody to be successful" and "would have expected a cytostatic, anti-erbB antibody to make the cancer cells *less* sensitive to radiation, and thereby have an adverse effect on the radiation therapy." *Id*. (emphasis in original).

*5. "Cytostatic effect"*

Each of independent claims 1, 5–7 and 11 recites that the administered antibody has a "cytostatic" effect on the claimed tumor cells. Petitioner shows sufficiently that the C225 antibody administered in Saleh inherently had a cytostatic effect on Saleh's A431 tumor cells.[7] *See* Pet. 19 (stating that it is permissible to use extrinsic evidence to establish that the characteristics of the C225 antibody are necessarily present, even though not explicitly discussed in Saleh, DeNardo or Balaban); *id* at 26–29. *See In re Imes*, 778 F.3d 1250, 1254-55 (Fed. Cir. 2015); *Schering Corp. v. Geneva*

[7] In the Preliminary Response, Patent Owner acknowledged that the antibody identified in Saleh and DeNardo, C225, induced a cytostatic effect. Prelim. Resp. 25. In its Patent Owner Response, however, Patent Owner argues that Patent Owner "has discovered new evidence that establishes that the C225 antibody employed in the A431 xenograft system of Saleh *did not have a cytostatic effect in that system*." PO Resp. 34 (emphasis in original).

*Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) ("An inherent structure, composition, or function is not necessarily known."). The '558 patent specification explains that disrupting tyrosine kinase activity results in a cytostatic effect on the tumor cell, and one way to disrupt tyrosine kinase is by inhibiting dimer formation between monomeric components. Ex. 1001, 24:6–9. The specification expressly states that "[d]isruption of tyrosine kinase activity, such as by inhibiting dimer formation between monomeric components, results in a cytostatic effect on the tumor cell." *Id.*

Petitioner (Pet. 28–29) refers to Goldstein (Ex. 1008), which teaches that C225 antibody has a growth inhibitory effect on tumor cells, stating that "C225 alone was found to be extremely effective in inhibiting the growth of A431 tumors."[8] Ex. 1008, 1314. In addition, Li (Ex. 1013) describes a crystal structure of the FabC225[9] fragment bound to the EGFR extracellular region of cells. Ex. 1013, 302, 308. Li states that, "FabC225 prevents the [EGF] receptor from adopting the extended conformation required for high-affinity ligand binding and dimerization." Ex. 1013, 308. Dr. Reise opines that the bound C225 prevents the EGFR "from adopting the conformation required for dimerization with another EGFR or p185." Ex. 1042 ¶ 62

[8] Patent Owner states that the '558 patent is directed to methods of treating erbB-mediated tumors by administering anti-cancer radiation after administering an antibody that "inhibits formation of the erbB protein dimers and that has a cytostatic effect (*growth inhibitory effect*) on the tumor cell." PO Resp. 9 (emphasis added).

[9] Petitioner explains that FabC225 is the antigen binding fragment of C225. Pet. 26 (citing Ex. 1013, 302). Thus, we agree with Petitioner that a skilled artisan would understand that the data in Li is applicable to C225 because the antigen binding region in FabC225 is the same as the antigen binding region in C225. *See id*. (citing Ex. 1042 ¶ 61 n.6).

(citing Ex. 1013, 308). Dr. Reise further explains that a skilled artisan "would understand that EGFR bound to C225 cannot adopt the extended untethered conformation required for dimerization with either a different EGFR or p185," and, thus, a skilled artisan "would understand that binding of C225, including the C225 administered in Saleh, to EGFR inhibits formation of erbB protein dimers—i.e., EGFR-EGFR homodimers and EGFR-p185 heterodimers." Ex. 1042 ¶ 63. Stated differently, a skilled artisan "would understand that when Saleh administered C225 to cells and to the mice in his study, the result was that C225 inhibited formation of erbB protein dimers." *Id*.

Moreover, Dr. Reise explains that a skilled artisan would have recognized that "stopping dimerization of EGFR with any erbB protein, such as p185 or EGFR, will result in reduced kinase activity because kinase activity occurs upon dimerization." Ex. 1042 ¶ 66 (citations omitted); *id*. at ¶¶ 64–72, 75. As explained by Dr. Reise, the Zhang II and Goldstein references demonstrate that blocking dimerization also blocks tyrosine kinase activity. *Id.* at ¶¶ 65–67, 70–71. Goldstein concludes that "[t]he 225 antibody . . . binds specifically to the human EGFR with an affinity equal to its ligand, competes with the ligand for binding, and blocks activation of tyrosine kinase activity" in A431 cells. Goldstein Ex. 1008, 1311. Patent Owner does not dispute that C225 inhibits formation of erbB protein dimers. *See* PO Resp. 41, n. 9; Tr. 35:23–36:4 (Patent Owner conceding that C225 inhibits protein dimer formation). The '558 patent specification also acknowledges that "[d]isruption of tyrosine kinase activity, such as by inhibiting dimer formation between monomeric components, results in a cytostatic effect on the tumor cells." Ex. 1001, 24:6–9. Therefore, we are

persuaded that Saleh's administration of the C225 antibody necessarily results in the claimed "cytostatic effect" in A431 cells.

Patent Owner argues that the C225 antibody employed in Saleh did not have a cytostatic effect, but rather had a cytotoxic effect. PO Resp. 34–35. For example, Patent Owner refers to Goldstein's (Ex. 1008) teaching that many of the animals treated with C225 alone were tumor free at the end of the protocol and that tumor-free animals followed for three months after treatment remained in complete remission. *Id*. at 35–36 (citing Ex. 1008, Abstract, 8). Patent Owner asserts that, because administering C225 killed tumor cells, a skilled artisan reading Goldstein would have understood that the C225 antibody had a cytotoxic effect. *Id*. at 36. Referring to Saleh II (Ex. 2055), Patent Owner also argues that the mechanisms of tumor cell killing in Saleh is apoptosis, further indicating that C225 treatment of A431 cells had a cytotoxic effect. PO Resp. 37 (citing Ex. 2055, 1, 5; Ex. 2040 ¶ 33). Patent Owner concludes that, "because C225 does not necessarily have a *cytostatic* effect on A431 cells, as confirmed by both Patent Owner's and Petitioner's experts, Petitioner's inherency argument must fail." *Id*. at 38 (emphasis in original).

Patent Owner's argument that C225 exhibits a cytotoxic effect on A431 cells is not persuasive. *See* Pet. Reply 8. Dr. Reise opines that C225 is both cytotoxic and cytostatic. Ex. 1065 ¶¶ 20, 23, 25. Indeed, Dr. Drebin, relied on by Patent Owner, confirmed that an antibody can be both cytotoxic and cytostatic at the same time. Ex. 1076, 41:9–20. Balaban also teaches that treatment with an anti-EGFR antibody induced both cell cycle arrest in the $G_1$ phase and apoptosis. Ex. 1016, 154. Although not expressly conceding that an antibody can have both a cytotoxic and cytostatic effect,

Patent Owner contends that it is "unknowable" whether an antibody has both effects at the same. *See* Tr. 35:6–36:21 (Patent Owner arguing that whether an antibody has had a cytostatic or cytotoxic effect on cells is "unknowable" because a cell assay "measures whether cells are proliferating or they're dead," and "if they're dead, there's been a cytotoxic effect" and "you can't tell what was happening to the cell at the time moment it died."); *id*. at 63:8–10 (Patent Owner's counsel stating "I don't know how it would be possible to have both. A cytotoxic agent can also arrest in $G_1$ and this is discussed in Balaban."). As discussed above, Petitioner has provided substantial evidence that the C225 antibody disclosed in Saleh has a cytostatic effect in A431 cells. *See* Ex. 1042 ¶¶ 62–72, 75; Ex. 1008, 1314; Ex. 1013, 308. We particularly credit the testimony of Dr. Reise that "even if the C225 increased apoptosis in A431 cells, it also had a cytostatic effect on the A431 cells" and "[t]hus, a POSA would conclude that C225, including the C225 administered in Saleh, has a cytostatic effect on A431 cells" (Ex. 1065 ¶ 23), in light of Goldstein's and Li's disclosures. Patent Owner does not provide persuasive evidence that an antibody that has a cytotoxic effect cannot also be cytostatic. Thus, Patent Owner's argument does not refute Petitioner's substantial evidence that Saleh's C225 has a "cytostatic" effect."

Additional record evidence supplies an independent basis for our factual finding on this point. Petitioner argues in the Petition that, "[a]s early as 1983, it was known that the *murine version* of C225 had a cytostatic effect on A431 cells." Pet. 28 (emphasis in original). Referring to Sato (Ex. 1017), Petitioner concludes that because the murine version, M255, was described as being cytostatic, a skilled artisan would "understand that the C225 administered in Saleh . . . has a cytostatic effect on the tumor cell." *Id.*

at 29; Pet. Reply 7–8. Patent Owner does not dispute that M225 is cytostatic in A431 cells. *See* Pet. Reply 7. Rather, Patent Owner argues that a skilled artisan would not have viewed M225 the same as C225. PO Resp. 35. According to Patent Owner, C225 is a chimeric antibody that has been "structurally and functionally altered as compared to the murine version." *Id*. (citing Ex. 2040 ¶¶ 30-31). In support, referring to Goldstein (Ex. 1008), Patent Owner contends that the affinity of C225 for the EGFR is increased compared to M225 and that C225 was more cytotoxic and more effective in in inhibiting tumor growth as compared to M225. *Id*. at 35–36 (citations omitted). Patent Owner concludes that "[b]ecause there are functional differences introduced by the chimerization of M225, a POSA would not have assumed that the C225 antibody was cytostatic, particularly in view of the tumor cell-killing observed in Goldstein." *Id*. at 37 (citation omitted).

The evidence, however, supports Petitioner's contention rather than Patent Owner's. For example, Dr. Reise, referring to Goldstein, states that "the goal of chimerization of M225 was to eliminate human antimouse antibody production while maintaining *the same biological effects seen in M225*." Ex. 1065 ¶ 14 (emphasis added). Dr. Reise further opines that although Goldstein shows a difference in binding affinity between M225 and C225, a skilled artisan would understand that M225 and C225 both elicit the same biological response when the difference in affinity is accounted for. Ex. 1065 ¶¶ 11, 15–17. Dr. Reise states that "the portion that is responsible for recognition of and binding to a target antigen is indeed identical in M225 and C225" and "'[b]oth antibodies were capable of inhibiting the proliferation of cultured A431 cells to the same extent.'" *Id*. at ¶¶ 11, 17 (citing Ex. 1008, 1313). Thus, Dr. Reise concludes that a skilled artisan

"would conclude that C225 has the same cytostatic effect on tumors as M225." *Id*. at ¶ 17.

In addition, Petitioner argues that Saleh's C225 antibody has a "cytostatic effect" on A431 cells even under Patent Owner's construction of the term. Pet. Reply 4–5. Petitioner explains that Saleh's A431 cells were dependent on EGFR for cell cycle progression. Pet. Reply 5. Prewitt (Ex. 1007) discloses that, "A431 is a human tumor cell line that expresses very high levels of EGFR" and "data indicate that stimulation of the EGFR was critical for the growth of A431 tumors, and blockade of receptor activation was sufficient to inhibit tumor growth." Ex. 1007, 420, 422. As discussed above, the C225 antibody, as disclosed in Saleh, inhibits EGFR signaling by binding to EGFR, which prevents the EGFR from adopting the dimerization competent configuration, and, thus, inhibits EGFR signaling. *See* Ex. 1042 ¶¶ 58–63, 91–93. Dr. Reise states that Li teaches that C225 disrupts the process that stimulates cells to "grow and proliferate," including cancer cells. *See* Ex. 1042 ¶ 93. In addition, Saleh II[10] states, "[o]ver a 72 h time course, we found C225 to produce an arrest in the G1 phase (data not

[10] Saleh II has a publication date of 1999, later than the 1998 effective filing date of the '558 patent, but may be relied upon for evidence to show an inherent property because the inherent feature need not be recognized at the time of the invention. *See Schering Corp. v. Geneva Pharms. Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition in the prior art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency); *see also Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1321 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention.").

shown) at one or two points which is similar to the reports of others." Ex. 2055, at 460–61. Patent Owner's expert, Dr. Craven, testified that "if the cell were dependent on EGFR for cell cycle progression, and its signaling were inhibited, the cells would accumulate in the G1 phase of the cell cycle." Ex. 1068, 140:18–141:5; *see also* Ex. 2040 ¶ 27 ("[I]t was well known to a person of ordinary skill in the art at the time that growth factor signaling affected transit through the cell cycle, and that inhibiting the signaling pathways activated by growth factors led the cells to accumulate in the $G_0/G_1$ phase of the cell cycle as compared to the S phase or the $G_2$/M phase."). Thus, we agree with Petitioner (Pet. Reply 5) that, even accepting Dr. Craven's opinion, C225 in A431 cells results in cell "accumulat[ion] in the $G_1$ phase of the cell cycle." *See* Ex. 1068, at 140:18–141:5. Moreover, even under Patent Owner's construction of the term "cytostatic"—"inhibition of tumor cell growth by accumulation of tumor cells in the $G_1$ (also known as the $G_0/G_1$) phase of the cell cycle" (PO Resp. 32)—Petitioner has shown sufficiently that administration of C225 in A431 cells has a cytostatic effect. Pet. Reply 5–6; Ex. 1042 ¶¶ 91–94. Furthermore, Petitioner has demonstrated that C225 has a cytostatic effect under Patent Owner's additional construction requiring growth of the tumor cells to resume. *See* PO Resp. 32. Specifically, Goldstein (Ex. 1008) shows that when administration of the C225 antibody was stopped, the A431 tumor cells that regressed but did not "disappear," i.e., die, began to grow. Ex. 1008, 1315.

We therefore determine that Petitioner has shown by a preponderance of the evidence that the C225 antibody administered in Saleh had a "cytostatic" effect on the claimed erbB protein mediated tumor cells.

*6. Order of Administration*

Each of independent claims 1, 5–7, 11, 26, and 27 is directed to a method of treating an individual who has a tumor by administering an antibody followed by anti-cancer or gamma radiation. For example, claim 1 recites "administering to said individual an antibody . . . *thereafter* exposing said individual to a therapeutically effective amount of anti-cancer radiation." Petitioner asserts that "[a]lthough Saleh does not explicitly state whether the radiation ("RT") was before, during, or after administration of the C225 antibody, DeNardo and Balaban explicitly disclose that administering the antibody *before* exposing tumor cells to radiation had a better therapeutic effect than administering the antibody *after* exposure to radiation." Pet. 29 (emphasis in original).

Specifically, Balaban reported that when exposing A431 tumor cells to an anti-EGFR antibody and gamma radiation, "a pronounced increase in radiation induced apoptosis was observed only when cells were *pretreated with [the anti-EGFR antibody]*…" Ex. 1016, 153 (emphasis added). Balaban concluded that "*pretreatment* with monoclonal antibodies to the EGFR may be advantageous as a combined therapy with radiation in human epidermoid carcinoma." *Id*. at 155 (emphasis added). In addition, DeNardo reported on "[t]he criticality of dose sequence, dose level, and timing relationships for synergy of separate apoptotic signals with RIT," and disclosed that when monoclonal antibody C225 "was given prior to RIT, the results showed *increase in therapeutic response* (CR) compared to RIT or MoAb c225 alone," but no therapeutic enhancement "if c225 followed RIT." Ex. 1004, 148–49 (emphasis added).

Patent Owner argues that "RIT" taught by DeNardo is not within the

scope of "anti-cancer" radiation." PO Resp. 27. As discussed above with respect to the claim construction of "anti-cancer" and "gamma" radiation, however, we do not adopt Patent Owner's proposed construction excluding RIT from the scope of these terms. Moreover, as Petitioner argues (Pet. Reply 14), even if we were to accept Patent Owner's construction excluding RIT from the scope of "anti-cancer" and "gamma" radiation, Balaban discloses gamma radiotherapy. Ex. 1016, 153; Ex. 1044 ¶ 49. Patent Owner does not dispute that Balaban's gamma radiation falls within the scope of the claimed "anti-cancer" and "gamma" radiation. *See* PO Resp. 39–43.

Accordingly, we determine that the combination of Saleh, Balaban, and DeNardo teach "administering to said individual an antibody . . . thereafter exposing said individual to a therapeutically effective amount of anti-cancer radiation," as recited in claim 1.

*7. p185/EGFR Heterodimers*

We determine that claims 5, 10, 14, 17, and 20 cover heterodimers of p185 and EGFR. Claims 10, 14, 17, and 20 require that the claimed antibody inhibits the formation of or kinase activity mediated by "a heterodimer of p185 and EGFR." In addition, claim 5 requires an antibody that disrupts kinase activity associated with a "multimeric receptor ensemble" ("MRE"), wherein the MRE includes "erbB heterodimers that are p185/EGFR heterodimers."

Petitioner avers that "[i]t is well established that A431 cells [the cells disclosed in Saleh] express p185 that forms p185/EGFR heterodimers." Pet. 35; Ex. 1003, 612. Patent Owner responds that "Petitioner . . . has not established that the particular A431 cells of Saleh *necessarily* expressed such p185: EGFR heterodimers." PO Resp. 44 (emphasis added).

Petitioner argues that Saleh inherently discloses the A431 cells described therein express p185: EGFR heterodimers and, in the alternative, that it was obvious that A431 cells express the heterodimers. Tr. 26:12–21 (Petitioner arguing that "So the weight of the evidence here shows that p185 is always expressed in A431 cells," "[b]ut even if the Board agreed that the weight of the evidence show[s] that A431 cells only sometimes express p185 and dimerize with EGFR, that is sufficient because prior art that sometimes but not always embodies the claimed invention nonetheless teaches that aspect of the invention."). Petitioner does not need to show that the particular A431 cells disclosed in Saleh, or that A431 cells, necessarily and always express p185: EGFR heterodimers. Indeed, Patent Owner does not cite legal authority for its position that Petitioner *must show* that Saleh's A431 cells necessarily expressed p185: EGFR heterodimers. Petitioner's unpatentability challenge is based on obviousness principles. A claim would have been obvious if "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 such subject matter pertains." 35 U.S.C. § 103(a). *Hewlett-Packard Co. v. Mustek Sys.*, 340 F.3d 1314, 1326 (Fed. Cir. 2003) ("Just as an accused product that sometimes, but not always, embodies a claimed method nonetheless infringes, a prior art product that sometimes, but not always, embodies a claimed method nonetheless teaches that aspect of the invention." (internal quotations and citation omitted); *see Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[C]ase law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success."); *id*. ("[O]nly a reasonable expectation of success, not a guarantee,

is needed."

According to Petitioner and Dr. Reise, Waterhouse (Ex. 1015), Gaborit (Ex. 1038), and Gulliford (Ex. 1025) disclose that A431 cells express p185: EGFR heterodimers. Pet. Reply 18–19 (citing Ex. 1042 ¶¶ 146–54); Ex. 1065 ¶ 34. For example, Waterhouse presented a "proof-of-principle study" demonstrating that a pair of secondary antibodies from different species could be used to "assess EGFR/HER2[11] dimerization in human cells lines," including A431 cells, and confirmed such dimerization in these cells. Ex. 1015, 731–733. Waterhouse expressly states that "Figure 3D showed that A431 cells stained with donor and acceptor compared to donor alone gave significantly lower lifetimes, indicative of the basal EGFR/HER2 dimerization in these cells (Figure 3C and 3D)." *Id*. at 731–32. According to Dr. Reise, "Waterhouse establishes that A431 cells express p185 and EGFR because EGFR-p185 heterodimers were detected using [the disclosed] assay." Ex. 1042 ¶ 149. Gaborit described "test[ing] an antibody-based TR-FRET assay for detecting and quantifying EGFR/HER2 heterodimers" and provided data quantifying EGFR and HER2 levels in various cell lines, including A341 cells. Ex. 1038, 11340–41, Table 1 (quantifying EGFR and HER2 levels in A431 cells). According to Dr. Reise, Gulliford's Figure 5 teaches that "heterodimerization of activated EGFR and transphorylated p185 is readily induced by EGF in A431 cells." Ex. 1042 ¶ 153; Ex. 1025, 2221, Fig. 5.

According to Patent Owner, the prior art is "replete" with teachings that the A431 cell line exists as many variants arising out of genetic

[11] HER2 is p185. Ex. 1042 ¶ 147.

instability, with the result that protein expression varies from one variant to another. PO Resp. 44 (citing Ex. 2040 ¶¶ 44-48; Ex. 2053, 2 (stating that A431 cells have been reported to "express high levels of EGFR but no p185"); Ex. 2053, 3 (reporting that A431 cells "express high levels of EGFR protein with little or no detectable HER-2 [p185] in culture")). Patent Owner also asserts that references published since the time of the invention further corroborate this position. PO Resp. 45 (citations omitted). Thus, Patent Owner concludes that "the art establishes that while A431 cells have been shown to express p185 in some instances, this is not necessarily always the case." *Id*. (citing Ex. 2040 ¶ 45).

Petitioner replies that "not a single study that Patent Owner and Dr. Craven cite was designed to determine whether A431 cells express p185," "Ullrich [a reference cited by Patent Owner] does not suggest that variability in gene expression would lead to variability in the expression of EGFR or p185 in A431 cells over time," and "the studies that Dr. Craven and Patent Owner cite lack the sensitivity to detect p185 in A431 cells." Pet. Reply 19–20. Petitioner concludes that a skilled artisan "would not credit any of the studies that Patent Owner cites over the studies in the record that were aimed at determining whether A431 cells express p185 and used detection methods sensitive enough to detect low levels of p185—Waterhouse, Gaborit, and Guiliford—which universally concluded that A431 cells express p185." *Id*.

Even assuming Patent Owner's position that A431 cells do not necessarily and always express p185: EGFR heterodimers, Petitioner has shown by a preponderance of the evidence that the challenged method claims at issue would have been obvious. As discussed above,

Waterhouse (Ex. 1015), Gaborit (Ex. 1038), and Gulliford (Ex. 1025) disclose that the A431 cells described therein express p185: EGFR heterodimers. Ex. 1042 ¶¶ 146–54; Ex. 1065 ¶ 34. Dr. Craven cites different references, but those references do not detract from the disclosures of Waterhouse, Gaborit, and Guilliford, which represent substantial evidence that A431 cells would have been understood at the time of the invention to express p185: EFGR heterodimers. That substantial evidence is not undercut by Dr. Craven's citation to additional references that do not report specific data, or explicitly determine, whether A431 cells express p185 or lack the sensitivity to detect p185:EGFR heterodimers in A431 cells. *See* Ex. 1065 ¶¶ 35, 38–44; Ex. 2014 ¶¶ 45–47. Thus, the relevant disclosures of the pertinent prior art establish that a skilled artisan would have had a reasonable expectation that A431 cells express p185: EGFR heterodimers. Saleh teaches treating A431 cells with C225. Ex. 1003, 612. In addition, a skilled artisan would have understood that C225 prevents EGFR dimerization with p185. For example, Li states that "FabC225 prevents the [EGF] receptor from adopting the extended conformation required for high-affinity ligand binding and dimerization." Ex. 1013, 308. *See* Ex. 1042 ¶ 62 (citing Ex. 1013, 308) (Dr. Reise opining that the bound C225 prevents the EGFR "from adopting the conformation required for dimerization with another EGFR or p185"); Ex. 1042 ¶ 63 (Dr. Reise explaining that a skilled artisan "would understand that binding of C225, including the C225 administered in Saleh, to EGFR inhibits formation of erbB protein dimers—i.e., EGFR-EGFR homodimers and EGFR-p185 heterodimers."). A skilled artisan would have also understood that C225 inhibits tyrosine kinase activity. Specifically, Goldstein concludes that "[t]he 225 antibody . . .

binds specifically to the human EGFR with an affinity equal to its ligand, competes with the ligand for binding, and blocks activation of the receptor tyrosine kinase" in A431 cells. Ex. 1008, 1311; *see also* Ex. 1042 ¶¶ 65–67, 70–71. Thus, a skilled artisan treating A431 cells with C225, as taught by Saleh, would have had a reasonable expectation of inhibiting, the formation of or kinase activity mediated by, "a heterodimer of p185 and EGFR," as required by the challenged claims in dispute.

Accordingly, we determine that the asserted references teach all the limitations of challenged claims 5, 10, 14, 17, and 20.

*8. Reason(s) to Combine the Asserted References*

Petitioner demonstrates sufficiently that a skilled artisan would have had reason to combine the teachings of Saleh, Balaban, and DeNardo. *See* Pet. 31–32. Specifically, Petitioner demonstrates that a skilled artisan would have had reason to administer C225 to erbB protein mediated tumor cells and thereafter expose the cells to radiation in order to achieve an increased therapeutic response.

We agree with Petitioner's expert, Dr. Reise, that a skilled artisan "would have reason to combine the teaching from Saleh that treatment of A431 cancer cells with C225 and radiation therapy 'showed increased cell kill compared to either treatment alone,' (Saleh at 612), with the teaching of Balaban." Ex. 1042 ¶ 55; Pet. 20, 31. Dr. Reise reasons that a skilled artisan "would have been motivated to treat the A431 cells, described in Saleh, with C225 before administering radiation because Balaban taught that 'monoclonal antibodies to the EGF receptor (EGFR) sensitize cells to radiation by facilitating radiation-induced apoptosis.'" *Id*. (citing Ex. 1016, 147). According to Dr. Reise, "[i]t is desirable to sensitize cells to radiation

because treatment of sensitized cells with radiation causes greater cancer cell death as compared to treatment of non-sensitized cells with radiation." *Id*. In addition, as Dr. Reise opines, DeNardo taught that when "'c225 was given prior to RIT, the results showed [an] increase in therapeutic response . . . compared to RIT or MoAb c225 alone.'" Ex. 1042 ¶ 56 (citing Ex. 1004, 149). According to Dr. Reise, a skilled artisan "would have understood that the increase in therapeutic response in mice receiving radiation after treatment with C225, as disclosed in DeNardo indicates that cancer patients will have better outcomes if they receive radiation after being treated with C225." Ex. 1042 ¶ 56.

Patent Owner disagrees, arguing that the prior art taught away from administering an antibody having a cytostatic effect before anti-cancer radiation or gramma radiation. PO Resp. 39–40. Patent Owner urges that a skilled artisan "looking to maximize cell-killing using anticancer radiation would not have administered an antibody that arrested cells in the $G_0/G_1$ phase of the cell cycle because that phase had long been recognized as less sensitive to radiation." *Id*. at 40. As discussed above, Patent Owner emphasizes that a skilled artisan "at the time of the invention would have understood that maximizing cell-killing using radiation requires dividing cells that transit through the cell cycle." *Id*. at 41. Thus, concludes Patent Owner, "even assuming, *arguendo*, that a [skilled artisan] would have read the Saleh abstract as teaching an antibody having a cytostatic effect, there would have been no motivation to administer the antibody before anti-cancer radiation." *Id*. (emphasis in original).

Patent Owner's argument is unavailing because the prior art taught a skilled artisan to administer an anti-EGFR antibody prior to radiation or RIT

to increase the therapeutic response. In other words, Balaban and DeNardo clarified the dosing sequence of Saleh by teaching that administering radiation after administering the C225 antibody increased the therapeutic response. Petitioner's argument is especially persuasive given that a skilled artisan had three choices as to when to administer radiation—before, simultaneous with, or after administering anti EGFR antibody. Furthermore, it is of no matter that the prior art might not have recognized the mechanism of operation. *See In re Lintner*, 458 F.2d 1013, 1016 (CCPA 1972) (reason to combine taught by the references differing from applicant's reason to combine did not alter the conclusion of *prima facie* obviousness). Specifically, as noted above, Balaban teaches that "monoclonal antibodies to the EGF receptor (EGFR) sensitize cells to radiation by facilitating radiation-induced apoptosis." Ex. 1016, 147; Ex. 1042 ¶ 49. Thus, we agree with Petitioner (Pet. Reply 15) that because it was known that it was desirable to sensitize cells to radiation (Ex. 1042 ¶ 55), a skilled artisan would have applied the teaching in Balaban to administer the C225 antibody before radiation in Saleh's treatment method, in which treatment of A431 cells with C225 and radiation showed increased cell kill compared to either treatment alone (Ex. 1003, 612). In addition, DeNardo disclosed an increased therapeutic response when the C225 antibody was given prior to RIT, further reinforcing the reason for a skilled artisan to pretreat patients with the C225 antibody, prior to radiation, in order to sensitize the tumor cells for increased RIT radiation-induced apoptosis. Ex. 1004, 149.

Moreover, Patent Owner's attempt to distinguish the mechanism of cell death in Balaban, apoptosis, from the alleged understanding at the time of the invention that "maximizing cell-killing using radiation requires

dividing cells" (i.e., "mitotic division") (PO Resp. 4, 41) is unavailing. As an initial matter, Patent Owner does not provide sufficient factual support for the assertion that dividing cells are required for radiation to kill cells or that cells arrested in the $G_1$ phase are radioresistant. For example, although Awwad (Ex. 2007) teaches that "there is a general tendency for $G_2$/M cells and the $G_1$/S boundary to be the most sensitive and the late S-phase to be the most radioresistant," Awwad recognizes that "[d]ifferent cell lines show different patterns of sensitivity variations during the cell cycle" and "[t]he pattern can also vary for the same cell type when grown *in vivo* or in *vitro*." Ex. 2007, 522. *See also* Ex. 1068, 158:7–160:6; Ex. 2040 ¶¶ 38, 43, 50. In addition, Balaban expressly teaches that the mechanism of cell death from radiation is apoptosis, a mechanism that kills cells. Ex. 1016, 147. Thus, we agree that this teaching would not deter a skilled artisan from combining a cytostatic antibody, such as Saleh's C225, with radiation. *See* Pet. Reply 16–17. Indeed, the '558 patent specification refers to apoptosis as the mechanism of cell death following administration of radiation. Ex. 1001, 10:36–45, 11:11–16, 48:18–19, 51:23–32.

Patent Owner's additional argument that Balaban taught away from administering any agent, including an antibody that induced arrest in the $G_1$ phase of the cell cycle, also is unpersuasive. PO Resp. 41–42 (citing *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc*., 567 F.3d 1314, 1326 (Fed. Cir. 2009) ("An inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements.")). According to Patent Owner, Balaban discloses that in the A431 cell system, EGF (Epidermal Growth Factor) "enhances resistance to radiation" by

arresting the cells in the $G_1$ phase. PO Resp. 41 (citing Ex. 1016, 154; Ex. 2040 ¶¶ 39–41). Thus, concludes Patent Owner, a skilled artisan motivated to enhance cell killing by reducing radiation resistance would not have administered an antibody that induces $G_1$ arrest because it would have been expected to increase radiation resistance via the same mechanism Balaban observed with EGF. *Id*. (citing Ex. 2040 ¶ 40).

Patent Owner's argument is unpersuasive because EGF is not an antibody and Patent Owner has not sufficiently shown that Balaban equates the effects of EGF to the effects of an antibody. Pet. Reply 15 (citing Ex. 1065 ¶¶ 28, 30). Balaban does not teach that a cytostatic antibody should not be administered prior to radiation. *See Ricoh Co., Ltd. v. Quanta Computer, Inc.*, 550 F.3d 1325, 1332 (Fed. Cir. 2008) (quoting *In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006)) ("A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant."). Rather, Balaban teaches that the administration of an anti-EGFR antibody, LA22[12], before radiation did result in an increase in apoptosis. Ex. 1016, 153, Ex. 1042 ¶ 49). As stated previously, Balaban taught a skilled artisan to pretreat patients with antibody in order to sensitize the tumor cells for increased radiation-induced apoptosis.

Patent Owner also notes that Wazer (Ex. 2008) taught that treating cancer cells with tamoxifen arrests cell growth in the $G_0/G_1$ phrase and that

[12] Balaban teaches that LA22 blocks EGFR tyrosine kinase (Ex. 1016, 155), which, according to the '558 specification, results in a cytostatic effect (Ex. 1001, 24:6–9).

when such proliferation is inhibited by tamoxifen, there is a marked reduction in radiosensitivity. PO Resp. 8 (citations omitted). Wazer describes administration of tamoxifen, a small molecule drug that Patent Owner has not shown resembles an anti-EGFR antibody in size, surface area, or mechanism, to MCF-7 cells. *See* Pet. Reply 17 (citations omitted). We, thus, agree with Petitioner that Wazer cannot teach away from using an anti-EGFR antibody in combination with radiation because Wazer does not address using an antibody or an anti-EGFR antibody. *Id.* (citing Ex. 1065 ¶¶ 26–29.

Patent Owner also argues that DeNardo does not provide a reason for combining the teachings because DeNardo discloses RIT, which Patent Owner again contends is not within the scope of "anti-cancer radiation," and therapies having known apoptotic effects. PO Resp. 42. According to Patent owner, a skilled artisan would have understood the RIT disclosed in DeNardo to work by an entirely different mechanism than external beam radiation. *Id*. (citations omitted). Thus, concludes Patent Owner, a skilled artisan "would read DeNardo as teaching the use of an antibody that has a cytotoxic effect and reported to cause apoptosis, in combination with RIT, which also works by apoptosis. *Id*. (citations omitted). This argument is unpersuasive, however, because as discussed above, we do not adopt a construction for "anti-cancer radiation" or "gamma radiation" that excludes RIT. Furthermore, DeNardo teaches an increased therapeutic response by administering the C225 antibody *before* RIT. Ex. 1004, 149; Pet. 21, Pet. Reply 15. A skilled artisan would have known, based on Saleh's teaching, that C225 could be administered before, simultaneously with, or after radiation. DeNardo at least suggests administering an antibody before

another therapeutic method, such as radiation.

Patent Owner further avers that the results reported in DeNardo were later confirmed by the same group as not statistically significant. PO Resp. 43 (citing Ex. 1049, 16; Ex. 2040 ¶¶ 40-41; Ex. 2093 ¶ 65). Thus, asserts Patent Owner, a skilled artisan would not have read DeNardo as teaching that cancer patients will have better outcomes if they receive radiation after being treated with C225. *Id*. (citing Ex. 2040 ¶ 38; Ex. 2093 ¶ 63). Patent Owner concludes that "*even if* a [skilled artisan] would have concluded anything from DeNardo's use of RIT, this failure was in the mind of the POSA at the time, and would have further directed a [skilled artisan] away from attempting the claimed method." *Id*. (emphasis in original). Patent Owner's alleged evidence that DeNardo's results were not "statistically significant," however, does not demonstrate that a skilled artisan would have been discouraged from administering radiation after administering C225. *See Ricoh Co.,* 550 F.3d at 1332; *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1330–31 (Fed. Cir. 2014) (finding that failure to generate statistically significant results did not amount to teaching away); *see also Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337, 1351 (Fed. Cir. 2015) (affirming district court's decision that even statistically insignificant data can serve as motivation to combine).

Therefore, based on the teachings of Saleh, Balaban, and DeNardo, we are persuaded that Petitioner has provided sufficient evidence to support its argument that a skilled artisan would have had reason to administer C225 to Saleh's A431 cells (erbB mediated tumor cells), and thereafter exposing them to radiation, in order to achieve an increased therapeutic response. *See* Ex. 1042 ¶ 57.

*9. Remaining Limitations and Claims*

We have reviewed Petitioner's arguments and the underlying evidence cited in support and are persuaded Petitioner sufficiently establishes that the remaining limitations of the challenged claims, including the dependent claims, are taught by the asserted references. We adopt Petitioner's factual assertions and arguments for purposes of this Decision. Pet. 24–58.

*10. Secondary Considerations*

We further determine that secondary considerations of nonobviousness do not weigh in favor of a finding of nonobviousness of these claims. Factual inquiries for an obviousness determination include secondary considerations based on evaluation and crediting of objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Secondary considerations may include any of the following: long-felt but unsolved needs, failure of others, unexpected results, commercial success, copying, licensing, and praise. *Graham*, 383 U.S. at 17. "[E]vidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). As the Federal Circuit noted, secondary considerations "may often be the most probative and cogent evidence" of nonobviousness. *Id*. "[T]he Board should give the objective indicia its proper weight and place in the obviousness analysis, and not treat objective indicia of nonobviousness as an afterthought." *Leo Pharmaceutical Products, Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013).

Patent Owner argues that the art taught away from the claimed invention and the claimed invention produced unexpected results. PO Resp.

53–56. All types of objective evidence of nonobviousness must be shown to have a nexus to the claimed invention. *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995) (nexus generally); *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996) (commercial success); *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364 (Fed. Cir. 2012) (copying); *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). The stronger the showing of nexus, the greater the weight accorded the objective evidence of nonobviousness. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 (Fed. Cir. 1985).

Patent Owner avers that the art taught away from the claimed invention. PO Resp. 53–54. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant . . . [or] if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *Tec Air, Inc*. v. *Denso Mfg. Mich. Inc*., 192 F.3d 1353, 1360 (Fed. Cir. 1999) (internal quotations and citation omitted). Patent Owner reasserts the argument that a skilled artisan would not have expected the claimed combination—administration of a cytostatic antibody followed by radiation, to provide a successful therapy because cytostatic cancer therapies were likely to decrease a cancer cell's sensitivity to radiation, and thus, have an adverse effect on radiation therapy. PO Resp. 54 (citation omitted). Thus, concludes Patent Owner, a skilled artisan "would not have administered a cytostatic antibody prior to radiation in view of this knowledge."

*Id*.

Patent Owner also asserts, similarly, that the claimed invention provided "unexpected results." PO Resp. 54–56. Specifically, Patent Owner contends that the inventors "discovered—in direct contrast to the expectations in the art—that inducing a cytostatic effect by inducing $G_1$ arrest by blocking ErbB receptor signaling would radiosensitize tumor cells, enhance apoptosis and decrease clonogenic survival." *Id*. at 54. According to Patent Owner, the inventors obtained synergistic results by administering radiation after inducing the cytostatic effect. *Id*. at 54–55. Specifically, Patent Owner argues that "[a]nti-erbB receptor antibodies that induced a cytostatic effect were known," "[a]dministering x-ray radiation and gamma radiation to treat tumor cells was known," but that "there was no prediction in the art that together these treatments would provide the synergistic results obtained by the inventors when administered in an order that was entirely counterintuitive to the state of the art." *Id*. at 55. Patent Owner concludes that the claimed invention resulted in a "synergistic improvement in tumor cell killing when the art taught that the claimed approach would have had an adverse effect on radiation therapy." PO Resp. 56.

Patent Owner's secondary considerations arguments are not persuasive. Patent Owner's "teaching away" argument makes substantially the same assertions with respect to Patent Owner's argument that a skilled artisan would not have had reason to combine the teachings of Saleh, Balaban, and DeNardo. *Compare* PO Resp. 39–43 *with id*. at 53–54. As an initial matter, we disagree that Petitioner did not address Patent Owner's "teaching away" argument. Petitioner specifically addresses this argument. Pet. Reply 14–18. For the same reasons, discussed above, underlying our

determination that a skilled artisan would have had reason to combine the teachings of Saleh, Balaban, and DeNardo, we are not persuaded by Patent Owner's "teaching away" secondary considerations argument. Patent Owner's "unexpected results" argument reasserts the same argument—it was unexpected that "inducing a cytostatic effect by inducing $G_1$ arrest by blocking ErbB receptor signaling would radiosensitize tumor cells, enhance apoptosis and decrease clonogenic survival." PO Resp. 54. As an initial matter, Patent Owner's conclusion that the claimed invention provided "unexpected results" is unsupported by evidence, such as expert testimony, and amounts to attorney argument. Moreover, for the reasons discussed above with respect to our determination that a skilled artisan would have had a reason to combine the asserted references, we are not persuaded by this argument. Therefore, we find that the secondary considerations do not weigh in favor of a finding of nonobviousness of the challenged claims.

*11. Conclusion*

For the foregoing reasons, we determine that Petitioner has established by a preponderance of the evidence that claims 1–7, 9–12, 14, 16, 17, and 19–31 of the '558 patent are unpatentable over Saleh, DeNardo, and Balaban.

## III. MOTION TO AMEND

As noted above, Patent Owner filed a Contingent Motion to Amend claims ("Mot.")[13] and a Reply in support of its to Contingent Motion to

[13] Patent Owner relies on the Declaration of Dr. Rolf Craven (Ex. 2040 (in support of Patent Owner's Contingent Motion to Amend)). Patent Owner also relies on the Declarations of Dr. Donald M. O'Rourke (Ex. 2086), Dr. Byeong-Woo Park (Ex. 2087), Dr. Chuanjin Wu (Ex. 2088), Dr. James G.

Amend ("PO Reply ISO Mot."). Petitioner opposes Patent Owner's motion ("Opp.").

In its motion to amend, Patent Owner proposes substitute claims 42–48 to replace claims 1, 5–7, 11, 26, and 27. Mot. 1. Patent Owner's motion is contingent in that a proposed substitute claim is at issue and considered only if the claim it replaces is found invalid. *Id.* Specifically, Patent Owner proposes the following.

> If each of claims 1–4, 16–17, and 21 is found invalid, the Board is requested to cancel claim 1 and replace it with substitute claim 42. If each of claims 5, 19, 20, and 22 is found invalid, the Board is requested to cancel claim 5 and replace it with substitute claim 43. If each of claims 6 and 23 is found invalid, the Board is requested to cancel claim 6 and replace it with substitute claim 44. If each of claims 7, 9, 10 and 24 is found invalid, the Board is requested to cancel claim 7 and replace it with substitute claim 45. If each of claims 11, 12, 14, and 25 is found invalid, the Board is requested to cancel claim 11 and replace it with substitute claim 46. If each of claims 26-31 is found invalid, the Board is requested to cancel claims 26 and 27 and replace them with substitute claims 47 and 48, respectively.

*Id.* Because we have determined that original claims 1, 5–7, 11, 26, and 27 are unpatentable, we reach the merits of Patent Owner's motion.

As the moving party, Patent Owner bears the burden of proof to establish that it is entitled to the relief requested. 37 C.F.R. § 42.20(c). Entry of the proposed amendments is not automatic, but only upon Patent

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Davis (Ex. 2089), Dr. Natasha Singh (Ex. 2090), Dr. John S. Swartley (Ex. 2091), Dr. Hongtao Zhang (Ex. 2092), Dr. Susan Knox (Ex. 2093), and Dr. Gail Massey (Ex. 2104) (all in support of Patent Owner's Contingent Motion to Amend).

Owner having demonstrated the patentability of those claims.

Patent Owner's proposed substitute claim 42 is illustrative of the proposed substitute claims. Substitute claim 42, with the new claim language added to original claim 1 underlined, is reproduced below.

> 42. A method of treating an individual who has an erbB protein mediated tumor which method comprises steps of:
>
> (a) administering to said individual an antibody which inhibits formation of erbB protein dimers that produce elevated tyrosine kinase activity in a tumor cell, said inhibition having a cytostatic effect on the tumor cell; and
>
> (b) thereafter exposing said individual to a therapeutically effective amount of anti-cancer radiation, wherein said anti-cancer radiation is selected from the group consisting of gamma radiation and x-rays, and does not include radioimmunotherapy.

Mot. 3. Patent Owner explains that substitute independent claims 42 and 45–48 amend original independent claims 1, 7, 11, 26, and 27, respectively, to define "anti-cancer radiation" as "selected from the group consisting of gamma radiation and x-rays, and does not include radioimmunotherapy." *Id*. at 1, 8; Opp. 9–10. Similarly, substitute independent claims 43 and 44 amend original independent claims 5 and 6, respectively, to define "wherein said gamma radiation does not include radioimmunotherapy." *Id*. at 1–2, 8; Opp. 9–10.

Petitioner argues that Patent Owner's proposed substitute claims are unpatentable for lack of written description under 35 U.S.C. § 112, as obvious over the prior art cited in the Petition under 35 U.S.C. § 103, and as obvious over known references cited in Patent Owner's contingent motion to amend. Opp. 1–25. We agree with Petitioner that the proposed substitute claims are unpatentable as having been obvious over the prior art cited in the

Petition.

Petitioner argues that the proposed substitute claims are unpatentable over the same of combination of references that render the original claims unpatentable. Opp. 10. Specifically, contends Petitioner, Balaban discloses the claimed "anti-cancer radiation," i.e, gamma radiation. *Id*. Balaban teaches that "[r]adiation was delivered to cells kept on ice in a Gamma-cell 40 chamber containing two sources of 137 Cs . . . at a dose of 100 cGy/min." Ex. 1016, 148–49. Dr. Knox, Patent Owner's expert, recognizes that $_{137}$Cs is a source of gamma radiation. Ex. 1066, 180:11–12. In addition, Dr. Hong, Petitioner's expert, states that a "Gamma-cell 40 chamber" provides external beam radiation and is not radioimmunotherapy. Ex. 1044 ¶ 46. Patent Owner argues that the references asserted in the Petition do not render the proposed substitute claims obvious, but does not dispute that Balaban discloses the claimed "anticancer" and "gamma" radiation in the proposed substitute claims. *See* Mot. 11–14; PO Reply ISO Mot. 6.

Rather, Patent Owner reasserts the arguments made in support of the original claims. *Id*. Patent Owner argues that the antibody disclosed in Saleh did not have a cytostatic effect, but was cytotoxic; Balaban's antibody was also cytotoxic; and Balaban teaches away from the use of a cytostatic antibody. *Id*. at 14; PO Reply ISO Mot. 6. Patent Owner argues that Petitioner's arguments relating to DeNardo are immaterial to the proposed substitute claims because they explicitly exclude RIT, and DeNardo "employs RIT-mediated cell killing." Mot. at 12; PO Reply ISO Mot. 6. Patent Owner, thus, avers that there would not have been a reason to combine DeNardo with Saleh and Balaban to arrive at claims 42-48. Mot. at 12–13 (citations omitted). Patent Owner also contends that at the time of the

invention, a skilled artisan "would have understood that cell damage caused by external beam radiation occurs as the cells traverse the $G_2$ phase of the cell cycle," and "it has long been recognized that if an agent 'causes $G_0/G_1$ arrest, this would prevent cells from progressing to the $G_2$ phase, therefore becoming less sensitive to the effect of radiation.'" *Id*. at 13 (citations omitted). Patent Owner further concludes that a skilled artisan "would not have had a reasonable expectation of success to modify Saleh by administering an antibody having a cytostatic effect *prior to* external beam radiation therapy because such cytostatic effect would be expected to negatively impact therapy by enhancing radioresistance." *Id*. at 13 (citation omitted).

We determine that the proposed substitute claims would have been obvious over the combination over Saleh and Balaban for the same reasons these references would have rendered the original claims obvious. Specifically, Saleh teaches the administration of an antibody that resulted in a "cytostatic effect" on A431 tumor cells and Balaban teaches the administration of an antibody to cells and thereafter administering gamma radiation to increase the therapeutic response.

Accordingly, we deny Patent Owner's motion to amend.

## IV. MOTION(S) TO EXCLUDE EVIDENCE

### *A. Petitioner's Motion to Exclude Evidence*

Petitioner filed a motion to exclude Patent Owner's evidence. Paper 64 ("Pet Mot. to Excl."). Patent Owner filed an opposition to Petitioner's motion. Paper 75. Patent Owner relies on Declarations of Dr. Mark I. Greene (Ex. 2121) and Shaun R. Vodde (Ex. 2122) and on supplemental Declarations of Dr. Donald M. O'Rourke (Ex. 2119), Dr. Gail Massey (Ex.

2120), Dr. Byeong-Woo Park (Ex. 2123), and Dr. Natasha Singh (Ex. 2124) all in support of Patent Owner's Opposition to Petitioner's Motion to Exclude Evidence. Petitioner subsequently filed a Reply in support of its motion. Paper 83.

Petitioner moves to exclude Patent Owner's Exhibits 2073–80 and 2048, which were filed by Patent Owner in support of Patent Owner's Contingent Motion to Amend. Pet. Mot. to Excl. 1. The basis for Petitioner's motion to exclude these exhibits is lack of authentication under FRE 901. *Id*. According to Petitioner, Patent Owner relies on these exhibits in support of its conception and due diligence in reducing to practice theories in support of its motion to amend. *Id*. at 1–12. Because our denial of Patent Owner's motion to amend does not rely on Patent Owner's conception and due diligence in reducing to practice theories, our decision does not rely on Exhibits 2073–80 and 2048. Therefore, we deny Petitioner's motion to exclude these exhibits as moot.

### *B. Patent Owner's Motion to Exclude Evidence*

Patent Owner filed a motion to exclude Petitioner's evidence. Paper 68 ("PO Mot. to Excl."). Petitioner filed an opposition to Patent Owner's motion. Paper 77. Petitioner relies on the Declarations of Dr. Robert L. Hong (Ex. 1109) in support of Petitioner's Opposition to Patent Owner's Contingent Motion to Amend. Patent Owner subsequently filed a Reply in support of its motion. Paper 84.

Patent Owner moves to exclude Exhibits 1077–1080, 1084–1086, 1089, 1090, and 1103. PO Mot. to Excl. 1. Patent Owner moves to exclude Exhibit 1077 (a webpage printout regarding the American Board of Medical Specialties Board Eligibility Policy), 1078 (American Board of Radiology

Initial Certification Board Eligibility Policy), and 1079 (a webpage printout regarding the American Board of Radiology Initial Certification Board Eligibility) as not properly authenticated under Fed. R. of Evid. 901, inadmissible hearsay under Fed. R. of Evid. 802, and irrelevant under Fed. R. of Evid. 402. PO Mot. to Excl. 2–4. Patent Owner moves to exclude Exhibit 1080 (an article summarizing the importance of board certification and maintaining board certification) as irrelevant under Fed. R. of Evid. 402. PO Mot. to Excl. 4. Patent Owner moves to exclude Exhibit 1084 (a webpage printout with description of J. L. Shepherd model 30 Mark I Cesium-137 irradiator) and Exhibit 1086 (J. L. Shepherd brochure for the model 30 Mark I Cesium-137 irradiator) as not properly authenticated under Fed. R. of Evid. 901 and inadmissible hearsay under Fed. R. of Evid. 802. PO Mot. to Excl. 4. Patent Owner moves to exclude Exhibit 1085 (webpage printout regarding the Mission Statement of United States Food and Drug Administration) as not properly authenticated under Fed. R. of Evid. 901 and irrelevant under Fed. R. of Evid. 402. PO Mot. to Excl. 5. Patent Owner moves to exclude Exhibits 1089 (webpage printout regarding the History and Commitment of Varian Medical Systems) and Exhibit 1090 (webpage printout regarding Atomic Energy of Canada Ltd. Cobalt-60 Therapy Machine from Canada Science and Technology Museum) as not properly authenticated under Fed. R. of Evid. 901 and inadmissible hearsay under Fed. R. of Evid. 802. Our decision does not rely on Exhibits 1077–1080, 1084–1086, 1089, and 1090. Therefore, we deny Petitioner's motion to exclude these exhibits as moot.

Patent Owner moves to exclude Exhibit 1103 (file history of U.S. Patent Application No. 14/729,798) as not properly authenticated under Fed.

R. of Evid. 901 because "[t]here is no certification from the U.S. Patent and Trademark Office attesting to the authenticity or completeness of Exhibit 1103" and Petitioner has not offered any other evidence to establish its authenticity. PO Mot. to Excl. 6. As Petitioner notes (Paper 77, 11), however, certification of authenticity is not required for USPTO records to which the public has access. Title 37 C.F.R. § 42.61(b), "Records of the Office," states that "[c]ertification is not necessary as a condition to admissibility when the evidence to be submitted is a record of the Office to which all parties have access." Patent Owner's Reply in support of its motion does not address Rule 42.61(b) or further request that Exhibit 1103 be excluded. *See* Paper 84. Given that Exhibit 1103 is authenticated as a USPTO public record, we deny Patent Owner's motion to exclude Exhibit 1103.

### *C. Conclusion*

Petitioner's motion to exclude is denied. Patent Owner's motion to exclude is denied.

## V. CONCLUSION

This is a Final Written Decision of the Board under 35 U.S.C. § 318(a).

We hold Patent Owner's claims 1–7, 9–12, 14, 16, 17, and 19–31 of the '558 patent to be unpatentable under 35 U.S.C. § 103 over the combination of Saleh, Balaban, and DeNardo.

## VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–7, 9–12, 14, 16, 17, and 19–31 of the '558 patent are cancelled; and

FURTHER ORDERED that Patent Owner's Contingent Motion to Amend is *denied*;

FURTHER ORDERED that Petitioner's motion to exclude Patent Owner's evidence is denied;

FURTHER ORDERED that Patent Owner's motion to exclude Petitioner's evidence is denied; and

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.

IPR2016-00458
Patent 7,625,558

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