Commissioner’s Decision #1466

Décision de la Commissaire #1466

TOPIC:	F00 (Novelty) O00 (Obviousness) B00 (Ambiguity or Indefiniteness)
SUJET:	F00 (Nouveauté) O00 (Évidence) B00 (Caractère ambigu ou indéfini)

Application No.: 2,322,592

Demande n°.: 2 322 592

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,322,592, having been rejected under subsection 30(3) of the *Patent Rules*, has subsequently been reviewed in accordance with paragraph 30(6)(*c*) of the *Patent Rules*. The recommendation of the Patent Appeal Board and the decision of the Commissioner are to refuse the application.

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INTRODUCTION

[1] This recommendation concerns the review of rejected patent application number 2,322,592, which is entitled "Use of a peptide or antibody in the manufacture of a medicament for treating an erbB protein mediated tumor in combination with irradiation" and is owned by the Trustees of the University of Pennsylvania. The outstanding defects to be addressed are whether the subject-matter of claims 1, 3 and 5 on file lacks novelty, whether the subject-matter of the claims on file would have been obvious and whether claims 8 and 9 on file are indefinite. A review of the rejected application has been conducted by the Patent Appeal Board pursuant to paragraph 30(6)(*c*) of the *Patent Rules*. As explained in more detail below, our recommendation is that the application be refused.

BACKGROUND

The application

[2] Patent application 2,322,592, based on a previously filed Patent Cooperation Treaty application, was effectively filed in Canada on March 4, 1999 and was opened to public inspection on September 10, 1999.

[3] The invention relates to the disruption of molecular complexes associated with receptors (erbB receptors) on the surface of cancer cells to render them more susceptible to subsequent radiation therapy. The erbB family of receptors includes erbB1 (receptor for epidermal growth factor (EGFR)), erbB2 (HER-2/p185/*neu*), erbB3 and erbB4. Different members of the erbB family of receptors are often overexpressed in human cancers and play important roles in promoting cancer. Multimeric receptors involving erbB family members include erbB heterodimers comprising monomeric components from different erbB family members that interact and form active heterodimeric kinase complexes. According to the

application, activation of erbB signaling pathways contributes to a cancer cell's resistance to irradiation treatment.

[4] The application teaches the use of antibodies or peptidomimetics of antibodies that disrupt the kinase activity associated with multimeric receptors comprising an erbB protein in order to sensitize tumors to a following anti-cancer radiation therapy.

Prosecution history

[5] On July 14, 2014, a Final Action ("FA") was written pursuant to subsection 30(4) of the *Patent Rules*. The FA explained that the subject-matter of claims 1 to 10 lacks novelty contrary to subsection 28.2(1) of the *Patent Act*; that the subject-matter of all the claims on file would have been obvious, contrary to section 28.3 of the *Patent Act*; and that the subject-matter of claims 1 and 2 on file is indefinite, contrary to subsection 27(4) of the *Patent Act*.

[6] In a response to the FA ("R-FA") dated January 14, 2016, the Applicant submitted an amended claim set (the "proposed claims set-1") that, according to the Applicant, put the application in allowable form as the proposed claims comply with the *Patent Act* and *Patent Rules*. The Applicant provided arguments as to why the subject-matter of the proposed claims was patentable and not open to objection for the reasons outlined in the FA.

[7] As the Examiner was not entirely persuaded by the Applicant's arguments, the application was forwarded to the Patent Appeal Board ("the Board") for review, along with a Summary of Reasons ("SOR") dated June 22, 2016, maintaining some of the defects identified in the FA for the claims on file, withdrawing others and further adding an indefiniteness defect. The SOR also concluded that the maintained defects were not overcome by the proposed amendments.

[8] In a letter dated July 13, 2016, the Board forwarded the Applicant a copy of the SOR and offered the Applicant an opportunity to attend an oral hearing and to make

further written submissions. On October 12, 2016, the Applicant expressed the wish to participate in an oral hearing and to provide submissions in response to the SOR. On April 19, 2017, the Applicant provided a response to the SOR ("R-SOR"), proposed a second amended claims set (the "proposed claims set-2") containing proposed claims 1 to 17 and submitted further detailed arguments as to why the patent application complies with the *Patent Act* and *Patent Rules*.

[9] The present Panel was formed to review the application under paragraph 30(6)(*c*) of the *Patent Rules* and make a recommendation to the Commissioner as to its disposition. In a letter dated March 13, 2018 (the "Panel Letter"), we set out our preliminary analysis and rationale as to why, based on the record before us, the subject-matter of claims 1, 3 and 5 on file is novel in view of the cited prior art, the subject-matter of the claims on file would have been obvious in view of the cited prior art and that some of the expressions found in claims 8 and 9 on file are not defined in a distinct and in explicit manner. Further, we expressed the view that the claims of the proposed claims set-2 do not constitute a "necessary" amendment under subsection 30(6.3) of the *Patent Rules* because our preliminary view with regard to the obviousness of the subject-matter of the claims on file would not have changed if the proposed claims had been adopted. The Panel Letter also invited the Applicant to provide further written submissions in response to the Panel's preliminary review.

[10] On April 6, 2018, the Applicant replied to the Panel Letter and indicated that an oral hearing was no longer desired and that written submissions would follow.

[11] On April 27, 2018, the Applicant provided written submissions with respect to the Panel's views (the "Reply Letter"). In the same letter, the Applicant also submitted a third amended claims set (the "proposed claims set-3").

ISSUES

[12] In view of the above, three issues are initially addressed in this review:

i) whether the subject-matter of claims 1, 3 and 5 on file lacks novelty, contrary to paragraph 28.2(1)(*b*) of the *Patent Act*;

ii) whether the subject-matter of claims 1 to 17 on file would have been obvious, contrary to section 28.3 of the *Patent Act*; and

iii) whether the subject-matter of claims 8 and 9 on file is not defined in distinct and in explicit terms, contrary to subsection 27(4) of the *Patent Act.*

[13] If we view that the subject-matter of the claims on file would not comply with the *Patent Act* and *Patent Rules* in respect of one or more of the potential defects identified above, then we may consider whether the proposed claim set-3 would overcome these defects and consider whether they would constitute amendments necessary for compliance with the *Patent Act* and *Patent Rules*.

LEGAL PRINCIPLES AND PATENT OFFICE PRACTICES

Purposive construction

[14] In accordance with *Free World Trust v Électro Santé Inc.*, 2000 SCC 66, essential elements are identified through a purposive construction of the claims done by considering the whole of the disclosure, including the specification and drawings (see also *Whirlpool Corp v Camco Inc*, 2000 SCC 67 at paras. 49(f) and (g) and 52). In accordance with the *Manual of Patent Office Practice*, revised June 2015 (CIPO) at §13.05, the first step of purposive claim construction is to identify the person of ordinary skill in the art ("POSITA") and their relevant common general knowledge ("CGK"). The next step is to identify the problem addressed by the inventors and

the solution disclosed in the application. Essential elements can then be identified as those elements of the claims that are required to achieve the disclosed solution.

Novelty

[15] Paragraph 28.2(1)(*b*) of the *Patent Act* sets out the conditions under which a claim may be found to lack novelty in view of a disclosure by a third party:

> 28.2 (1) The subject-matter defined by a claim in an application for a patent in Canada (the "pending application") must not have been disclosed
>
> (a) more than one year before the filing date by the applicant, or by a person who obtained knowledge, directly or indirectly, from the applicant, in such a manner that the subject-matter became available to the public in Canada or elsewhere;
>
> (b) before the claim date by a person not mentioned in paragraph (a) in such a manner that the subject-matter became available to the public in Canada or elsewhere.

[16] There are two separate requirements in order to show that a prior art document anticipates a claimed invention: a prior disclosure of the claimed subject-matter; and the prior disclosure must enable the claimed subject-matter to be practised by the POSITA: *Apotex Inc v Sanofi Synthelabo Canada Inc*, 2008 SCC 61 (*Sanofi*) at paragraphs 24-29.

[17] "Prior disclosure" means that the prior art must disclose subject-matter which, if performed, would necessarily result in infringement of the patent. The POSITA looking at the disclosure is "taken to be trying to understand what the author of the description [in the prior patent] meant" (*Sanofi* at para 32). At this stage, there is no room for trial and error or experimentation by the POSITA. The prior art is simply read "for the purposes of understanding it": see *Sanofi*, at para 25, citing *Synthon BV v SmithKline Beecham plc*, [2006] 1 All ER 685, [2005] UKHL 59.

[18] "Enablement" means that the POSITA would have been able to perform the invention without undue burden. The POSITA is assumed to be willing to make trial and error experiments to get it to work: *Sanofi*, at paras 26-27.

Obviousness

[19] Section 28.3 of the *Patent Act* sets out the statutory requirement that the claimed subject-matter must not have been obvious to the POSITA:

> The subject matter defined by a claim in an application for a patent in Canada must be subject matter that would not have been obvious on the claim date to a person skilled in the art or science to which it pertains, having regard to
>
> (a) information disclosed more than one year before the filing date by the applicant, or by a person who obtained knowledge, directly or indirectly, from the applicant in such a manner that the information became available to the public in Canada or elsewhere; and
>
> (b) information disclosed before the claim date by a person not mentioned in paragraph (a) in such a manner that the information became available to the public in Canada or elsewhere.

[20] In *Sanofi* at para 67, the Supreme Court of Canada stated that it is useful in an obviousness inquiry to follow the following four-step approach:

> (1) (a) Identify the notional "person skilled in the art";
> (b) Identify the relevant common general knowledge of that person;
>
> (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
>
> (3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;
>
> (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

Indefiniteness

[21] Subsection 27(4) of the *Patent Act* states:

> The specification must end with a claim or claims defining distinctly and in explicit terms the subject-matter of the invention for which an exclusive privilege or property is claimed.

[22] In *Minerals Separation North American Corp. v. Noranda Mines Ltd.*, [1947] Ex CR 306, 12 CPR 99 at 146, the Court emphasized the obligation for an Applicant to make clear in the claims the ambit of the monopoly sought and the requirement for terms used in the claims to be clear and precise:

> By his claims the inventor puts fences around the fields of his monopoly and warns the public against trespassing on his property. His fences must be clearly placed in order to give the necessary warning and he must not fence in any property that is not his own. The terms of a claim must be free from avoidable ambiguity or obscurity and must not be flexible; they must be clear and precise so that the public will be able to know not only where it must not trespass but also where it may safely go.

ANALYSIS

Purposive construction

[23] We consider that claim 1 on file is representative of the claims identified as having defects. Claim 2 on file, the only other independent claim, differs from claim 1 only in terms of the therapeutic agent used. An antibody is used in claim 1 whereas a peptide is used in claim 2. Claim 1 on file reads as follows:

> 1. Use of an antibody for the treatment of cancer that disrupts the kinase activity associated with multimeric receptor ensembles comprising an erbB protein in the manufacture of a medicament for administration in combination with anti-cancer radiation for treating an individual who has a tumor, wherein said tumor is characterized by tumor cells that have multimeric receptor ensembles comprising an erbB protein which provides tyrosine kinase activity associated with a transformed phenotype, said multimeric receptor ensembles being erbB heterodimers that are pl85/EGFR heterodimers, pl85/mutant EGFR heterodimers, pl85/erbB3 heterodimers, pl85/erbB4 heterodimers or EGFR/mutant EGFR

> heterodimers, wherein disruption of said kinase activity has a cytostatic effect on the tumor cells, and sensitizes the cells to radiation and wherein said medicament is for administration prior to irradiation.

The POSITA and the relevant CGK

[24] In the Panel Letter, we restated the definition of the POSITA presented on page 6 of the FA:

> The [POSITA] is a radiation oncologist or medical oncologist, especially a clinician-scientist with knowledge of ErbB signal transduction and its oncogenic role. Also, the [POSITA] is a radiation biologist, cancer biologist or molecular biologist (such as one working in Experimental Therapeutics) exploring methods of increasing cancer cell kill with radiation and/or by disrupting ErbB-mediated oncogenic signals.

[25] The Applicant did not indicate disagreement with that definition in the Reply Letter.

[26] With respect to the CGK possessed by the POSITA, we stated in the Panel Letter that such a person would know the following:

- Different members of the erbB family of receptors, including EGFR and p185, are often overexpressed in human cancers and play important roles in promoting cancer (as evidenced by the instant description on pages 2-5, Fan & Mendelsohn, *Current Opinion in Oncology*, vol. 10, pages 67-73, January 1998 (*Fan*) on pages 67 and 68, and the review article O'Rourke & Greene, *lmmunol Res.*, vol. 17, Pages 179-189, January 1998 (*O'Rourke*) on pages 180 to 182);

- Epidermal growth factor (EGF) receptor family members and p185 interact and form active heterodimeric kinase complexes (as evidenced by the instant description on pages 3, lines 9 to 15 and *O'Rourke* on pages 181 and 182);

- Blockade of EGF receptor family members by antibodies disrupts the

kinase activity associated with multimeric receptors comprising an erbB protein and such disruption of associated kinase activity with antibodies generally results in a cytostatic rather than cytotoxic effect on cancer cell proliferation (as evidenced by *Fan* on page 68, right column and *O'Rourke* on page 182, left column);

- The rationale of blocking the function of the EGF receptor family members with antibodies to treat cancer was generally known (as evidenced by *Fan*, the whole document and *O'Rourke* on pages 183 to 185);

- Irradiation and conventional chemotherapeutic agents cause cell death resulting from different mechanisms of action, including damaging DNA, interfering with DNA repair, interfering with DNA replication and blocking progression of the cell cycle. Generally, fast-dividing cells (i.e., tumors) with high growth rates are more sensitive to conventional chemotherapeutic agents and irradiation; and

- The promising combination therapies comprising the blockade of EGF receptor family members by antibodies, including anti-p185 antibodies, and different conventional cytotoxic chemotherapeutic agents as well as the underlying rationale for exploring these combinations: inhibiting the proliferation of cancer cells with blocking anti-EGF receptor family member antibodies is not sufficient to cure cancer (as evidenced by *Fan* on pages 68 and 69).

[27] The Panel Letter accepted the Applicant's previous submission that the POSITA would know that the outcome of inhibiting erbB receptors is not necessarily inherently cytostatic because there are reports wherein blockade of EGF receptors with antibodies resulted in apoptotic cancer cell death. However, we expressed the view that the POSITA would consider that, in the vast majority of cases, the

blockade of EGF receptor and disruption of associated kinase activity with antibodies would result in a cytostatic rather than cytotoxic effect on cancer cell proliferation. We further noted that the instant description on page 34, lines 23-24 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".

[28] Finally, we expressed the view that the POSITA would understand that the cytostatic or cytotoxic effect of an anti-erbB antibody on a cancer cell is governed by the cell's response to the disruption of its receptor-associated kinase activity by the antibodies, and that the effect is not attributable to functional characteristics unique to particular subclass(es) of anti-erbB receptor antibodies.

[29] In the Reply Letter, the Applicant did not indicate disagreement with the recited elements of CGK or our more specific views regarding the POSITA's common understanding of the expected effects associated with the blockade of EGF receptors and disruption of associated kinase activity with antibodies, namely that it would generally result in a cytostatic rather than cytotoxic effect on cancer cell proliferation. Of note, the Applicant appears to adopt in the Reply Letter, for the purpose of some of its arguments, our view with regard to the expected effects associated with blocking EGF receptors with antibodies:

> By contrast, the Panel recognizes that the state of the art was that "disruption of associated kinase activity with antibodies generally [but not invariably] results in a cytostatic rather than cytotoxic effect on cancer cell proliferation" (s*ee* pages 7-8 of the Panel's observations).

Meaning of specific terms

[30] In the Panel Letter, we expressed the view that the POSITA would consider that the phrase "sensitizes the cells to radiation" means, in the context of the claims, that disruption of tyrosine kinase activity causes radioresistant tumor cells to become radiosensitive in light of the passage on page 34, lines 22 to 24 of the description.

We also expressed the view that the expression "cytostatic effect" would be understood by the POSITA to mean an effect "that slows or stops the growth of cells, including cancer cells, without killing them", an ordinary and customary meaning in the art based on the online National Cancer Institute Dictionary of Cancer terms (retrieved from https://www.cancer.gov/publications/dictionaries/cancer-terms).

[31] The Applicant did not indicate disagreement with these interpretations in the Reply Letter.

The problem to be solved and the proposed solution

[32] In the Panel Letter, we identified the problem to be solved as "a need for the treatment of erbB-associated tumors that are resistant to radiation".

[33] With respect to the solution, we expressed the view in the Panel Letter that the proposed solution is "to administer a composition which disrupts the kinase activity associated with erbB dimers prior to an irradiation treatment".

[34] The Applicant did not indicate disagreement with these assessments in the Reply Letter.

The essential elements that solve the identified problem

[35] In the Panel Letter, we expressed the view that the following elements of the claims on file contribute to the proposed solution and are therefore essential:

- The use of an antibody (independent claim 1 on file) or a peptide (independent claim 2 on file) that disrupts the kinase activity associated with multimeric receptor ensembles comprising an erbB protein in combination with irradiation wherein said multimeric receptor ensembles are pl85/EGFR heterodimers, pl85/mutant EGFR heterodimers, pl85/erbB3 heterodimers, pl85/erbB4 heterodimers or EGFR/mutant EGFR heterodimers;

- The treatment of an individual who has a radioresistant erbB-associated tumor;

- The disruption of the kinase activity has a cytostatic effect on the tumor cells and sensitizes the cells to radiation; and

- The antibody or peptide is to be administered prior to irradiation.

[36] In the Panel Letter, we noted that independent claims 1 and 2 are "Swiss" style use claims. The form of this type of claims is typically *the use of compound X in the manufacture of a medicament for the treatment of Y*. A literal interpretation may suggest that the contemplated use is simply for the manufacture of a medicament but the format also permits an interpretation of the claim as relating to a therapeutic use for the compound, the latter interpretation being in line with the jurisprudence (for example, see *GD Searle & Co v Canada (Minister of Health)*, 2008 FC 437, aff'd 2009 FCA 35; *Eli Lilly Canada Inc v Apotex Inc*, 2008 FC 142; and *Pfizer Canada Inc v Apotex Inc*, 2007 FC 971, aff'd 2009 FCA 8). Although the use recited in the preamble of claims 1 and 2 is focused on the manufacture of a medicament, the claims specify a therapeutic use. In our view, the claimed uses go beyond utilizing the recited antibody or peptide to make a medicament; they further require the actual administration of that medicament to treat erbB-associated tumors that are resistant to radiation. Accordingly, we consider that although claims 1 and 2 are worded in the "Swiss" format, they essentially claim a therapeutic use for the recited antibody or peptide.

[37] We also noted that dependent claims 3 to 17 on file further specify that the antibody or peptide interacts with a monomeric component of the multimeric receptor (claims 3 and 4), that the antibody or peptide inhibits formation of a heterodimer of p185 and EGFR (claims 5 and 6), that the antibody is an anti-p185 antibody (claim 7), the p53 status of the tumor cells (claims 8 and 9) and the specific amino acid sequence of the

peptide (claims 10 to 17). Accordingly, we considered that these claims further characterize or limit the essential elements recited above.

[38] As the Applicant did not indicate disagreement with the above assessments in the Reply Letter, we therefore adopt for the purposes of this review the above identifications of the POSITA and the relevant CGK, the interpretations of specific terms, as well as the characterization of the problem to be solved, the solution and the essential elements.

Novelty of claims 1, 3 and 5 on file

[39] The FA and the SOR referred to the disclosure of the scientific publication Balaban et al., *Biochem Biophys Acta*, 1314, pages 147-156, 1996 (*Balaban*) in assessing the novelty of claims 1, 3 and 5 on file.

[40] According to the FA, *Balaba*n anticipates the subject-matter of claims 1, 3 and 5 on file essentially because:

> "Balaban et al. independently disclose the co-use of the anti-ErbB C225 antibody and anti-cancer radiation to kill A431 human epidermoid caricoma cells *in vitro* and to treat the corresponding tumour *in vivo.* The anti-ErbB antibody inhibits ErbB heterodimer-mediated cancer cell proliferation and survival, and its co-use with radiation enhances tumour kill, thereby improving cancer treatment".

[41] Although the submissions found in the R-FA and R-SOR were made with respect to the proposed claims set-1 and proposed claims set-2 respectively, we stated in the Panel Letter that they were also relevant to the subject-matter of the claims on file. In the Panel Letter, we summarized the Applicant submissions as to why *Balaban* does not teach each and every element of the claims, and therefore does not anticipate these claims as well as why the POSITA, when reading the disclosure in *Balaban*, will not in every case and without possibility of error be led to the claimed invention.

[42] One of those submissions is that *Balaban* does not specifically disclose cells having the specific heterodimers recited in the claims. In a context wherein different publications show that expression of p185 across A431 cell lines varies, the Applicant argued that *Balaban* does not, and cannot, disclose either disruption of kinase activity associated with such heterodimers or the consequent increase in radiation sensitivity.

[43] Having reviewed *Balaban*, we first noted in the Panel Letter that the study disclosed in *Balaban* was not designed to determine whether A431 cells express p185 and the disclosure is thus silent about p185 expression or lack thereof. We also acknowledged the conflicting evidence presented in the FA and by the Applicant in the R-FA and R-SOR with regard to the expression of p185 in A431 cell lines. In the absence of a clear indication that the A431 cells used in *Balaban* express p185 and because there are reasonable grounds to believe that A431 cell lines do not inherently express pl85, we expressed the view that the A431 cells disclosed in *Balaban* do not necessarily express pl85.

[44] The scope of claims 1, 3 and 5 on file is limited to tumor cells expressing specific heterodimers that must comprise either p185 or a mutant EGFR in combination with another erbB component. Given our view that the tumor cells used in *Balaban* do not necessarily express pl85 and given that the prosecution record does not indicate or suggest that the tumor cells used in *Balaban* express a mutant EGFR, we are of the view that *Balaban* does not disclose subject-matter which, if performed, would necessarily result in infringement of claims 1, 3 and 5 on file.

Conclusion on novelty of claims 1, 3 and 5 on file

[45] In view of the above, we are of the view that the subject-matter of claims 1, 3 and 5 on file is novel in view of *Balaban* and complies with paragraph 28.2(1)(*b*) of the *Patent Act*.

Obviousness of the claims on file

[46] The relevant date for considering CGK as it relates to obviousness is the claim date. The FA stated that the claim date for the subject-matter of the claims on file is July 8, 1998, the filing date of the second of the two previously regularly filed applications for which priority requests have been made. Having reviewed the priority documents (U.S. Provisional Application 60/076,788 filed on March 4, 1998 and U.S. Provisional Application 09/111,681 filed on July 8, 1998), we stated in the Panel Letter that we considered July 8, 1998 as the claim date for the purposes of the review. The Applicant has not expressed disagreement with the above assessment of the claim date and we therefore retain it for the instant obviousness analysis.

[47] In accordance with the four-step approach to performing an obviousness assessment put forward in *Sanofi*, we present below our analysis with respect to the claims on file.

Identify the POSITA and the relevant CGK

[48] The POSITA and the relevant CGK have been set out above as part of the purposive construction of the claims. Although the identification of the relevant CGK above was performed on the basis of the common knowledge of the worker skilled in the art to which the patent relates as of the publication date of the instant application in accordance with *Free World* at para 54 and *Whirlpool* at para 55, we consider that the identified elements of knowledge also formed part of the POSITA's CGK as of the claim date.

Identify the inventive concept

[49] On page 15 of the Panel Letter, we identified the inventive concept of the claims on file:

> We are of the view that the POSITA would consider that the inventive concept of independent claims 1 and 2 on file is the use of an antibody (claim 1) or a peptide (claim 2) that disrupts the kinase activity associated with multimeric receptor

> ensembles comprising an erbB protein in combination with irradiation, wherein said multimeric receptor ensembles are pl85/EGFR heterodimers, pl85/mutant EGFR heterodimers, pl85/erbB3 heterodimers, pl85/erbB4 heterodimers or EGFR/mutant EGFR heterodimers, for the treatment of an individual who has a radioresistant erbB-associated tumor, wherein the disruption of the kinase activity has a cytostatic effect on the tumor cells and sensitizes the cells to radiation, and wherein the antibody or peptide is administered prior to irradiation.
>
> Dependent claims 3 to 17 on file further specify that the antibody or peptide interacts with a monomeric component of the multimeric receptor (claims 3 and 4), that the antibody or peptide inhibits formation of a heterodimer of p185 and EGFR (claims 5 and 6), that the antibody is an anti-p185 antibody (claim 7), the p53 status of the tumor cells (claims 8 and 9) and the specific amino acid sequence of the peptide (claims 10 to 17). Accordingly, we consider that these claims further limit the inventive concept recited above.

[50] Although the Reply Letter expressed the Applicant's disagreement with our preliminary view reached in the Panel Letter with respect to the obviousness of the claims on file, the Applicant has not indicated specific disagreement with our assessment of the inventive concept.

Differences between the matter cited as forming part of the "state of the art" and the inventive concept

[51] The following five prior art references are cited in the obviousness analysis presented in the Panel Letter:

- *Balaban*, introduced above;
- DeNardo et al. *Cancer*, vol. 80, pages 2583-2590, 1997 (*DeNardo*);
- Saleh et al., Abstract from the *Proceedings of the American Association Of Cancer Research*, abstract #4197, 1996 (*Saleh*);
- Ezekiel et al., Abstract from the Proceedings of the American Society Of Clinical Oncology, abstract #1522, April 15, 1998 (*Ezekiel*);
- WIPO international patent application WO 96/34617, published in 1996; inventor: Greene & Zhang (*Greene*).

[52] Having reviewed the documents above, we stated the following in the Panel Letter with regard to their respective disclosures.

[53] *Balaban* discloses studies conducted on A431 cells, a model human cell line (epidermoid carcinoma) that is commonly used in studies of cancer-associated cell signaling pathways. The disclosed studies involved the testing of cell resistance or sensitivity to radiation-induced apoptosis (cell death) in different conditions, including conditions wherein the activation of EGFR is blocked by the use of a monoclonal anti-EGFR antibody (mAb LA22).

[54] *Balaban* discloses that "EGFR tyrosine phosphorylation is increased in response to radiation or EGF treatment of A43l cells, and that the EGF treatment protects these cells against radiation damage" (see page 148, right column). With respect to the effect of the blocking anti-EGFR antibody, *Balaban* discloses that "monoclonal antibodies to the EGF receptor (EGFR) sensitize [A431] cells to radiation by facilitating radiation-induced apoptosis" (see page 147, abstract).

[55] More specifically, *Balaban* discloses that:

> low levels of apoptosis were observed either in irradiated (with no EGF added) or in irradiated and EGF-treated [A431] cells. A pronounced increase in radiation-induced apoptosis was observed only when [A431] cells were pretreated with LA22, even when treated together with EGF. However, as shown, EGF reduced the LA22 augmentation of radiation-induce [*sic*] apoptosis. At the same time, treatment with either EGF or LA22 (without radiation) produced almost no effects on the level of apoptosis (not shown)" [see page 153, right column and figure 5, emphasis added].

[56] *Balaban* concludes that "pretreatment with monoclonal antibodies to the EGFR may be advantageous as a combined therapy with radiation in human epidermoid carcinoma" (see page 155, right column).

[57] To summarize, we considered that *Balaban* teaches the use of an anti-EGFR blocking antibody that disrupts the kinase activity associated with multimeric

receptor ensembles comprising an erbB protein to sensitize radioresistant erbB-associated tumor to radiation.

[58] *DeNardo* discloses the use of an anti-EGFR antibody (mAb C225) to sensitize cancers cells to radioimmunotherapy (RIT) with ^{90}Y-ChL6, an antibody-linked radioisotope that target cancer cells. *DeNardo* teaches that C225 is an anti- EGFR monoclonal antibody that interferes with binding of EGF to EGFR. In cells with functional EGFR, C225 inhibits activation of an EGFR-related kinase and subsequent cell proliferation (see page 2584, left column, first paragraph). *DeNardo* further discloses that the anti-EGFR antibody alone did not affect the tumors (see page 2586, left column, last full paragraph) and that only when the anti-EGFR antibody was given prior to RIT, the results showed increase in therapeutic response compared to RIT alone. *DeNardo* further states that the anti-EGFR antibody needs to be given before RIT to exert its positive effect (see page 2588, right column, first paragraph).

[59] *Saleh* teaches that anti-EGFR antibodies have been shown to augment the cytotoxicity of anti-neoplastic agents by interfering with DNA repair processes and states that the disclosed study was undertaken to determine whether anti-EGFR mAb exposure would also augment the cytotoxic effects of radiation therapy. *Saleh* further discloses that the use of an anti-EGFR antibody (mAb C225) in combination with radiation therapy showed increased cell kill compared to either treatment alone. Finally, *Saleh* states that further studies to determine the complementarity to sensitize erbB protein-mediated tumour cells to radiation-induced cell death in the treatment of an erbB protein-mediated tumor are contemplated.

[60] *Ezekiel* states that there is experimental evidence that anti-EGFR monoclonal antibodies enhance the effects of chemotherapy and radiotherapy on human tumor xenografts expressing EGFR. *Ezekiel* further states that the disclosed study was undertaken to determine the safety profile of different dose levels of an anti-EGFR antibody (mAb C225) given concurrently with conventional radiotherapy to patients

with advanced squamous cell carcinoma of the head and neck. *Ezekiel* discloses that the patients received an initial infusion the anti-EGFR antibody on day 1 followed by eight weekly infusions and that the radiotherapy only started on day 8. Four major responses have been observed. *Ezekiel* does not disclose the effect of either treatment alone.

[61] *Greene* discloses the use of a peptide to prevent or treat an erbB-mediated tumor. The peptide is characterized by its ability to bind to p185 and thereby prevent the dimerization with other erbB proteins and the associated kinase activity. The elimination or reduction of tyrosine kinase activity results in an elimination or reduction in cell proliferation levels prevent. The peptides disclosed in *Greene* have the general formula defined on pages 4 and 5. An example of such a peptide is FCGDGFYACYMDV (SEQ ID NO: 184) that corresponds to SEQ ID NO: 1 of the instant application.

[62] In the Panel Letter we summarized the following relevant elements with regard to the teachings of the above cited "state of the art":

- Blocking anti-EGFR antibodies that disrupt the kinase activity associated with the receptor have been used in combination with therapeutic irradiation (see *Balaban*, *DeNardo*, *Saleh* and *Ezekiel*) and other conventional cytotoxic agents (see *Saleh* and *Ezekiel*).

- Two independent studies teach that administration of a blocking anti-EGFR antibody prior the administration of therapeutic irradiation sensitizes the cancer cells to the radiation-induced cancer cell death (see *Balaban* and *DeNardo*).

- The use of a peptide characterized by its ability to bind to p185 and thereby prevents the dimerization with other erbB proteins, inhibits the associated kinase activity and results in elimination or reduction in cell proliferation levels (see *Greene*).

[63] We considered in the Panel Letter that the main differences between the cited "state of the art" and the inventive concept of independent claims 1 and 2 on file is that the "state of the art" does not teach the use of an antibody (claim 1) or a peptide (claim 2) that disrupts the kinase activity associated with multimeric receptor comprising specifically p185 or a mutant EGFR.

[64] In the Reply Letter, the Applicant has not addressed directly the above assessment but submitted in different arguments that the Panel improperly ignored the claim limitation "wherein disruption of said kinase activity has a cytostatic effect on the tumor cells". As mentioned above, we expressed the view in the Panel Letter that the POSITA would consider that, in the vast majority of cases, the blockade of EGF receptor and disruption of associated kinase activity with antibodies would result in a cytostatic rather than cytotoxic effect on cancer cell proliferation. The POSITA would also understand that the cytostatic or cytotoxic effect of an anti-erbB antibody on a cancer cell is governed by the cell's response to the disruption of its receptor-associated kinase activity by the antibodies, and that the effect is not attributable to functional characteristics unique to particular subclass(es) of anti-erbB receptor antibodies. In other words, the POSITA would understand that the recited limitation fails to functionally distinguish peptides or antibodies that disrupt the kinase activity associated with the recited erbB multimeric receptor ensembles as the POSITA generally expect such capacity from blocking anti-EGF receptor family member antibodies. In any case, we have taken into account this specific element in the following fourth section of the obviousness analysis.

Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

[65] In the Panel Letter, we summarized the submissions of the R-FA and R-SOR that were relevant as to why the subject-matter of the claims on file would not have been obvious to the POSITA in view of the cited prior art as follows:

- CGK and/or *Balaban* teach away the present invention. The art recognized that deterring cell division would be counter-productive prior to radiation, because if an agent causes G0/G1 arrest, this would prevent cells from progressing to the G2 phase, therefore becoming less sensitive to the effect of radiation. Further, the POSITA reading *Balaban* and motivated to enhance cell killing would not have used an antibody that induces G1 arrest because the POSITA would have expected increased radiation resistance via the same mechanism *Balaban* observed with EGF.

- The POSITA is not in a position to assess whether the anti-EGFR antibodies as taught by the prior art documents could solve the technical problem of sensitizing radioresistant tumor cells that are characterized by the presence of specific heterodimers as recited in claims 1 and 2 (heterodimers that must comprise either p185 or a mutant EGFR).

- None of *Saleh*, *Balaban*, and *DeNardo* teaches the use of a cytostatic anti-erbB receptor antibody.

- There was no motivation to combine *DeNardo* with *Saleh*, *Balaban*, or *Ezekiel*. The teaching of *DeNardo* would not have meaningfully informed or even suggested to the POSITA on how to modify the method of *Saleh* or *Balaban* because there is a difference in mechanisms of killing between RIT and external beam anti-cancer radiation.

[66] On pages 18 to 20 of the Panel Letter, we addressed the above submissions and expressed the preliminary view that the subject matter of the claims on file would have been obvious to the POSITA:

> With regard to the submissions that the POSITA would have intuitively believed that the use of blocking antibodies against members of the EGFR family prior to irradiation would be counter-productive because it was CGK that non-dividing cells are more resistant to radiation and that the POSITA would have expected increased radiation resistance via the same mechanism *Balaban* observed with EGF (i.e., G0/G1 arrest), we consider that the CGK identified above tends to

indicate that the generally known cytostatic effect associated with the disruption of the kinase activity associated with multimeric receptors comprising an erbB protein was not a sufficient basis to not pursue combination therapies with cytotoxic agents that were commonly known to be more effective on dividing cells. To the contrary, the generally expected cytostatic effect of blocking anti-erbB receptor antibodies formed part of the rationale for exploring the CGK combinations of blocking antibodies to members of the EGFR family with conventional cytotoxic chemotherapy because inhibiting the proliferation of cancer cells with blocking anti-erbB receptor antibodies is not sufficient to cure cancer.

Further, we consider that the significance of such considerations is also greatly diminished in the context of a radioresistant cancer cell population. In such context, we consider that the paradigm of increased irradiation effectiveness toward dividing versus non-dividing cells is not as relevant to the POSITA because irradiation is not effective against radioresistant dividing cancer cells to begin with.

In any event, we consider that the alleged concerns or negative expectations derived from the CGK or inferred from the increased radiation resistance observed with EGF in *Balaban* are addressed by the actual experimental results disclosed in *Balaban*. *Balaban* disclosed that the use of an anti-EGFR blocking antibody prior to irradiation is not counter-productive to sensitize radioresistant cancer cells to irradiation; on the contrary, it is rather effective. For the reasons detailed above, we consider that *Balaban* teaches that an observed cancer cell resistance to radiation is mediated by the activation of EGFR and that the prior administration of an anti-EGFR blocking antibody sensitizes the cancer cells to radiation-induced apoptosis.

We turn now to the submission that the POSITA is not in a position to assess whether the anti-EGFR antibodies as taught by the prior art documents could solve the technical problem of sensitizing radioresistant tumor cells that are characterized by the presence of specific heterodimers that must comprise either p185 or a mutant EGFR. We consider that it was CGK at the claim date to disrupt the kinase activity associated with multimeric receptors comprising an erbB protein with blocking antibodies against different erbB proteins, including p185 and EGFR, to inhibit the proliferation of cancer cells that express the corresponding erbB heterodimers. What was not commonly known was that the disruption of the associated kinase activity with blocking antibodies also sensitizes radioresistant-cancer cells to irradiation. Then *Balaban* disclosed that disrupting kinase activity by anti-EFGR antibodies has also the effect of sensitizing cancer cells to radiation-induced apoptosis.

In view of the above, we are of the preliminary view that it would have been obvious to the POSITA taught by *Balaban* to first disrupt the kinase activity associated with any erbB heterodimers expressed by a tumor, including the well-

known erbB heterodimers recited in the claims on file, with the corresponding known blocking antibody or peptidomimetic of antibody to sensitize radioresistant-tumor cells and then proceed with subsequent therapeutic irradiation.

As noted above in the CGK section, we consider that the POSITA was aware that different members of the erbB family of receptors, including EGFR and p185, are often overexpressed in human cancers, interact and form active heterodimeric kinase complexes. In the case of a tumor expressing heterodimers comprising p185 and EGFR, we consider that it would have been obvious to the POSITA, i.e., it would not require any degree of invention, to use corresponding blocking antibodies such as CGK blocking anti-EGFR antibodies, CGK blocking anti-p185 antibodies (e.g. 4D5-derived antibodies such as Herceptin) or the peptidomimetics disclosed by *Greene* prior to a irradiation treatment. Therefore, we consider that the identified differences between the inventive concept and the cited prior art documents *Balaban* and *Greene* can be bridged by the POSITA using only the relevant CGK.

Further and with regard to *DeNardo*, although we acknowledge the Applicant's submission that the radioimmunotherapy disclosed in *DeNardo* may kill cancer cells by a mechanism that may have been understood to be different from external beam anti-cancer radiation, we are of the view that the POSITA would have considered the teachings of *DeNardo* relevant to the claimed subject-matter. First, the scope of the claims is not limited to external beam anti-cancer radiation and not limited to a particular mechanism of cell death. Second, and more importantly, we are of the view that *DeNardo* actually strengthens the teachings of *Balaban* with regard to the sensitization of radioresistant-cancer cells with a blocking anti-EGFR antibody and otherwise indicates to the POSITA that the therapeutic utility of blocking anti-EGFR antibodies to sensitize radioresistant-cancers cells as disclosed in *Balaban* is also relevant to radioimmunotherapy.

We also consider that the teachings of *Ezekiel* and *Saleh* tend to indicate a motivation to combine the disruption of the kinase activity associated with an erbB heterodimers expressed by a tumor with a blocking antibody and irradiation.

Having also considered dependent claims 3 to 17 on file, we do not consider that an inventive step would have been required from the POSITA in respect of their further limitations to the use of an antibody or peptide that interacts with a monomeric component of the multimeric receptor (claims 3 and 4), the use of an antibody or peptide that inhibits formation of a heterodimer of p185 and EGFR (claims 5 and 6), an anti-p185 antibody (claim 7), the p53 status of the tumor cells (claims 8 and 9) and the use of a specific peptide that is an obvious analogue of the ones disclosed in *Greene* (claims 10 to 17).

Conclusion on obviousness

In view of the above, we are of the preliminary view that the subject-matter of claims 1 to 17 on file would have been obvious at the claim date to the POSITA taught by *Balaban* in view of the of the teachings of *Greene* and the relevant CGK.

Further, the consideration of the teachings of *DeNardo*, *Ezekiel* and/or *Saleh* in addition to the teachings of *Balaban* and *Greene* strengthens our preliminary view that the subject-matter of claims 1 to 17 on file would have been obvious at the claim date to the POSITA.

[67] In the Reply Letter, the Applicant submitted arguments in response to our preliminary analysis. These submissions, that include prior arguments as well as arguments directed to the Panel's preliminary views, can be summarized as follows:

- *Balaban* and the CGK teach away the present invention:
    - *Balaban* does not teach the use of an antibody having a cytostatic effect prior to irradiation. The anti-EGFR antibody used in the disclosed experiments has a cytotoxic effect on the A431 cells, a fact confirmed later by a later publication by the same group. In any case, the POSITA would not have concluded that the anti-EGFR antibody had a cytostatic effect because *Balaban* teaches that EGF and the anti-EGFR antibody had the opposite effect on EGFR signaling.
    - A key teaching of *Balaban* is that cytostatic cells (G1 arrested) were more radioresistant. Accordingly, the POSITA reading *Balaban* and motivated to enhance cell killing would not have used an antibody that induces G1 arrest because the POSITA would have expected increased radiation resistance via the same mechanism *Balaban* observed with EGF. As such, *Balaban* does not provide any motivation to arrive at the present invention as claimed.
    - The POSITA would have had the unusual characteristics of the A431 cell-based experimental system in mind when interpreting the results

of *Balaban*, and would not have given these teachings significant weight.

- CGK teaches away the present invention. The art recognized that deterring cell division would be counter-productive prior to radiation, because if an agent causes G0/G1 arrest, this would prevent cells from progressing to the G2 phase, therefore becoming less sensitive to the effect of radiation.

- *DeNardo* does not strengthen the teachings of *Balaban* and *Saleh* and *Ezekiel* do not provide motivation to arrive at the claimed invention.

[68] With regard to the submission that *Balaban* teaches that the anti-EGFR antibody LA22 used in the disclosed experiments has a cytotoxic effect on the A431 cells, we stated in the Panel Letter that the POSITA would not understand from *Balaban*, taken as a whole, that the anti-EFGR mAb LA22 has a cytotoxic effect by itself:

> Turning now to the submission that *Balaban* teaches that the anti-EGFR antibody used has a cytotoxic effect on the A431 cells, notably because *Balaban* explicitly states on page 155 that "EGF, which activates the tyrosine kinase activity of EGFR, could delay mAb LA22-induced apoptosis", we respectfully disagree. We consider that the POSITA would not understand from *Balaban*, taken as a whole, that the anti-EFGR mAb LA22 has a cytotoxic effect by itself. The relevant paragraph (page 155, left column) from which the statement cited by the Applicant has been extracted reads as follows:
>
> > We measured the initial apoptotic response of A431 cells to EGF, to radiation and to mAb (LA22) to EGFR (which inhibits EGF and TGFa binding to the receptor and its Tyrs phosphorylation [24]). EGF alone slightly inhibited apoptosis, while LA22 slightly enhanced apoptosis in these cells. Moreover, radiation alone induced very low levels of apoptosis, but LA22 highly enhanced radiation-induced apoptosis by preventing the EGFR activation. We thus found that radiation-induced apoptosis could be enhanced by LA22, which blocks EGFR tyrosine kinase. EGF, which activates the tyrosine kinase activity of EGFR, could delay mAb LA22-induced apoptosis. In sum, only combined treatment of mAbs to EGFR (which inhibit EGFR activity) together with radiation enhanced apoptosis.

> When taken in the context of the whole paragraph and the entire disclosure, we are of the view that the statement identified by the Applicant would not be considered by the POSITA to clearly teach a cytotoxic effect for the anti-EFGR mAb LA22. Rather, it would be understood to be an imprecise reformulation of the corresponding statement "EGF reduced the LA22 augmentation of radiation-induce [*sic*] apoptosis" found in the corresponding experimental results section on page 153, right column.
>
> Further, given the experimental results that either EGF or LA22 (without radiation) produced almost no effects on the level of apoptosis and the teaching that "[I]n an epithelial tumor cell line with elevated EGFR, such as A43l cells, an optimal concentration of EGF is required to enhance proliferation. Higher concentrations of EGF can inhibit growth" (see page 154, bottom of left column and top of right column), we are of the view that the POSITA would not infer a cytotoxic effect for the anti-EFGR mAb LA22 from the "teaching that EGF (ligand), which *activates* the tyrosine kinase activity of EGFR, *causes G1 arrest of A431 cells*" as submitted by the Applicant.

[69] In the Reply Letter, the Applicant resubmitted that the anti-EGFR antibody LA22 has a cytotoxic effect on the A431 cells and that such effect on A431 cells is confirmed in Goldkorn et al., *Biochem. Biophys. Acta*, 1358, 289-299, 1997 (*Goldkorn*), a subsequent publication by the same research group. Having reviewed *Goldkorn*, it appears the relevant passage referred to by the Applicant is the following:

> We have recently measured the initial apoptotic response of A431 cells to EGF, to radiation and to mAb (LA22) to EGF receptor. EGF alone slightly inhibited apoptosis, while LA22 slightly enhanced apoptosis in these cells. Moreover, radiation alone induced very low levels of apoptosis, but LA22 highly enhanced radiation-induced apoptosis by preventing the EGF receptor activation. We thus found that radiation-induced apoptosis could be enhanced by LA22. EGF, which activates the tyrosine kinase activity of EGF receptor, could delay mAb LA22-induced apoptosis. In sum, only combined treatment of mAbs to EGF receptor which inhibit EGF receptor tyrosine kinase activity together with radiation enhanced apoptosis. These results demonstrated that in cancer cells such as A431, which overexpress the EGF receptor, radiation activates predominantly the EGF receptor to induce resistance to apoptosis, while anti-EGF receptor antibodies were shown to sensitize the cells to radiation by inducing apoptosis.

[70] First, we note that *Goldkorn* does not independently test the anti-EGFR antibody LA22 cytotoxicity on A431 cells. Rather, *Goldkorn* summarizes the findings of *Balaban* using almost the exact same language found on page 155, left column of *Balaban* (cited above), a passage already considered by the Panel in the context of the entire publication. Therefore, we are still of the view that the POSITA would not consider that *Balaban* teaches that the anti-EGFR antibody LA22 has a significant cytotoxic effect on the A431 cells by itself, i.e., the general A431 cells' response to the disruption of its erbB receptor-associated kinase activity by the anti-EGFR antibody LA22 is not cell death.

[71] In the Reply Letter, the Applicant also submits that, in any case, the POSITA would not have concluded that the anti-EGFR antibody had a cytostatic effect because *Balaban* teaches that EGF and the anti-EGFR antibody had the opposite effect on EGFR signaling. The Applicant essentially argues that EGF (the ligand), which *activates* the tyrosine kinase activity of EGFR, causes G1 arrest of the tumor cells, and the anti-EGFR antibody, which *inhibits* the tyrosine kinase activity of EGFR, cannot have the same effects as EGF on the same cell line. Based on that information, the Applicant submits that "[g]iven Balaban's teaching that EGF induced cytostatic effect in A431 cells, the POSITA would ***not have concluded*** that the anti-EGFR antibody LA22 had a cytostatic effect on these cells. In fact, the POSITA would have interpreted the results of Balaban as teaching that LA22 *blocked* the cytostatic effect of EGF on A431 cells, thus restoring radiosensitivity. This is *the opposite* of the claimed invention" [emphasis in original].

[72] We respectfully disagree. First, we consider that the POSITA would not interpret the results of *Balaban* as teaching that "restoring" the radiosensitivity of A431 cells by the anti-EGFR antibody LA22 is an effect that involve "blocking" the cytostatic effect of EGF because radiosensitization of A431 cells by the anti-EGFR antibody LA22 was also observed *in absence of EGF* (see Figure 5 and the description of Figure 5 on page 153, right column). Second, we consider that *Balaban* itself explains the seeming contradiction that EGF, which activates the tyrosine kinase

activity of EGFR, and the anti-EGFR antibody, which inhibits the tyrosine kinase activity of EGFR, can have the same cytostatic effect that is generally expected from blocking the tyrosine kinase activity of EGFR. On page 154, bottom of left column to top of right column, *Balaban* states:

> In an epithelial tumor cell line with elevated EGFR, such as A431 cells, an optimal concentration of EGF is required to enhance proliferation. Higher concentrations of EGF can inhibit growth. There may be a quantitative relationship between EGFR kinase activity and growth response, and when an optimal amount of kinase activation is exceeded, growth inhibition may result. [Citations omitted]

[73] Taking into account the above passage and given that we are still of the view that the POSITA would commonly know that blocking EFGR signaling with monoclonal antibodies would typically result in a cytostatic effect and more rarely result in a cytotoxic effect (a finding that was not disputed by the Applicant in the Reply Letter), we consider that the results and teachings disclosed in *Balaban* are aligned with the CGK identified above. In our view, the POSITA would understand that both inhibiting EFGR activation and promoting EFGR activation over a certain threshold have generally a cytostatic effect on tumor cells with elevated EGFR but, ultimately and most importantly, would also understand that the key finding of *Balaban* is that EFGR signaling activation promotes radioresistance. In other words, we consider that the POSITA would understand from *Balaban* that blocking EFGR signaling is essential to sensitize the tumor cells to ionizing radiation, regardless of whether blocking EFGR signaling with a monoclonal antibody may also inhibit an independent and concurrent cytostatic effect induced by the presence of supra-optimal concentrations of EGF in addition to the radiosensitization of the tumor cells.

[74] Further, in our view the POSITA would not accept the implied corollary to the Applicant's argument in which the POSITA would purportedly understand from *Balaban* that blocking EGFR signaling with a monoclonal antibody would relieve the radioprotective effect by *promoting* the proliferation of tumor cells (i.e., the

implied opposite of the cytostatic effect induced by supra-optimal concentration of EGF).

[75] Finally, we are of the view that the POSITA would consider that the A431 cell line is a model of human cancers with known limitations that are generally present in *in vitro* models, but would nevertheless consider the A431 cell line as a relevant and widely used cell line for human cancers that overexpress erbB family of receptors because they also express abnormally high levels of the EGFR. With regard to the submission that *Balaban* highlights just how unique the A431 cells were by reporting that EGF, which activates the tyrosine kinase activity of EGFR, caused G1 arrest of A431 cells, we explained above how these observations were in line with what it is expected from an tumor cell line with elevated EGFR when in presence of supra-optimal concentrations of EGF.

[76] In light of the above, we are of the view that the POSITA would not consider that the monoclonal antibody used in *Balaban* is cytotoxic, would not consider that *Balaban* teaches that the monoclonal antibody used in the experiments had no cytostatic effect, and thus would consider that disrupting the erbB receptor-associated kinase activity with the blocking antibody LA22 prior to irradiation had the expected and typical cytostatic effect on the tumor cells and, more importantly, also had the newly discovered radiosensitization effect on the tumor cells.

[77] In the Reply Letter, the Applicant further submits that a key teaching of *Balaban* is that cytostatic cells (G1 arrested cells) treated with EGF were more radioresistant and thus, argues that the POSITA reading *Balaban* and motivated to enhance cell killing would not have used an antibody that has a cytostatic effect because the POSITA would have expected increased radiation resistance via the same mechanism *Balaban* observed with EGF.

[78] Again, we respectfully disagree. As mentioned above, we are of the view that the POSITA would consider that the key teaching of *Balaban* is instead that EGFR

activation and signaling has a dominant role in the observed radioresistance and that blocking EGFR signaling with an antibody sensitizes cells to radiation-induced apoptosis. The conclusions of *Balaban* on page 155 read as follows:

> Our results clearly suggest that EGFR activation has a dominant role in protecting A431 cells from radiation damage at clinically-relevant radiation doses, while antibodies directed against the EGFR sensitize cells to radiation by inducing apoptosis. Thus, pretreatment with monoclonal antibodies to the EGFR may be advantageous as a combined therapy with radiation in human epidermoid carcinoma.

[79] We note that the passage above clearly states the motives behind combining *pretreatment* of tumors with anti-EGFR monoclonal antibodies and ionizing radiation and we further note that said passage refers to the use of anti-EGFR monoclonal antibodies in a broad manner and does not distinguish or warn against the use of blocking anti-EGF receptor antibodies for the treatment of tumors wherein the disruption of the kinase activity has a cytostatic effect on the tumor cells. We therefore consider that the POSITA would have been particularly motivated by *Balaban* to use blocking anti-EGF receptor family member antibodies known in the art, including those reported as having a typical cytostatic rather than cytotoxic effect on cancer cell proliferation (i.e., the vast majority of the blocking antibodies known at the claim date) prior to irradiation in order to sensitize tumor cells to radiation-induced apoptosis.

[80] With respect to the submission that the CGK teaches away the present invention because the art recognized that deterring cell division would be counter-productive prior to radiation, we stated the following in the Panel Letter:

> [W]e consider that the CGK identified above tends to indicate that the generally known cytostatic effect associated with the disruption of the kinase activity associated with multimeric receptors comprising an erbB protein was not a sufficient basis to not pursue combination therapies with cytotoxic agents that were commonly known to be more effective on dividing cells. To the contrary, the generally expected cytostatic effect of blocking anti-erbB receptor antibodies formed part of the rationale for exploring the CGK combinations of blocking antibodies to members of the EGFR family with conventional cytotoxic

> chemotherapy because inhibiting the proliferation of cancer cells with blocking anti-erbB receptor antibodies is not sufficient to cure cancer.
>
> Further, we consider that the significance of such considerations is also greatly diminished in the context of a radioresistant cancer cell population. In such context, we consider that the paradigm of increased irradiation effectiveness toward dividing versus non-dividing cells is not as relevant to the POSITA because irradiation is not effective against radioresistant dividing cancer cells to begin with.
>
> In any event, we consider that the alleged concerns or negative expectations derived from the CGK or inferred from the increased radiation resistance observed with EGF in *Balaban* are addressed by the actual experimental results disclosed in *Balaban*. *Balaban* disclosed that the use of an anti-EGFR blocking antibody prior to irradiation is not counter-productive to sensitize radioresistant cancer cells to irradiation; on the contrary, it is rather effective. For the reasons detailed above, we consider that *Balaban* teaches that an observed cancer cell resistance to radiation is mediated by the activation of EGFR and that the prior administration of an anti-EGFR blocking antibody sensitizes the cancer cells to radiation-induced apoptosis.

[81] In the Reply Letter, the Applicant stated the following with regard to the above Panel's observations:

> In response, the Panel contends that the significance of the teaching of Sklar and Awwad is "greatly diminished in the context of a radioresistant cancer cell population … because irradiation is not effective against radioresistant dividing cancer cells to begin with" (see Office letter, Panel's observations at page 18).
>
> The Panel's rationale, however, is flawed since it does not explain why the POSITA would have been motivated to use an order of administration using a cytostatic antibody ***prior to*** radiation — a method that was expected to be counter-productive to the use of radiation. If anything, given the common general knowledge at the time, a person of skill would have sought to enhance cell division prior to radiation treatment to increase radiation sensitivity.

[82] We explained above why the POSITA would have been specifically motivated by *Balaban* to use blocking anti-EGF receptor family member antibodies known in the art as having a typical cytostatic effect on cancer cell proliferation *prior* to irradiation. Further, we are still of the view that the POSITA would consider that the relevance of the known paradigm regarding fast-proliferating cells and sensitivity to

irradiation therapy is diminished in the context of proliferating radioresistant tumor cells. With regard to the submission that "[i]f anything, given the common general knowledge at the time, a person of skill would have sought to enhance cell division prior to radiation treatment to increase radiation sensitivity", we respectfully disagree. We are of the view that the POSITA would not have sought to promote cancer growth of already proliferating and radioresistant tumor cells in a therapeutic context.

[83] As noted above in the CGK section, we consider that it was CGK at the claim date that different members of the erbB family of receptors, including EGFR and p185, are often overexpressed in human cancers, interact and form active heterodimeric kinase complexes. It was also CGK to disrupt the kinase activity associated with multimeric receptors comprising an erbB protein with blocking antibodies against different erbB proteins, including p185 and EGFR, to inhibit the proliferation of cancer cells that express the corresponding erbB heterodimers. What was not commonly known was that the disruption of the associated kinase activity with blocking antibodies also sensitizes radioresistant cancer cells to irradiation. Then *Balaban* provided the proof of principle that disrupting kinase activity by anti-EFGR antibodies prior to irradiation has also the effect of sensitizing cancer cells to radiation-induced apoptosis.

[84] In view of the above, we consider that it would have been obvious to the POSITA taught by *Balaban*, i.e., it would not require any degree of invention, to first disrupt the kinase activity associated with any erbB heterodimers expressed by a tumor, including the well-known erbB heterodimers recited in the claims on file, with a corresponding blocking antibody such as a CGK blocking anti-EGFR antibody, CGK blocking anti-p185 antibody (e.g. 4D5-derived antibodies such as Herceptin) or the peptidomimetics disclosed by *Greene* prior to an irradiation treatment with ionizing radiation.

[85] Having also considered dependent claims 3 to 17 on file, we do not consider that an inventive step would have been required from the POSITA in respect of their further limitations to the use of an antibody or peptide that interacts with a monomeric component of the multimeric receptor (claims 3 and 4), the use of an antibody or peptide that inhibits formation of a heterodimer of p185 and EGFR (claims 5 and 6), an anti-p185 antibody (claim 7), the p53 status of the tumor cells (claims 8 and 9) and the use of a specific peptide that is an obvious analogue of the ones disclosed in *Greene* (claims 10 to 17).

[86] In the Panel Letter we also expressed the view that *DeNardo* strengthens the teachings of *Balaban* with regard to the sensitization of radioresistant cancer cells with a blocking anti-EGFR antibody and considered that the teachings of *Ezekiel* and *Saleh* tend to indicate a motivation to combine the disruption of the kinase activity associated with an erbB heterodimers expressed by a tumor with a blocking antibody and irradiation. In the Reply Letter, the Applicant submitted that *DeNardo* does not strengthen the teachings of *Balaban* because: i) the difference in mechanisms of killing between radioimmunotherapy and external beam anti-cancer radiation; ii) the results of *DeNardo* were known to be statistically insignificant; and iii) the cell line in *DeNardo* does not express p185. With respect to *Saleh* and *Ezekiel*, the Applicant argued that *Saleh* and *Ezekiel* do not provide motivation to arrive at the claimed invention which contain the limitation "wherein disruption of said kinase activity has a cytostatic effect on the tumor cells". Further, as argued by the Applicant, the POSITA would have recognized that the C225 antibody used in *Saleh* has a cytotoxic rather than a cytostatic effect on A431 cells. Finally, the Applicant contends that *Ezekiel* does not provide any information as to whether the antibody contributes to the response or whether the effect is attributable to the radiation only.

[87] As expressed above, we consider the subject matter of the claims on file would have been obvious at the claim date to the POSITA in view of the teachings of *Balaban* in light of the CGK or the combined teachings of *Balaban*, and *Greene* in light of the CGK. Accordingly, we do not consider necessary for the present review to address

in details the Applicant's submissions with regard *DeNardo, Saleh and Ezekiel* beyond reaffirming our views that these documents tend to indicate a general motivation in the art to combine the disruption of the kinase activity associated with an erbB heterodimers expressed by a tumor with a blocking antibody and irradiation.

Conclusion on obviousness of the claims on file

[88] In view of the above, we consider that the subject-matter of claims 1 to 17 on file would have been obvious at the claim date to the POSITA in view *Balaban* and the relevant CGK (claim 1 and all dependent claims thereon) or in view of the combined teachings of *Balaban, Greene* and the relevant CGK (claim 2 and all dependent claims thereon), contrary to section 28.3 of the *Patent Act*.

Indefiniteness of claims 8 and 9 on file

[89] The SOR explained that expressions "p53 (+) tumor cell" and "p53 (-) tumor cell" do not serve to distinctly and explicitly define the intended subject-matter because, as an example, it is not clear whether the expression "p53 (+) tumor cell" contemplates a tumor cell that contains both wildtype and mutant p53 alleles or only wildtype p53 alleles.

[90] In the R-SOR, the Applicant asserted that "while it is believed that a POSITA, when construing the claims with a mind willing to understand and in view of the teaching found in art would understand such expression, it is proposed amending claim 8 to recite 'the tumor cell has a wild-type p53,' and amending claim 9 to recite 'the tumor cell does not have a wild-type p53.'"

[91] In the Panel Letter we noted that that the expressions "p53 (+) tumor cell" and "p53 (-) tumor cell" are not found in the originally filed application. Further, we also noted that the Applicant's submissions do not even broadly explain on which basis "of the teaching found in art" the POSITA would understand such expressions and do not attempt to explain what exactly should be understood from these expressions

by the POSITA. In light of that, we expressed that view that the above identified expressions do not define in distinct and explicit terms the contemplated tumor cell as having a wild-type p53 or as not having a wild-type p53 and that the identified expressions cause an avoidable lack of clarity with regard to the claimed subject-matter.

Conclusion on indefiniteness of claims 8 and 9 on file

[92] In view of the above, we are of the view that the subject-matter of claims 8 and 9 on file is not defined in distinct and in explicit terms, contrary to subsection 27(4) of the *Patent Act*.

ANALYSIS OF THE PROPOSED CLAIMS

[93] On April 27, 2018, the Applicant submitted the proposed claims set-3 containing claims 1 to 18 wherein proposed independent claims 1 and 2 are amended to recite "for treating an individual who has an-erbB-protein mediated radiation-resistant tumor" and "sensitizes the cells to the anti-cancer radiation and wherein said medicament is for administration prior to the anti-cancer radiation, wherein the anti-cancer radiation is selected from the group consisting of gamma rays and x-rays". Proposed claims 8 and 9 are respectively amended to recite "the tumor cell has a wild-type p53." and "the tumor cell does not have a wild-type p53." Finally, new proposed claim 18 depends on claim 1 and recites "wherein the use results in synergistic apoptosis of the tumor cells".

[94] We note that there is a clear correspondence between the proposed claims set-3 and the claims on file, that the proposed claims set-3 do not broaden the scope of the corresponding claims on file and do not necessitate another prior art search. Accordingly, the proposed claims set-3 could be considered for amendment if it is determined that they overcome the defects noted above with regard to the claims on file, and do not introduce another defect. For these reasons, we have provided our views on these claims as well.

Novelty of the proposed claims set-3

[95] We have presented our view that the subject-matter of claims 1, 3 and 5 on file is novel in view of *Balaban* and complies with paragraph 28.2(1)(*b*) of the *Patent Act*, for the reasons given above.

[96] As the only significant differences between claims 1, 3 and 5 on file and corresponding claims of the proposed claims set-3 is the further characterization of the tumor to be treated (i.e., an-erbB-protein mediated radiation-resistant tumor) and of the anti-cancer radiation treatment (i.e., selected from the group consisting of gamma rays and x-rays), we are of the view that the proposed claims set-3 comply with paragraph 28.2(1)(*b*) of the *Patent Act* for the reasons provided previously with respect to the claims on file.

Obviousness of the proposed claims set-3

[97] We have presented our view that the subject-matter of claims 1 to 17 on file would have been obvious at the claim date to the POSITA in view of the teachings of *Balaban* and the relevant CGK or the combined teachings of *Balaban* and *Greene* and the relevant CGK.

[98] The only significant difference between claims 1 to 17 on file and corresponding claims of the proposed claims set-3 is that the tumor to be treated is explicitly defined as an-erbB-protein mediated radiation-resistant tumor and that the anti-cancer radiation treatment is limited to gamma rays and x-rays.

[99] Given that proposed claims 1 to 17 encompass subject-matter already considered obvious, we are of the view that the subject-matter of proposed claims 1 to 17 would have been obvious to the POSITA at the claim date for the reasons provided with respect to the claims on file.

[100] With regard to proposed dependent claim 18 which specifies "wherein the use results in synergistic apoptosis of the tumor cells", the Applicant submitted the following in the Reply Letter:

> Claim 18, which depends on claim 1, further specifies that "the use results in synergistic apoptosis of the tumor cells." The cited prior art, alone or in combination, could not have predicted that administered, ***prior to*** radiation, a reagent that caused a cytostatic effect on the tumor cell, specifically an anti-ErbB receptor antibody, would achieve a "synergistic apoptosis of the tumor cells." Therefore, the Panel should find claim 18 nonobvious.

[101] As explained above, we are of the view that *Balaban* teaches that only a combined treatment of a blocking anti-EGFR antibody together with radiation significantly enhance apoptosis. Accordingly, we consider that *Balaban* teaches an interaction between two treatments that causes the total effect of the treatments to be greater than the sum of the individual effects of each treatment, i.e., the prior use of the blocking anti-EGFR antibody to sensitize the tumor cells to irradiation results in synergistic apoptosis of the tumor cells.

[102] Therefore, we are of the view that the proposed claims set-3 do not comply with section 28.3 of the *Patent Act* for the reasons provided previously with respect to the claims on file.

Indefiniteness of claims 8 and 9 of proposed claims set-3

[103] Given that proposed claims 8 and 9 respectively recite "the tumor cell has a wild-type p53" and "the tumor cell does not have a wild-type p53", we are of the view that the proposed claims 8 and 9 do not lack clarity and comply with subsection 27(4) of the *Patent Act*.

Conclusion with respect to the proposed claims set-3

[104] In view of the above, we are of the view that the claims of proposed claims set-3 do not meet the requirements of a "necessary" amendment under subsection 30(6.3) of the *Patent Rules*.

RECOMMENDATION OF THE BOARD

[105] We recommend that the application be refused on the basis that the subject-matter of claims 1-17 on file would have been obvious, contrary to section 28.3 of the *Patent Act* and that the subject-matter of claims 8 and 9 on file is not defined in distinct and in explicit terms, contrary to subsection 27(4) of the *Patent Act*.

[106] Given that the proposed claims set-3 would not remedy the obviousness defect of the claims on file, we decline to recommend that the Applicant be notified under subsection 30(6.3) of the *Patent Rules* that said proposed claims are necessary to comply with the *Patent Act* and *Patent Rules*.

Marcel Brisebois Member	Ed MacLaurin Member	Lewis Robart Member

DECISION

[107] I concur with the findings of the Patent Appeal Board and its recommendation that the application should be refused because the subject-matter of the claims on file would have been obvious, contrary to section 28.3 of the *Patent Act* and the subject-matter of claims 8 and 9 on file is not defined in distinct and in explicit terms, contrary to subsection 27(4) of the *Patent Act*.

[108] Accordingly, I refuse to grant a patent on this application. Under section 41 of the *Patent Act*, the Applicant has six months within which to appeal my decision to the Federal Court of Canada.

Johanne Bélisle
Commissioner of Patents
Dated at Gatineau, Quebec,
this 30th day of October, 2018.