Citation: Biocon Limited, 2023 CACP 20
Commissioner's Decision #1653
Décision du commissaire no 1653
Date: 2023-07-17

TOPIC:	B00	Ambiguity or indefiniteness
	O00	Obviousness

SUJET:	B00	Caractère ambigu ou indéfini description
	O00	Évidence

Application No.: 2,947,354

Demande nº 2 947 354

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,947,354 having been rejected under subsection 199(1) of the *Patent Rules*, has consequently been reviewed in accordance with paragraph 86(7)(c) of the *Patent Rules*. The recommendation of the Patent Appeal Board and the decision of the Commissioner are that the application be refused unless necessary amendments are made.

Agent for the Applicant:

Kirby Eades Gale Baker

55 Murray Street, Suite 300
Ottawa, Ontario
K1N 5M3

INTRODUCTION

[1] This recommendation concerns the review of rejected Canadian patent application number 2,947,354, which is entitled "Targeted/immunomodulatory fusion proteins and methods for making same". Biocon Limited is the sole Applicant. A review of the rejected application has been conducted by a Panel of the Patent Appeal Board pursuant to paragraph 86(7)(c) of the *Patent Rules*.

[2] As explained in more detail below, our recommendation is that the Commissioner of Patents inform the Applicant by notice pursuant to subsection 86(11) of the *Patent Rules* that certain amendments to the claims are necessary to make the application allowable.

BACKGROUND

The Application

[3] The present application is a divisional of parent application 2,871,706 which was filed under the Patent Cooperation Treaty (PCT) and has an effective filing date in Canada of March 13, 2013. The parent application was laid open to public inspection on November 7, 2013.

[4] The rejected application relates to chimeric fusion proteins to be used in cancer therapy. The chimeric fusion proteins comprise a targeting moiety to target a cancer cell and an immunomodulating moiety that counteracts immune tolerance. In particular, the claims are directed to a chimeric fusion protein comprising anti-HER2/Neu antibody as the targeting moiety to target cancer cells expressing the HER2 receptor and transforming growth factor beta receptor II (TGF-βRII) as the immunomodulating moiety which binds to TGF-β to inhibit the proliferation of the cancer cells.

[5] The application has 14 claims on file that were received at the Patent Office on July 8, 2019.

Prosecution History

[6] On April 16, 2021, a Final Action was written under subsection 86(5) of the *Patent*

Rules. The Final Action states that the subject-matter of claims 1 to 14 on file is obvious contrary to section 28.3 of the *Patent Act* and that claims 1 to 3 on file are also indefinite contrary to subsection 27(4) of the *Patent Act*.

[7] The Response to the Final Action dated August 12, 2021, disagrees with the obviousness assessment and further includes an amended claim set, containing proposed claims 1 to 11, that it submits is allowable.

[8] On September 21, 2022 the application was forwarded to the Patent Appeal Board for review under paragraph 86(7)(c) of the *Patent Rules* along with a Summary of Reasons explaining that the rejection is maintained as the arguments presented in the Response to the Final Action are not persuasive and the proposed amendments presented in the Response to the Final Action do not overcome all of the defects identified in the Final Action.

[9] In a letter dated September 22, 2022, the Patent Appeal Board forwarded a copy of the Summary of Reasons to the Applicant and requested that they confirm their continued interest in having the application reviewed.

[10] In a letter dated December 21, 2022, the Applicant confirmed their interest in having the review proceed.

[11] The present Panel was formed to review the rejected application under paragraph 86(7)(c) of the *Patent Rules*. On June 7, 2023, the Panel sent a Preliminary Review letter detailing our preliminary analysis and opinion that the subject-matter of claims 1 to 3 on file is obvious and indefinite contrary to section 28.3 and subsection 27(4) of the *Patent Act*, respectively. The Preliminary Review letter also expresses the preliminary opinion that the subject-matter of proposed claim 1 is obvious and indefinite. The Preliminary Review letter also provided the Applicant with an opportunity to make oral and/or written submissions.

[12] On June 20, 2023, the Applicant declined the opportunity for an oral hearing and further indicated that there would be no written submissions.

Issues

[13] In view of the above, the following issues are considered in this review:

- whether the claims on file are obvious contrary to section 28.3 of the *Patent Act*; and

- whether claims 1 to 3 on file are indefinite contrary to subsection 27(4) of the *Patent Act*.

[14] In addition to the claims on file, the proposed claims have also been considered.

PURPOSIVE CONSTRUCTION

Legal Background

[15] According to Free World Trust v Électro Santé Inc, 2000 SCC 66 [Free World Trust] and Whirlpool Corp v Camco Inc, 2000 SCC 67 [Whirlpool], a purposive construction of the claims is performed from the point of view of the person skilled in the art in light of the relevant common general knowledge and considers the specification and drawings. In addition to interpreting the meaning of the terms of a claim, purposive construction distinguishes the essential elements of the claim from the non-essential elements. Whether or not an element is essential depends on the intent expressed in or inferred from the claim, and on whether it would have been obvious to the person skilled in the art that a variant has a material effect upon the way the invention works.

[16] In carrying out the identification of essential and non-essential elements, all elements set out in a claim are presumed essential unless it is established otherwise or where such a presumption is contrary to the claim language.

Analysis

The person skilled in the art and the relevant common general knowledge

[17] The Preliminary Review letter, on pages 4 to 8, states the following with regard to the identity of the person skilled in the art and their expected common general knowledge:

> On page 3, the Final Action identifies the person skilled in the art and the relevant common general knowledge:

> The person skilled in the art is a team comprising a biochemist, a molecular biologist, and an oncologist.
>
> […]
>
> The common general knowledge of the person skilled in the art includes the structure of antibodies, including that of the constant region and variable regions; knowledge of antibody types (e.g., monoclonal and polyclonal) and the antigen-binding fragments derived therefrom; the association of the expression of HER2/Neu with cancer; the known monoclonal antibodies that specifically bind to anti-HER2/Neu (e.g., Herceptin); the activity of TGβRII as an immunomodulator; and the construction and use of fusion proteins carrying a therapeutic moiety targeted to cancer cells expressing a specific surface antigen by fusing said therapeutic moiety to a monoclonal antibody.

The Response to the Final Action, on page 13, disagrees with both of these characterizations and submits that the characterization of the person skilled in the art as a team of high-level professionals overreaches the definition established in Beloit Canada Ltd v Valmet OY (1986), 8 CPR (3d) 289 (FCA) [Beloit]. This mischaracterization of the person skilled in the art has led to an unreasonable and unrealistic combination of high-level skills and attributes being identified as common general knowledge.

The Response to the Final Action does not propose an alternate identification of either the person skilled in the art or the relevant common general knowledge.

Regarding the person skilled in the art, we note that subsequent to Beloit, several court decisions have provided additional context for their identification. For example, the Supreme Court of Canada explained that although the person skilled in the art is deemed to have no scintilla of inventiveness or imagination, a patent specification is addressed to "skilled individuals sufficiently versed in the art to which the patent relates to enable them on a technical level to appreciate the nature and description of the invention": Whirlpool at para 53. Moreover, "in the case of patents of a highly technical and scientific nature, that person may be someone possessing a high degree of expert scientific knowledge and skill in the particular branch of science to which the

patent relates": Consolboard v MacMillan Bloedel (Sask) Ltd, [1981] 1 SCR 504 at page 525.

In addition, the person skilled in the art can represent a composite of scientists—highly skilled and trained persons who conduct scientific research to advance knowledge in an area of interest—and researchers: Bayer Aktiengesellschaft v Apotex Inc [1995] 60 CPR (3d) 58 at page 79

> The notional skilled technician can be a composite of scientists, researchers and technicians bringing their combined expertise to bear on the problem at hand: "This is particularly true where the invention relates to a science or art that transcends several scientific disciplines." (*Per* Wetston J. in *Mobil Oil Corp. v. Hercules Canada Inc.* (unreported, September 21, 1994, F.C.T.D., at p. 5 [now reported 57 C.P.R. (3d) 488 at p. 494, 82 F.T.R. 211].)

With the above considerations in mind and having reviewed the specification as a whole, we disagree with the submissions in the Response to the Final Action that the characterization of the person skilled in the art presented in the Final Action is not reasonable. For example, para 2 of the present description identifies the technical field of the invention as relating generally "to the field of generating fusion proteins to be used in cancer therapy, and more specifically, to nucleotide sequences encoding the fusion proteins, wherein the fusion or chimeric polypeptides comprises at least one targeting moiety and at least one immunomodulatory moiety that counteracts the immune tolerance of cancer cells." Further the subject-matter of the claims on file relates to the use and preparation of a chimeric fusion protein wherein the targeting moiety is anti-HER2/Neu antibody and the immunomodulating moiety is TGF-βRII.

Given the technical field to which the present patent application relates and the subject-matter of the claims on file, we consider that the characterization of the person skilled in the art as a team comprising a biochemist, a molecular biologist, and an oncologist is reasonable. We would further add that, in our preliminary view, this team is familiar with immunological/biological concepts relating to therapeutic antibody production and their use in the treatment of cancers associated with the overexpression of HER2/Neu.

Regarding the identification of the common general knowledge, it is our preliminary view that, although it was provided in the context of the obviousness analysis, the above identified information was also relevant common general knowledge as of the publication date of the present application.

It is well established that the common general knowledge is limited to knowledge which is generally known by persons skilled in the field of art or science to which a patent relates: Apotex Inc v Sanofi–Synthelabo Canada Inc, 2008 SCC 61 at para 37 [Sanofi]; Free World Trust at para 31. Accordingly, the common general knowledge is with respect to the subset of patents, journal articles and technical information which is generally acknowledged by persons skilled in the art as forming part of the common general knowledge in the field to which a patent relates.

Established reference works (such as textbooks, review articles, handbooks, etc.) or demonstrated commonality of certain knowledge in a number of disclosures in the field are relevant to the inquiry: see the Manual of Patent Office Practice (CIPO) at 12.02.02c, revised October 2019.

As explained at para 100 of the description, the practice of the invention will employ “conventional techniques of immunology, molecular biology, microbiology, cell biology and recombinant DNA, which are within the skill of the art”. Therefore, given the technical field to which the present patent application relates and the subject-matter of the claims on file, we consider that the information regarding antibodies, HER2, TGFβRII and fusion proteins as set out in the Final Action would have been generally known by the person skilled in the art as defined above who is “sufficiently versed in the art to which the patent relates to enable them on a technical level to appreciate the nature and description of the invention”: Whirlpool at para 53.

Regarding the knowledge of the structure of antibodies, we note that the Summary of Reasons introduces two references to demonstrate that it was common general knowledge that recombinant production of antibodies in Chinese Hamster Ovary cells results in charge heterogeneity due to the partial removal of carboxy-terminal lysine residues from the heavy chain: Harris, R.J., “Processing of C-terminal lysine and arginine residues of proteins isolated from mammalian cell culture”, Journal of Chromatography A, 705, pages 129 to 134, 1995 and Perkins, M. et al., “Determination of the origin of charge heterogeneity in a murine monoclonal antibody”, Pharmaceutical Research, 17(9), pages 1110 to 1117, 2000.

Having reviewed both of these references, we agree that the loss of the carboxy-terminal lysine on one or both heavy chains of antibodies is one of the most common structural variants observed in production in cell culture. Moreover, the design of microvariants, including the deletion of carboxy-terminal lysine residues (to decrease the number of charge variants) to improve homogeneity was also well known as evidenced by the following review articles: Beck, A. et al., “Strategies and challenges for the next generation of therapeutic antibodies”, Nature Reviews Immunology, 10, pages 345 to 352, 2010 [Beck et al.] and Harris, R.J.,

> "Heterogeneity of recombinant antibodies: linking structure to function" in Mire-Sluis A.R., ed, 122, State of the Art Analytical Methods for the Characterization of Biological Products and Assessment of Comparability (Basel, Switzerland: Karger, 2005), pages 117 to 127 [Harris]. Regarding the design of a variant antibody with a deletion of the heavy chain carboxy-terminal lysine, Harris explains on page 120 that "[t]he presence or absence of heavy chain Lys residues has no effect on antigen binding, and is not likely to influence Fc effector functions, clearance, or any other biological property." It is our preliminary view that the above teachings are representative of what the above defined person skilled in the art would commonly know/believe regarding carboxy-terminal lysine residues in the context of therapeutic antibody production.
>
> Regarding the production of fusion proteins using Chinese Hamster Ovary cells as an expression system, we note that the Summary of Reasons asserts that the use of these cells for producing fusions proteins and antibodies is well-known in the art. We agree that Chinese Hamster Ovary cells is one of the most common mammalian expression systems used for the production of recombinant proteins and therapeutic antibodies as evidenced by the following review article: Zhu, J., "Mammalian cell protein expression for biopharmaceutical production", Biotechnology Advances, 30, pages 1158 to 1170, available online 2011 [Zhu]. Further, Zhu explains that optimization of protein expression in these cells can involve codon optimization, controlling lactate accumulation and temperature shifts: see pages 1162 to 1163. It is our preliminary view that the above teachings are representative of what the above defined person skilled in the art would commonly know/believe regarding optimizing therapeutic antibody expression in Chinese Hamster Ovary cells.

[18] In the absence of submissions from the Applicant, we adopt the above characterizations of the person skilled in the art and the relevant common general knowledge for our final analysis.

The claims on file

[19] There are are 14 claims on file. Independent claims 1 and 4 are taken as being representative of the independent claims and read as follows:

> 1. A chimeric fusion protein comprising at least one targeting moiety to target a cancer cell and at least one immunomodulating moiety that counteracts immune tolerance, wherein the targeting moiety and the immunomodulating moiety are linked by an amino acid

spacer of sufficient length of amino acid residues so that both moieties can successfully bind to their individual targets, wherein the immunomodulating moiety is transforming growth factor, beta receptor II (TGF-βRII) consisting of amino acid sequence of SEQ ID NO. 4; wherein the amino acid spacer consists of SEQ ID NO:3; and wherein the targeting moiety is Anti-HER2/Neu antibody consisting of heavy chain SEQ ID NO:1 and light chain SEQ ID NO: 2, wherein SEQ ID NO: 4 is attached via the amino acid spacer to the C-terminus of heavy chain SEQ ID NO:1 or light chain SEQ ID NO:2 of the Anti-HER2/Neu antibody, wherein binding of the immunomodulating moiety TGF-βRII to transforming growth factor beta (TGFβ) inhibits proliferation of cancer cells**.**

4. A method of preparing the chimeric fusion protein according to claim 1, the method comprising,

   preparing an expression vector comprising a codon optimized nucleotide sequence encoding the chimeric fusion protein, wherein the codon optimized nucleotide sequence comprises an increase of CG sequences for expression of Chinese Hamster Ovary (CHO) host cells.

   introducing the expression vector into the CHO host cells capable of transient or continued expression.

   introducing and growing the CHO host cells in a fermentation medium under suitable conditions for growing and allowing the CHO host cells to express the chimeric fusion protein wherein the fermentation medium comprises a zinc salt; and

   purifying the expressed chimeric fusion protein to provide a purified chimeric fusion protein and optionally checking any bi-specific binding capabilities of the chimeric fusion protein to its targets.

[20] Independent claim 2 is similar to claim 1 but further specifies that the chimeric fusion protein is for use to lyse cells. Likewise, independent claim 3 defines the use of the chimeric fusion protein to lyse cells.

[21] The dependent claims 5 to 14 define further limitations regarding the zinc salt (claims 5 to 7), the reduction in lactate (claim 8), the temperature of the fermentation medium (claim 9), the cell count of CHO cells (claim 10), the purification of the chimeric fusion protein (claims 11 to 13) and storage of the fusion proteins (claim 14).

[22] In the absence of submissions from the Applicant, we adopt the above

identification of claims 1 and 4 as being representative of the independent claims. Likewise, we adopt the above characterization of dependent claims 5 to 14 as providing further limitations regarding the zinc salt, the reduction in lactate, the temperature of the fermentation medium, the cell count of CHO cells, the purification of the chimeric fusion protein and storage of the fusion proteins.

Essential elements

[23] As stated above, all of the elements set out in a claim are presumed essential unless it is established otherwise or where such a presumption is contrary to the claim language. Further, a claim element is essential when it would have been obvious to the person skilled in the art that its omission or substitution would have a material effect on the way the invention works: Free World Trust at para 55.

[24] The Preliminary Review letter, on page 9, states the following with regard to the elements in the claims that the person skilled in the art would consider to be essential:

> With respect to claim language, our preliminary view is that the person skilled in the art reading claims 1 to 14 in the context of the specification as a whole and in view of their common general knowledge would understand that there is no use of language in any of the claims indicating that any of the elements are optional, preferred or were otherwise intended as being non-essential. Therefore, our preliminary view is that the person skilled in the art would consider all of the elements in the claims to be essential.

[25] In the absence of submissions from the Applicant, we adopt the above identification of the claim elements that are essential in this recommendation.

OBVIOUSNESS

Legal Background

[26] Section 28.3 of the *Patent Act* requires that the subject-matter of a claim not be obvious to the person skilled in the art:

> 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 before the one-year period immediately preceding the filing date or, if the claim date is before that period, before the claim 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.

[27] In Sanofi at para 67, the Supreme Court of Canada states 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?

Analysis

[28] The Preliminary Review letter, on pages 11 to 16, explains that in our preliminary view claims 1 to 3 on file define subject-matter that would have been obvious to the person skilled in the art in view of the cited prior art and the relevant common general knowledge but that claims 4 to 14 on file are not obvious:

The person skilled in the art and the relevant common general knowledge

The person skilled in the art and the relevant common general knowledge have been identified as part of the purposive construction of

the claims. As explained above, the information is considered common general knowledge at the publication date and the claim date and is therefore relevant for assessing obviousness.

Identify the inventive concept of the claim in question or, if that cannot readily be done, construe it

The Final Action on page 3 identifies a single inventive concept for the claims on file:

> The inventive concept of the instant claims pertains to a fusion protein in which TGFβRII consisting of SEQ ID NO: 4 is attached via the amino acid spacer consisting of SEQ ID NO:3 to the C-terminus of the heavy chain consisting of SEQ ID NO: 1 or the C-terminus of the light chain consisting of SEQ ID NO:2 of an anti-HER2/Neu antibody and wherein the fusion protein inhibits the proliferation of cancer cells.

The Response to the Final Action does not contest or comment on this characterization.

As mentioned above, our preliminary view is that the person skilled in the art would consider all of the elements in the claims to be essential, and so they should be reflected in the inventive concepts of the claims. Therefore, for the purposes of this assessment we take into account all of the essential elements of the claims. In our preliminary view, the combination of essential elements of independent claims 1 to 4 represents their inventive concepts as well.

Our preliminary view is also that the elements of the dependent claims relating to the zinc salt, the reduction in lactate, the temperature of the fermentation medium, the cell count of CHO cells, the purification of the chimeric fusion protein and storage of the fusion proteins, as set out above, are part of the respective inventive concepts of dependent claims 5 to 14.

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

The Final Action cites the following document as relevant art:

D1: WO 2011/109789 A2 Bedi and Ravi September 9, 2011

D1 discloses chimeric fusion proteins to be used in cancer therapy. The chimeric fusion proteins comprise a targeting moiety to target a cancer

cell which is linked by an amino acid spacer to an immunomodulating moiety that counteracts immune tolerance. Specifically disclosed is a chimeric fusion protein comprising anti-HER2/Neu antibody as the targeting moiety to target cancer cells expressing the HER2 receptor and the extracellular domain of TGF-βRII as the immunomodulating moiety which binds to TGF-β to inhibit the proliferation of the cancer cells. The extracellular domain of TGF-βRII can be fused to either the carboxy-terminus of the Fc region of the heavy chain of anti-HER2/Neu antibody or to the light chain: see para 182. Figure 2 of D1 provides an embodiment of a chimeric fusion protein comprising an anti-HER2/Neu antibody heavy chain linked via an amino acid spacer to the extracellular domain of TGF-βRII consisting of SEQ ID NO: 1 and an anti-HER2/Neu antibody light chain consisting of SEQ ID NO: 70.

In our preliminary view the main difference between the inventive concepts of the claims on file and D1 lies in the specific sequence of the chimeric fusion protein comprising anti-HER2/Neu antibody heavy chain and the extracellular domain of TGFβ-RII. In D1, the amino acid sequence of the heavy chain of the anti-HER2/Neu antibody contains a carboxy-terminal lysine, however, in the claims on file this carboxy-terminal lysine is absent.

Additional differences over claims 4 to 14 on file include the expression system used for the production of the chimeric fusion protein, design of the expression vector, culture conditions and purification and storage conditions for the chimeric fusion protein.

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?

Although the Court in Sanofi provides a four-step approach for addressing the issue of obviousness, it is important to remember that the obviousness analysis is concerned with whether bridging the difference between the prior art and a second point constitutes steps that require any degree of invention: Bristol-Myers Squibb Canada Co v Teva Canada Limited, 2017 FCA 76 at para 65

> It may be helpful to keep in mind that the obviousness analysis asks whether the distance between two points in the development of the art can be bridged by the Skilled Person using only the common general knowledge available to such a person. If so, it is obvious. The first of those points is the state of the prior art at the relevant date. References in the jurisprudence to “the inventive concept”, “the

solution taught by the patent", "what is claimed" or simply "the invention" are attempts to define the second point.

In the present case, it is our preliminary view that that what must be considered is whether it would have required any degree of invention from the person skilled in the art, based on D1 and the relevant common general knowledge, to use a chimeric fusion protein comprising an anti-HER2/Neu antibody and the extracellular domain of TGFβ-RII, wherein the carboxy-terminal lysine of the heavy chain is absent, to lyse cancer cells that express HER2/Neu and inhibit the proliferation of said cells. Another consideration is whether it would have required any degree of invention from the person skilled in the art, based on D1 and the relevant common general knowledge, to use an expression system comprising zinc salts to reduce accumulation of lactate during culturing.

As explained above, the person skilled in the art would have known from D1 the sequence of a chimeric fusion protein comprising an anti-HER2/Neu antibody and the extracellular domain of TGFβ-RII. The anti-HER2/Neu antibody acts as a targeting moiety which specifically binds HER2/Neu while the extracellular domain of TGFβ-RII acts as an immunomodulatory moiety and inhibits the activity or function of TGFβ to counteract tumor-induced immune tolerance.

In addition, the loss of the carboxy-terminal lysine on one or both heavy chains of antibodies are one of the most common structural variants observed in production in cell culture, including Chinese Hamster Ovary cells, which leads to charge heterogeneity. Indeed, the design of microvariants, including the deletion of carboxy-terminal lysine residues (to decrease the number of charge variants) to improve homogeneity was also well known see Beck et al. and Harris. In our preliminary view, the person skilled in the art would have been motivated to delete the carboxy-terminal residue from the heavy chain of the anti-HER2/Neu antibody to improve homogeneity.

Further, the production of such variants could be easily accomplished using "conventional techniques of immunology, molecular biology, microbiology, cell biology and recombinant DNA, which are within the skill of the art": see description para 100. Indeed, starting with the sequences provided in D1, only a single amino acid modification, the deletion of the carboxy-terminal lysine from the heavy chain of the anti-HER2/Neu antibody, would be required to arrive at the specific sequence of the claims on file.

Moreover, given the role of the anti-HER2/Neu antibody as a targeting moiety, it is our preliminary view that the person skilled in the art, in view of the common general knowledge identified above, would have

expected that the deletion of the carboxy-terminal lysine from the heavy chain would not affect the ability of such a variant anti-HER2/Neu antibody to bind to HER2/Neu: see Harris.

Although the claimed chimeric fusion protein is structurally different from the fusion protein disclosed in D1, the sole amino acid difference does not appear to be associated with a previously unknown or unexpected effect. In this view, we note that the exemplary support in the present description is limited to the expression and characterization of a chimeric fusion protein comprising an anti-HER2/Neu antibody and the extracellular domain of TGFβ-RII wherein the heavy chain carboxy-terminal lysine is present: see Example 1, SEQ ID NOs: 12 and 13, Figure 40. There is no expression or characterization of a corresponding chimeric fusion wherein the heavy chain carboxy-terminal lysine has been deleted.

In light of the above, it is our preliminary view that it would not have required any degree of invention from the person skilled in the art to use a chimeric fusion protein comprising an anti-HER2/Neu antibody and the extracellular domain of TGFβ-RII, wherein the carboxy-terminal lysine of the heavy chain is absent, to lyse cancer cells that express HER2/Neu and inhibit the proliferation of said cells. Consequently, it is our preliminary view that the subject-matter of claims 1 to 3 is obvious having regard to D1 in view of the common general knowledge.

Further, in view of our preliminary findings that the person skilled in the art would have known that it was desirable in the context of therapeutic antibody production to remove the carboxy-terminal lysine from the heavy chain of the anti-HER2/Neu antibody to improve charge homogeneity, it is not necessary to consider an obvious to try analysis at this point of the review process.

Regarding the production of a chimeric fusion protein, D1 simply states “the fusion proteins of the invention can be produced using a host cell well known in the art.” Therefore, although Chinese Hamster Ovary cells are not explicitly disclosed in D1, they are one of the most common mammalian expression systems used for the production of recombinant proteins and therapeutic antibodies. As such, it is our preliminary view that the person skilled in the art reading D1 would consider that Chinese Hamster Ovary cells are an example of “a host cell well known in the art” for the production of fusion proteins. Further, as identified earlier, it was also common general knowledge that optimization of protein expression in these cells can involve codon optimization, controlling lactate accumulation and temperature shifts: see Zhu pages 1162 to 1163.

However, the use of zinc salts to control lactate accumulation is not disclosed in D1 and does not form part of the common general knowledge described above. Therefore, it is our preliminary view that it

> would not have been obvious to the person skilled in the art that the inclusion of a zinc salt to the fermentation medium would control lactate accumulation during culturing. Consequently, it is our preliminary view that the subject-matter of method claim 4 and claims dependent thereon is not obvious.
>
> **Conclusion on obviousness**
>
> In light of the above considerations, it is our preliminary view that claims 1 to 3 on file are directed to subject-matter that would have been obvious to the person skilled in the art, as of the relevant date, having regard to D1 and the relevant common general knowledge, contrary to section 28.3 of the *Patent Act*. It is also our preliminary view that claims 4 to 14 on file are directed to subject-matter that complies with section 28.3 of the *Patent Act*.

[29] In the absence of submissions from the Applicant, we adopt the foregoing reasoning and conclude that claims 1 to 3 on file define subject-matter that would have been obvious to the person skilled in the art, as of the relevant date, having regard to D1 and the relevant common general knowledge, contrary to section 28.3 of the *Patent Act*. We also conclude that claims 4 to 14 on file define subject-matter that complies with section 28.3 of the *Patent Act*.

INDEFINITENESS

Legal Background

[30] Subsection 27(4) of the *Patent Act* requires claims to distinctly and explicitly define the subject-matter of the invention:

> 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.

[31] In Minerals Separation North American Corp v Noranda Mines Ltd, [1947] Ex CR 306 at 352, 12 CPR 99, the Court emphasized the obligation of an Applicant to make clear in the claims the scope of the monopoly sought, as well as the requirement that the terms used in the claims 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

[32] The Preliminary Review letter, on pages 16 to 18, explains why in our preliminary view claims 1 to 3 are indefinite:

> The Final Action, on page 7, indicates that claims 1 to 3 are indefinite because it is unclear how many copies of the targeting moiety and immunomodulating moiety are present in the fusion protein and because the type of cancer cells inhibited by the chimeric fusion protein is not identified:
>
> > [Emphasis in original] These claims recite a fusion protein comprising <u>at least one</u> targeting moiety and further define <u>the</u> targeting moiety as being anti-HER2/Neu antibody consisting of heavy chain SEQ ID NO:1 and light chain SEQ ID NO:2, making it uncertain whether the at least one targeting moiety is one copy of the anti-HER2/Neu antibody or may include multiple copies of said anti-Her2/Neu antibody, thereby causing a lack of clarity. Analogously, these claims recite <u>at least one</u> immunomodulating moiety and further define <u>the</u> immunomodulating moiety as being TGFβRII, making it uncertain whether the at least one immunomodulating moiety is one copy of TGFβRII or may include multiple copies of said TGFβRII, thereby causing a lack of clarity. In addition to the above, the comma "," appears to be superfluous in the context of the term "transforming growth factor, beta receptor II".
> >
> > […]
> >
> > The type of cancer cells inhibited by the chimeric fusion protein is not identified, thereby causing a lack of clarity. The chimeric fusion protein of the aforementioned claims will only inhibit the proliferation of (claims 1 to 3) or lyse (claim 2) cancer cells expressing the

> HER2/Neu protein. Cancer cells not expressing said HER2/Neu protein will not be affected by said chimeric fusion protein.
>
> The Response to the Final Action does not comment on or contest the above views and instead submits that the proposed claims "are in an allowable form."
>
> Having reviewed claims 1 to 3 we agree with the Final Action that claims 1 to 3 refer to chimeric fusion proteins that are not clearly defined. However, we do not agree that the cancer cell of claims 1 to 3 needs to be defined as expressing HER2/Neu protein.
>
> The test for claim clarity analogizes claim terminology to fences that define its boundaries. It also considers whether the "public will be able to know not only where it must not trespass but also where it may safely go." It is our preliminary view that the skilled person would not be able to readily determine the scope of the monopoly defined by the chimeric fusion proteins in claims 1 to 3. It is not clear how many copies of the targeting moiety and how many copies of the immunomodulating moiety are meant to be present in the contemplated chimeric fusion proteins.
>
> However, it is our preliminary view that the person skilled in the art would understand the scope of the cancer cells in claims 1 to 3 is limited to those cancer cells which express HER2/Neu given that the targeting moiety is anti-HER2/Neu antibody. Given that these claims suffer from other clarity defects as identified above, it is our preliminary view that claims 1 to 3 do not comply with subsection 27(4) of the *Patent Act*.

[33] In the absence of submissions from the Applicant, we adopt the foregoing reasoning and conclude that claims 1 to 3 on file are indefinite, contrary to subsection 27(4) of the *Patent Act*.

THE PROPOSED CLAIMS DO NOT REMEDY THE DEFECTS

[34] As indicated above, with the Response to the Final Action the Applicant submitted proposed claims 1 to 11. A review of the proposed claims indicates that claim 1 on file has been amended to address the clarity defects identified in the Final Action and claims 2 and 3 on file have been cancelled. In addition, claim 4 on file has been amended to include the limitations of claim 6 on file and claim 6 on file has been cancelled.

[35] According to page 2 of the Summary of Reasons, proposed claim 1 is similar in scope to claims 1 to 3 rejected in the Final Action and does not overcome the

obviousness defect. In addition, proposed claim 1 introduces a new lack of clarity defect.

[36] The Preliminary Review letter, on pages 18 to 19, explains our preliminary view that proposed claim 1 would not overcome the obviousness defect and that proposed claim 1 is further indefinite:

> With regard to the obviousness defect identified above for claims 1 to 3 on file, as there is no meaningful difference between the claims, our preliminary view is that proposed claim 1 would not comply with section 28.3 of the *Patent Act* for the same reasons provided above for claims 1 to 3 on file.
>
> With regard to the clarity defect in proposed claim 1, the Summary of Reasons indicates on page 2 the reasons that proposed claim 1 is considered to be indefinite:
>
> > The clause “SEQ ID NO: 4 via a peptide bond is attached to the amino acid spacer and a peptide bond to the C-terminus of heavy chain SEQ ID NO: 1 or light chain SEQ ID NO: 2 of the Anti-HER2/Neu antibody” is inherently ambiguous. A spacer, by definition, is an intervening connector between two parts, in this case between SEQ ID NO:4 and the C-terminus of one of the two antibody chains. The above wording suggests that SEQ ID NO:4 is attached directly, via its N-terminus, to the C-terminus of one of the two antibody chains and, via its C-terminus, to the spacer, thereby appending the spacer to the C-terminus of the fusion proteins instead of inserting it between the two components thereof.
>
> Having reviewed proposed claim 1, we preliminarily agree that it is defective for the same reasons outlined in the Summary of Reasons. As worded, proposed claim 1 provides that “the targeting moiety and immunomodulating moiety are linked by an amino acid spacer”. However, proposed claim 1 also suggests that the spacer is only attached to the immunomodulating moiety consisting of the amino acid sequence of SEQ ID NO: 4. Therefore, the location of the amino acid spacer within the chimeric fusion protein is unclear and it is our preliminary view that proposed claim 1 does not comply with subsection 27(4) of the *Patent Act*.
>
> **Conclusion on proposed claims**

> Our preliminary view is therefore that proposed claim 1 does not comply with section 28.3 of the *Patent Act* or subsection 27(4) of the *Patent Act*. Accordingly, it is our preliminary view that the proposed amendments do not meet the requirements of a necessary amendment under subsection 86(11) of the *Patent Rules*.

[37] In the absence of submissions from the Applicant, we adopt the foregoing reasoning and conclude that the proposed amendments do not meet the requirements of a necessary amendment under subsection 86(11) of the *Patent Rules*.

CONCLUSIONS

[38] We have determined that claims 1 to 3 on file are obvious contrary to section 28.3 of the *Patent Act* and that claims 1 to 3 are further indefinite contrary to subsection 27(4) of the *Patent Act*.

[39] We have also determined that claims 4 to 14 on file are not obvious and comply with section 28.3 of the *Patent Act*.

[40] In our view, proposed claim 1 submitted with the Response to the Final Action would not overcome the obviousness defect and is further indefinite. Therefore, proposed claims 1 to 11 are not considered a necessary amendment for compliance with the *Patent Act* and *Patent Rules* as required by subsection 86(11) of the *Patent Rules*.

RECOMMENDATION OF THE BOARD

[41] In view of the above, the Panel recommends that the Applicant be notified, in accordance with subsection 86(11) of the *Patent Rules*, that the following specific amendment is necessary for compliance with the *Patent Act* and *Patent Rules*, and that you intend to refuse the application unless this amendment, and only this amendment, is made:

- deletion of claims 1 to 3 on file; and
- renumber the remaining claims accordingly.

Christine Teixeira	Marcel Brisebois	Maria Mill
Member	Member	Member

DECISION OF THE COMMISSIONER

[42] I concur with the conclusions and recommendation of the Board. In accordance with subsection 86(11) of the *Patent Rules*, I hereby notify the Applicant that the following amendment, and only this amendment, must be made in accordance with paragraph 200(b) of the *Patent Rules* within three (3) months of the date of this decision, failing which I intend to refuse the application:

- deletion of claims 1 to 3 on file; and
- renumber the remaining claims accordingly.

Konstantinos Georgaras
Commissioner of Patents

Dated at Gatineau, Quebec

this 17 day of July 2023.