Citation: Regents of the University of Minnesota, 2022 CACP 18

Commissioner's Decision #1625
Décision du commissaire nº 1625
Date: 2022-08-16

TOPIC: O00 Obviousness

SUJET: O00 Évidence

Application No. : 2,607,213

Demande nº 2 607 213

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,607,213 having been rejected under subsection 30(3) of the *Patent Rules* (SOR/96-423) as they read immediately before October 30, 2019 (the former *Patent Rules*), has consequently been reviewed in accordance with paragraph 199(3)(c) of the *Patent Rules* (SOR/2019-251). 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 Canadian patent application number 2,607,213, which is entitled “Use of NK cell inhibition to facilitate persistence of engrafted MHC-I negative cells”. Regents of the University of Minnesota is the sole Applicant. A review of the rejected application has been conducted by a Panel of the Patent Appeal Board pursuant to paragraph 199(3)(c) of the *Patent Rules*.

[2] As explained in more detail below, our recommendation is that the Commissioner of Patents refuse the application.

BACKGROUND

The Application

[3] The application was filed under the *Patent Cooperation Treaty* and has an effective filing date in Canada of May 5, 2005. It was laid open to public inspection on November 16, 2006.

[4] The rejected application generally relates to the use of a means for inhibiting Natural Killer (NK) cell function to increase persistence and/or engraftment of major histocompatibility complex (MHC)-I negative cells, such as multipotent adult progenitor cells (MAPCs).

[5] The claims under review are claims 1 to 15 dated August 13, 2015 that were rejected in the Final Action (the claims on file).

Prosecution History

[6] On December 10, 2018, a Final Action was written under subsection 30(4) of the former *Patent Rules*. The Final Action states that the present application is defective on the ground that the claims on file are obvious and do not comply with section 28.3 of the *Patent Act*. The Final Action further states that the specification does not comply with subsection 27(3) of the *Patent Act* because it makes reference to foreign practice or law that do not correctly and fully describe the invention.

[7] In the response to the Final Action dated June 10, 2019, the Applicant argues that the subject-matter of the claims on file should not be considered obvious. The response to the Final Action also proposed the addition of a new claim.

[8] On August 26, 2019, the application was forwarded to the Patent Appeal Board for review under paragraph 30(6)(c) of the former *Patent Rules* along with a Summary of Reasons explaining that the Applicant's arguments presented in the response to the Final Action are not persuasive and the rejection is maintained.

[9] In a letter dated August 28, 2019, 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 November 21, 2019, the Applicant confirmed their interest in having the review proceed.

[11] The present Panel was formed to review the rejected application under paragraph 199(3)(c) of the *Patent Rules*. On February 22, 2022, the Panel sent a Preliminary Review letter detailing our preliminary analysis and opinion that all the claims on file, as well as the new proposed claim, are obvious and do not comply with section 28.3 of the *Patent Act*. In that letter, the Panel further expressed the preliminary opinion that a statement regarding the rights of foreign governments to the invention and a statement regarding foreign practice or law should be removed from the description. The Preliminary Review letter also provided the Applicant with an opportunity to make oral and/or written submissions.

[12] The Applicant ultimately declined the opportunity for an oral hearing but submitted a written response to the Preliminary Review letter on March 23, 2022 arguing for the patentability of the claims on file and addressing both statements regarding the rights of foreign governments to the invention and regarding foreign practice or law with amended description pages. We also understand that the Applicant's response to the Preliminary Review letter raises abuse of process, denial of procedural fairness and irreparable prejudice issues in view of the Preliminary Review letter.

[13] We will first address the Applicant's procedural arguments prior to addressing the two substantive issues on which the rejection of the application is based.

PROCEDURAL MATTER

[14] We understand that the response to the Preliminary Review letter submits that some aspects of the Preliminary Review letter constitute an abuse of process, denial of procedural fairness and/or cause irreparable prejudice to the Applicant.

[15] More specifically, the response to the Preliminary Review letter submits that:

i) introducing ten new documents as new evidence of common general knowledge (CGK) represents an abuse of process and a denial of procedural fairness;

ii) refocusing the obviousness inquiry on a document that was, until the Preliminary Review, a secondary prior art reference fails to provide procedural fairness and effectively denies Applicant with a right of appeal within CIPO;

iii) the Preliminary Review letter effectively amounts to an acknowledgement that the conclusion reached by the Examiner in the Final Action regarding section 28.3 of the *Patent Act* was incorrect and untenable, and thus the Patent Appeal Board should have recommended reversing the Examiner and remanding the patent application to the Examiner for further prosecution with regard to points i) and ii) above; and

iv) even if the Patent Appeal Board were minded to remand prosecution of the present application back to the Examiner in response to the submissions made herein, Applicant's rights before the Examiner (current or new) and the Patent Appeal Board (current or reconstituted Panel) have been irreparably prejudiced as no different conclusion would be reached given the existence of the analysis in the Preliminary Review letter regarding points i) and ii) above.

[16] The Panel has considered the Applicant’s submissions and offers the following in response.

[17] The Patent Appeal Board is an administrative body comprised of senior Patent Office officials, whose role is to provide an independent review of a rejected application as required by paragraph 199(3)(c) of the *Patent Rules*, and to provide a recommendation to the Commissioner as to the final disposition of the application within the Patent Office.

[18] The Final Action issued according to subsection 30(4) of the former *Patent Rules*, the prescribed time period passed, the conditions of subsection 30(6) of the former *Patent Rules* and corresponding paragraph 199(3)(c) of the *Patent Rules* were fulfilled, and its corresponding prescriptions were applied. There is no mechanism in subsection 30(6) of the former *Patent Rules*, or in corresponding paragraph 199(3)(c) of the *Patent Rules*, for returning an application to the examiner for another requisition once the review by the Commissioner has begun. Consequently, a right of appeal of a recommendation of the Patent Appeal Board to the Commissioner or a right of appeal of a Commissioner's decision within CIPO cannot be denied as it does not exist.

[19] The Panel also notes that in accordance paragraph 199(3)(c) of the *Patent Rules*, it is the rejected application that is subject to a review by the Commissioner.

[20] To the extent that the Applicant submits that introducing new documents as new evidence of CGK and refocusing the obviousness inquiry on a different prior art document effectively expands the existing factual record with no prior notice to the Applicant and/or essentially introduces a new defect to the existing record in the form of a different obviousness analysis, we note that, pursuant to subsection 86(9) of the *Patent Rules*, a review by a Panel of the Patent Appeal Board may raise defects other than those indicated in the Final Action notice:

> If, during the review of a rejected application for a patent, the Commissioner has reasonable grounds to believe that the application does not comply with the Act or these Rules in respect of defects other than those indicated in the final action notice, the Commissioner must by notice inform the applicant of those defects and invite the applicant to submit arguments, not later than one month after the date of the notice, as to why the application does comply.

[21] Having in mind subsection 86(9) of the *Patent Rules* above and the principle of procedural fairness which includes giving a notice of the issues to be addressed and a meaningful opportunity to respond, we consider that it was appropriate for the Panel to introduce, within the Preliminary Review letter, new evidence of CGK that is relevant to an obviousness defect already on file, to consider the prior art documents already on file in a different light and/or to present a preliminary analysis of a defect that differs from the analysis presented in the Final Action.

[22] The Preliminary Review letter gave notice to the Applicant of the issues to be

addressed as it provided detailed reasons why some disputed elements of knowledge should be considered CGK and why all claims on file of the reviewed application were found to be obvious. In the same letter, we offered the Applicant an opportunity to provide written submissions and to attend an oral hearing. Although the Applicant ultimately chose not to avail itself the opportunity for an oral hearing, the Applicant submitted detailed written submissions in response to the Panel's preliminary analysis of the obviousness defect.

ISSUES

[23] The following issues are considered in this review:

- Are the claims on file obvious and therefore non-compliant with section 28.3 of the *Patent Act*?
- Is the specification non-compliant with subsection 27(3) of the *Patent Act* because it makes reference to foreign practice or law that do not correctly and fully describe the invention.

LEGAL PRINCIPLES AND PATENT OFFICE PRACTICE

Purposive construction

[24] According to *Free World Trust v Électro Santé Inc*, 2000 SCC 66 and *Whirlpool Corp v Camco Inc*, 2000 SCC 67, a purposive construction of the claims is performed from the point of view of the person of ordinary skill in the art (POSITA) in light of the CGK 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.

[25] We consider that all elements set out in a claim are presumed essential unless it is established otherwise or such presumption is contrary to the claim language.

Obviousness

[26] Section 28.3 of the *Patent Act* requires that the subject-matter of a claim not be 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 before the one-year period immediately preceding 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.

[27] In *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 at para 67 [*Sanofi*], 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?

[28] In the context of the fourth step, the Court in *Sanofi* states that it may be appropriate in some cases to consider an "obvious to try" analysis.

[29] The Court in *Sanofi* identifies the following non-exhaustive factors to be considered in an obvious to try analysis [defined terms added]:

> Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identifiable predictable solutions known to persons skilled in the art? [the Self-Evident Factor]
>
> What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine? [the Extent and Effort Factor]
>
> Is there a motive provided in the prior art to find the solution the patent addresses? [the Motive Factor]

References to foreign practice or law

[30] *Manual of Patent Office Practice* section 14.05.07 (CIPO, December 2010) states:

> Where an application includes a statement whose correctness is dependent on foreign patent prosecution practices or laws, such a statement may be inaccurate or liable to cause confusion in the context of Canadian law. Where this is the case, the statement must be removed. The statements may be viewed as being "incorrect", and therefore a defect under subsection 27(3) of the *Patent Act* [see 14.09].
>
> An indication that the application is a continuation-in-part or a divisional of a foreign patent document, for example, is not correct in the context of the Canadian *Patent Act* and must be removed.
>
> A statement regarding the rights of foreign governments to the invention may also be misleading, and should be removed if it is inaccurate.

ANALYSIS OF THE CLAIMS ON FILE

Purposive construction

The claims on file

[31] There are 15 claims on file. Claims 1 to 6 are independent claims and read as follows:

> 1. A composition for the treatment of an adverse immune response comprising (1) an agent for inhibiting natural killer cell function, (2) non-embryonal stem (non-ES), non-embryonal germ (non-EG), non-germ cells wherein the non-ES, non-EG, non-germ cells express one or more of telomerase, oct 3/4, rex-1, rox-1 or sox-2, are CD45 negative and CD34 negative, and (3) a pharmaceutically

acceptable carrier, wherein the non-ES, non-EG, non-germ cells can differentiate into ectodermal, endodermal and mesodermal cell types, wherein the adverse immune response is a renal, pancreatic, cardiac, hepatic, neurological, vascular, cancer, autoimmune, genetic or hematological disease.

2. Use of (1) an agent for inhibiting natural killer cell function and (2) a pharmaceutically acceptable carrier in the preparation of a medicament for increasing engraftment and/or persistence of non-embryonal stem (non-ES), non-embryonal germ (non-EG), non-germ cells in a subject, wherein the medicament is formulated for sequential or co-administration with the non-ES, non-EG, non-germ cells wherein the non-ES, non-EG, non-germ cells express one or more of telomerase, oct 3/4, rex-1, rox-1 or sox-2, are CD45 negative and CD34 negative, and can differentiate into ectodermal, endodermal and mesodermal cell types.

3. Use of (1) non-embryonal stem (non-ES), non-embryonal germ (non-EG), non-germ cells wherein the non-ES, non-EG, non-germ cells express one or more of telomerase, oct 3/4, rex-1, rox-2 or sox-2, are CD45 negative and CD34 negative, and (2) a pharmaceutically acceptable carrier, in the preparation of a medicament for increasing engraftment and/or persistence of the non-ES, non-EG, non-germ cells in a subject, wherein the non-ES, non-EG, non-germ cells can differentiate into ectodermal, endodermal and mesodermal cell types, wherein the medicament is formulated for sequential or co-administration with an agent for inhibiting natural killer cell function.

4. Use of an agent that inhibits natural killer cell function in the preparation of a medicament for increasing engraftment and/or persistence of non-embryonal stem (non-ES), non-embryonal germ (non-EG), non-germ cells in a subject wherein the non-ES, non-EG, non-germ cells express one or more of telomerase, oct 3/4, rex-1, rox-1 or sox-2, and are CD45 negative and CD34 negative, wherein the non-ES, non-EG, non-germ cells can differentiate into ectodermal, endodermal and mesodermal cell types.

5. Use of (1) an agent that inhibits natural killer cell function and (2) of non-embryonal stem (non-ES), non-embryonal germ (non-EG), non-germ cells in the preparation of a medicament for increasing engraftment and/or persistence of the non-ES, non-EG, non-germ cells in a subject, wherein the medicament is formulated for sequential or co-administration of the agent that inhibits natural killer cell function and the non-ES, non-EG, non-germ cells, wherein the non-ES,

non-EG, non-germ cells express one or more of telomerase, oct 3/4, rex-1, rox-1 or sox-2, and are CD45 negative and CD34 negative, wherein the non-ES, non-EG, non-germ cells can differentiate into ectodermal, endodermal and mesodermal cell types.

6. Use of (1) non-embryonal stem (non-ES), non-embryonal germ (non-EG), non-germ cells and (2) an agent that inhibits natural killer cell function in the preparation of a medicament for increasing engraftment and/or persistence of the non-ES, non-EG, non-germ cells in a subject, wherein the non-ES, non-EG, non-germ cells express one or more of telomerase, oct 3/4, rex-1, rox-1 or sox-2, and are CD45 negative and CD34 negative, wherein the non-ES, non-EG, non-germ cells can differentiate into ectodermal, endodermal and mesodermal cell types.

[32] Dependent claims 7 to 15 define further limitations with regard to: the presence of an additional component, the subject, the nature of the injury, the nature of the non-ES, non-EG, non-germ cells, and the nature of the agent that inhibits NK cell function.

Identify the POSITA

[33] The Preliminary Review letter, on pages 5 to 6, generally accepted the Applicant's identification of the POSITA, albeit with further characterizations:

> Having reviewed the specification as a whole, we agree with the Applicant and are therefore of the view that the POSITA comprises a team including a clinician, an immunologist and a molecular/cell biologist.
>
> We would further add that, in our preliminary view, the POSITA described above is familiar with techniques and immunological/biological concepts relating to cellular therapy and cellular engraftments/transplants.

[34] The response to the Preliminary Review letter did not contest or otherwise comment on the Panel's characterization of the POSITA. Therefore, we adopt the above characterization for this analysis.

The relevant common general knowledge

[35] The Preliminary Review letter, on pages 6 to 11, introduced argued elements of CGK, legal principles relating to the assessment of the relevant CGK, new

documents pertinent to identifying the CGK surrounding the claimed subject-matter and our corresponding preliminary views on the matter.

As for the CGK, the FA on page 3 states that the relevant CGK includes:

- the preparation and use of compositions for the treatment of adverse immune responses and for increasing engraftment and/or persistence of certain stem cell and progenitor cell types;
- various stem cell and progenitor cell types, including MAPCs, and their potential therapeutic uses;
- functions of NK cells;
- methods to inhibit the activity or level of NK cells; and
- NK cells are cytotoxic to MHC-I negative cells, such as MAPCs.

The RFA expressed disagreement with the CGK as defined in the FA, more specifically with respect to the assertion that the POSITA would know that NK cells are cytotoxic to MHC-I negative cells, such as MAPCs, as the FA does not provide evidence for it. In that regard, the RFA expressed the positions that the document identified as D7 does not support the finding and that it is wholly improper to rely on Applicant's own application as the basis for demonstrating the CGK.

Further, the RFA submitted that the FA has not qualified the teachings of documents identified as D9, D10 and D11 as providing a teaching that rises to the level of the CGK.

The assessment of CGK is governed by the principles stated in *Eli Lilly & Co v Apotex Inc*, 2009 FC 991 at para 97, upheld by 2010 FCA 240, citing *General Tire & Rubber Co v Firestone Tyre & Rubber Co Ltd*, [1972] RPC 457, [1971] FSR 417 (UKCA) at pages 482 and 483 (of RPC):

> The common general knowledge imputed to such an addressee must, of course, be carefully distinguished from what in the patent law is regarded as public knowledge. This distinction is well explained in Halsbury's Law of England, Vol. 29, para 63. As regards patent specifications, it is the somewhat artificial (see per Lord Reid in the *Technograph* case, [1971] F.S.R. 188 at 193) concept of patent law that each and every specification, of the last 50 years, however unlikely to be looked at and in whatever language written, is part of the relevant public knowledge if it is resting anywhere in the shelves of the Patent Office. On the other hand, common general knowledge is a different concept derived from a common sense approach to the practical question of what would in fact be known to an appropriately skilled

addressee—the sort of man, good at his job, that could be found in real life.

The two classes of documents which call for consideration in relation to common general knowledge in the instant case were individual patent specifications and “widely read publications”.

As to the former, it is clear that individual patent specifications and their contents do not normally form part of the relevant common general knowledge, though there may be specifications which are so well known amongst those versed in the art that upon evidence of that state of affairs they form part of such knowledge, and also there may occasionally be particular industries (such as that of colour photography) in which the evidence may show that all specifications form part of the relevant knowledge.

As regards scientific papers generally, it was said by Luxmoore, J. in *British Acoustic Films* (53 R.P.C. 221, at 250):

“In my judgment it is not sufficient to prove common general knowledge that a particular disclosure is made in an article, or series of articles, in a scientific journal, no matter how wide the circulation of that journal may be, in the absence of any evidence that the disclosure is accepted generally by those who are engaged in the art to which the disclosure relates. A piece of particular knowledge as disclosed in a scientific paper does not become common general knowledge merely because it is widely read, and still less because it is widely circulated. Such a piece of knowledge only becomes general knowledge when it is generally known and accepted without question by the bulk of those who are engaged in the particular art; in other words, when it becomes part of their common stock of knowledge relating to the art.” And a little later, distinguishing between what has been written and what has been used, he said:

“It is certainly difficult to appreciate how the use of something which has in fact never been used in a particular art can ever be held to be common general knowledge in the art.”

Those passages have often been quoted, and there has not been cited to us any case in which they have been criticised. We accept them as correctly stating in general the law on this point, though reserving for further consideration whether the words “accepted without question” may not be putting the position rather high: for the purposes of this case we are disposed, without seeking to present a complete definition, to substitute the words “generally considered as a good basis to continue”.

Having in mind the principles above, it is our preliminary view that the relevant question is whether a given piece of knowledge was generally known and accepted without question by the bulk of those who are engaged in the particular fields of cellular therapy and cellular engraftments/transplants at the relevant time.

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 therefore relevant to the inquiry. To that end, we introduce here a list of prior art documents that is relevant to the issue of identifying the CGK possessed by the POSITA as defined above. The list includes documents introduced in the FA and additional documents discovered through a review of the literature pertinent to the claimed subject-matter such as the functions of NK cells, as well as the fields of cellular therapy and cellular engraftments/transplants:

D7: Bix, M. et al, *Nature,* 349**,** pages 329-331, January 24, 1991

D8: WO 02/064748 Furcht, L. T. and Verfailleie, C.M. August 22, 2002

D9: Moretta, A. et al, *Ann Rev lmmunol,* 19, pages 197-223, 2001

D10: Öhlén, C. et al, *Science,* 246**,** pages 666-668, November 3, 1989

D11: WO 01/11011 Furcht, L. T. et al. February 15, 2001

D12: Moretta, A. et al, *Ann Rev lmmunol,* 14, pages 619-648, 1996

D13: Miller J., Experimental Hematology, 29, pages 1157-1168, 2001

D14: Natarajan, K. et al, *Ann Rev lmmunol,* 20, pages 853-885, 2002

D15: Liu, J. et al, *Methods in Molecular Biology, vol. 121: Natural Killer Cell Protocols: Cellular and Molecular Methods*, pages 61-71, 2000

D16: Scalzo, A. et al, *Methods in Molecular Biology, vol. 121: Natural Killer Cell Protocols: Cellular and Molecular Methods*, pages 163-177, 2000

D17: Chargui, J. et al, *Thymus*, 24, pages 233-246, 1997

D18: Asea, A. and Stein-Streilein, J., *Immunology*, 93, pages 296-305, 1998

D19: Kim, S., *Proceedings of the National Academy of Sciences*, 97, pages 2731-2736, 2000

D20: Yoshino, H., *Bone Marrow Transplantation*, 26, pages 1211-1216, 2000

D21: Cho, S.G. et al, *Experimental Hematology*, 32, pages 1246-1254, 2004

Further, it is our preliminary view that information in the instant specification may be evidence of the CGK as it could be reasonable to consider general or broadly worded assertions of conventional practice or knowledge as CGK (see *Corning Cable Systems LLC v Canada (Attorney General)*, 2019 FC 1065 and *Newco Tank Corp v Canada (Attorney General)*, 2015 FCA 47).

Having considered the disputed CGK, and reviewed the specification as a whole as well as the scientific literature pertinent to the claimed subject-matter, it is our preliminary view that the following pieces of knowledge and methods were generally known and accepted without question by the bulk of those who are engaged in the particular fields of cellular therapy and cellular engraftments/transplants and, with respect to methods, commonly used in the art at the relevant time.

We generally agree with the CGK identified in the FA and listed above with the notable exception of MAPCs and knowledge related thereto for the reasons that follow.

Although we consider that MAPCs and their phenotypic characteristics, including being MHC-I negative, did not constitute knowledge that had risen to the level of CGK at the relevant date, we consider that the knowledge that MHC-I negative cells and allogeneic cells in general are susceptible to the host NK cells killing activity was CGK. This observation gave rise to the widely accepted “missing self” hypothesis according to which host NK cells will preferentially eliminate target cells that do not express proper inhibitory MHC-I molecules at their surface. We also consider said hypothesis as being CGK (as evidenced by the review articles D9, D12, and D14).

Our preliminary view is further supported by the following passage found on page 4 of the description that contains broad and general statements regarding NK functions and the cells targeted by their cytolytic activity, i.e., cells which do not express significant MHC-I:

> Natural Killer (NK) cells are characterized, in part, by cytolytic activity against cells which do not express significant major histocompatibility complex (MHC) class I molecules, such as MAPCs and embryonic stem (ES) cells. The MHC family of proteins encoded by the clustered genes of the major histocompatibility complex are expressed on cells of all higher vertebrates. They were first demonstrated in mice and called H-2 antigens (histocompatibility-2 antigens). In humans, they are sometimes also referred to as HLA antigens (human-leucocyte-associated antigens) because they were first demonstrated on leucocytes (white blood cells).

And on page 22 of the description:

> Natural Killer (NK) cells are a subset of large granular lymphocytes that are cytotoxic cells. NK cells make up approximately 15% of the human

> white blood cells and are characterized by cytolytic activity against cells which do not express major histocompatibility complex (MHC) class I molecules (e.g., tumor cells or virally infected cells). They kill (lyse) target cells using perforins, granzymes and proteoglycans. They are called “natural” killers because they do not need to recognize a specific antigen before lysing cells. NK cells have no immunological memory and are independent of the adaptive immune system.

Although these passages are found within the sections titled “Summary of the invention” and “Detailed Description of the Invention” respectively, we consider that both passages relate for the most part to CGK background immunology information regarding NK cells activity and MHC molecules that serves to introduce the embodiments of the invention described later in each sections.

In addition, we consider that means for inhibiting the host NK cells activity were generally known in the art. More specifically, *in vivo* inoculation of antibodies was a CGK protocol for elimination of specific cell populations and we further consider that the use of depleting anti-NK cells antibodies, including anti-NK1.1 and anti-asialo GM1 antibodies, were generally known and commonly used in experimental procedures requiring inhibition of NK cells functions at the relevant date, including in the context of transplantation of cells that do not express the proper inhibitory MHC-I molecules at their surface (common usage as evidenced by D15 (textbook), D16 (textbook), D17, D18, D19, D20 and D21, when considered as a whole).

Further, the statement “[t]here are several antibodies available in the art which inhibit NK cell function, including but not limited to… anti-asialo-GM1 (immunogen is the glycolipid GA1), anti-NK.1.1 antibodies or monoclonal anti-NK-cell antibodies (5E6; Pharmingen, Piscataway, NJ)” found on the bridging portion of pages 23-24 independently supports our preliminary finding.

Finally and as mentioned above, we are of the preliminary view that although the characterization of MAPCs, including their lack of significant expression of MHC-I molecules, was disclosed in D8 and D11, MAPCs and their phenotypic characteristics did not constitute knowledge that had risen to the level of CGK at the relevant date.

[36] The response to the Preliminary Review letter, on pages 9 and 10, submits that:

- The CGK of the POSITA includes the preparation and use of compositions for the treatment of adverse immune responses and for increasing engraftment and/or persistence of certain stem cell and progenitor cell types.

- The POSITA would be familiar with various stem cell and progenitor cell types, including MAPCs, and their potential therapeutic uses.

- The CGK identified by the Panel is objectionable because: i) it was done with impermissible hindsight after reviewing the record in the prosecution of the present application and determining that evidence of purported CGK was lacking; and ii) the Panel distilled the content of fourteen non-patent documents in an exercise of picking and choosing from the documents to arrive at a definition of CGK that ignores other teachings of the documents to recreate the claimed invention.

[37] We agree with the Applicant that the CGK of the POSITA includes the preparation and use of compositions for the treatment of adverse immune responses and for increasing engraftment and/or persistence of certain stem cell and progenitor cell types. We also agree with the Applicant that the POSITA would be familiar with various stem cell and progenitor cell types and their potential therapeutic uses. These elements were also identified as CGK in the Final Action.

[38] However, it is our view that the CGK possessed by a team including an immunologist and a molecular/cell biologist as defined above is not limited to the above characterization as suggested by the Applicant. In our view, the POSITA is also familiar with common techniques and fundamental immunological/biological concepts relating to the functions of NK cells, cellular therapy and cellular engraftments/transplants. In the Preliminary Review letter we inquired as to whether the remaining disputed elements of knowledge were such common techniques and fundamental concepts that should be considered CGK or not and to what extent.

[39] In the Preliminary Review letter, we determined that the following elements of knowledge were in dispute:

- methods to inhibit the activity or level of NK cells;
- NK cells are cytotoxic to MHC-I negative cells; and
- whether MAPCs are established MHC-I negative cells.

[40] The relevant inquiry was therefore whether the elements of knowledge that MHC-I negative cells are susceptible to the host NK cells killing activity, that MAPCs are MHC-I negative cells, and the means for inhibiting the host NK cells were CGK or

not.

[41] To that end, we reviewed the specification as a whole as information in the instant specification may be evidence of the CGK as it could be reasonable to consider general or broadly worded assertions of conventional practice or knowledge as CGK (*Corning Cable Systems LLC v Canada (Attorney General)*, 2019 FC 1065 and *Newco Tank Corp v Canada (Attorney General)*, 2015 FCA 47)). We identified such general or broadly worded assertions in the instant specification with respect to the knowledge that MHC-I negative cells in general are susceptible to the host NK cells killing activity and the means for inhibiting the host NK cells. Those assertions alone are evidence that support that the knowledge that MHC-I negative cells are susceptible to the host NK cells killing activity and the means for inhibiting the host NK cells were CGK. The applicant did not contest or otherwise comment on those preliminary views.

[42] We further reviewed the scientific literature pertinent to these elements not because evidence of purported CGK was lacking but because a review of the literature pertinent to the claimed subject-matter at the relevant time would inform us with regard to what elements of knowledge were generally known and accepted without question by the bulk of those who are engaged in the particular fields of cellular therapy and cellular engraftments/transplants and, with respect to methods, commonly used in the art at the relevant time. Further, such review could reveal evidence supporting that it was or was not reasonable to consider the whole or a portion of the general or broadly worded assertions of conventional practice or knowledge found in the description as CGK. Our review of the relevant literature revealed that a portion of the two disputed pieces of knowledge were generally known and accepted without question by the bulk of those who are engaged in the particular fields of cellular therapy and cellular engraftments/transplants at the relevant time with evidence of commonality throughout a number of disclosures. However, and on the basis of the same review, we also expressed the view that MAPCs and their phenotypic characteristics, including being MHC-I negative, did not constitute knowledge that had risen to the level of CGK at the relevant date.

[43] With regard to the submission that the Panel distilled the content of fourteen non-patent documents in an exercise of picking and choosing from the documents to arrive at a definition of CGK that ignores other teachings of the documents to

recreate the claimed invention, we reiterate that the inquiry was focused on the elements of knowledge that were in dispute. The newly introduced documents may very well disclose additional elements of the CGK but it would not benefit our analysis of the elements of knowledge at issue.

[44] Finally, we note that the response to the Preliminary Review letter states on page 12 that the Applicant does not dispute that the “missing self” hypothesis was known as of the claim date for the present application” and further states on page 13 that the Applicant does not disagree with the finding in the Preliminary Review letter that means for inhibiting NK cell function were also generally known in the art at the claim date.

[45] In view of the above and the reasons explained in the Preliminary Review letter, it is our view that the following elements of knowledge are CGK:

- the knowledge that MHC-I negative cells and allogeneic cells in general are susceptible to the host NK cells killing activity; and
- several means for inhibiting the host NK cells activity, and more specifically *in vivo* inoculation of antibodies of depleting anti-NK cells antibodies, including anti-NK1.1 and anti-asialo GM1 antibodies.

Essential elements

[46] The Preliminary Review letter, on page 11, expresses the preliminary view that the person skilled in the art would consider all of the elements in the claims to be essential.

[47] The response to the Preliminary Review letter did not contest or comment on this preliminary identification of the essential elements. Therefore, we adopt the above identification of the essential elements for this analysis.

Obviousness

[48] All 15 claims on file were rejected in the Final Action for obviousness.

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

[49] The POSITA and the CGK have been identified as part of the purposive construction of the claims. Although in this context the information forming the relevant common general knowledge is identified using the publication date, this information is also considered CGK at 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

[50] The Preliminary Review letter, on page 13, agrees with the Applicant that the underlying effect of the recited agent for inhibiting NK cell function is part of the inventive concept of the independent claims and identifies the inventive concept as follows:

> Having reviewed the claims on file as well as of the instant description, we consider that the POSITA would understand that the underlying effect of the recited agent for inhibiting natural killer cell function is part of the inventive concept of the independent claims. Therefore, it is our preliminary view that an inventive concept that is common to the independent claims is the use of a composition comprising particular progenitor cells in combination with an agent that inhibits NK cell function, thereby reducing the probability of rejection of the transplanted cells, for the treatment of an adverse immune response or for increasing the engraftment and/or persistence of said particular progenitor cells. The particular progenitor cells are defined in all independent claims as non-ES, non-EG, non-germ cells that express one or more of telomerase, oct 3/4, rex-1, rox-1 or sox-2, are CD45 negative and CD34 negative, and can differentiate into ectodermal, endodermal and mesodermal cell types.

[51] The response to the Preliminary Review letter, on page 11, acknowledges the Panel's characterization of the inventive concept.

[52] In view of the above, we consider that the inventive concept for the purposes of this review is the use of a composition comprising progenitor cells that are phenotypically equivalent to MAPCs in combination with an agent that inhibits NK cell function, said agent thereby reducing the probability of rejection of the transplanted cells (i.e., the transplanted cells are the transplanted progenitor cells that are phenotypically equivalent to MAPCs), for the treatment of an adverse immune response (claim 1 and 11 to 15) or for increasing the engraftment and/or persistence of the transplanted progenitor cells that are phenotypically equivalent to MAPCs (claims 2 to 15).

[53] We further specify that the POSITA would understand that the inventive concept does not encompass embodiments wherein MAPCs themselves constitute the agent that inhibits NK cell function as suggested by several of the arguments raised in the response to the Preliminary Review letter, arguments that will be addressed below in following sections. The passage found on page 56, lines 2 to 8 of the instant specification that was referred to by the Applicant to support the "technical effect" of achieving reduction of the probability of rejection of the transplanted MAPCs clearly excludes the transplanted MAPCs (MHC-I negative cells) as the agent inhibiting NK cell function:

> In one embodiment, administration of a means for inhibiting NK function can be performed sufficiently long before administration of MHC-I negative cells (for example, for a period of about 1-4 weeks) such that an advantageous alteration in the amounts of sub-populations or the activity/function of NK cells is obtained. In this manner, the beneficial effects of NK inhibition can be obtained prior to administering MHC-1 negative cells, thereby reducing the probability of rejection of the transplanted cells.

[54] Although the specification on page 53, lines 20 to 24 discloses that MAPCs could be genetically modified to produce an agent which inhibits the function of NK cells within the vicinity of the transplanted MAPCs, the claims are not limited in any manner to the use of such genetically modified MAPCs capable of producing an agent for inhibiting NK cell function and thus, the claims and their inventive concept include embodiments wherein the encompassed agent inhibiting NK cell function is a CGK means for inhibiting NK cell function. Such embodiments are explicitly encompassed by dependent claim 11 and otherwise encompassed by dependent claims 14 and 15.

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

[55] The Preliminary Review letter, on page 14, applies the following document against the claims on file:

D8: WO 02/064748 Furcht, L. T. and Verfaillie, C.M. August 22, 2002

[56] D8 discloses the use of non-embryonic, non-germ, multipotent adult stem cells (MASCs), which are phenotypically equivalent to the MAPCs described in the

instant application, for repopulating tissues upon transplantation and differentiation into cell type of mesodermal, ectodermal and endodermal origin. Undifferentiated MASCs express oct 3/4 and telomerase, are negative for CD34, CD45, MHC-I and are capable of differentiation into ectodermal, endodermal and mesodermal cell types. D8 discloses that MASCs could be used to replace damaged, diseased, dysfunctional or dead cells in the body of a mammal as well as in the therapeutic treatment of a variety of diseases and conditions such as cancer, cardiovascular disease, metabolic disease, liver disease, diabetes, hepatitis, hemophilia, degenerative or traumatic neurological conditions, autoimmune disease, genetic deficiency, connective tissue disorders, anemia and infectious disease.

[57] The Preliminary Review letter also states that the main differences between the above cited prior art disclosure and the inventive concept of the independent claims is that D8 does not teach that preventing an adverse immune response or increasing the engraftment and/or persistence of cells that are phenotypically equivalent to MAPCs can be achieved with an agent that inhibits NK cell function.

[58] With regard to the D8 disclosure, the response to the Preliminary Review letter submits, starting on page 12, that the Panel's summary of D8 is incomplete:

> A POSITA reviewing D8 would understand it is focussed on treatment of a variety of different diseases and conditions in which cell therapy or genetically transformed cells could be used. While treatment of transplant rejection is one of them, the PR does not explain why a POSITA would: (i) focus on this condition to the exclusion of other, and (ii) be led to combine D8 with any other teaching to prevent an adverse immune response or increase the engraftment and/or persistence of cells that are phenotypically equivalent to MAPCs. D8 on its face appears to instruct the POSITA to follow its teachings without the need to include another agent, let alone an agent for inhibiting natural killer cell function.
>
> While Applicant does not dispute that the "missing self' hypothesis was known as of the claim date for the present application, there is nothing in D8 that would have led a POSITA to envision using the cell therapy for inhibiting natural killer cell function beyond the effects of natural killer cells on the MASC themselves.
>
> In fact, based on the mechanism of action posited in D8 on page 12, line 22-26 (i.e., cell engraftment to augment, reconstitute or provide for the first time the defective function of a cell or organ), a POSITA as likely would have believed that the MASCs were going to be used as a vehicle to deliver a gene product or as a vehicle to differentiate into functional cells that could replace those that were injured or diseased.

> See also, page 12, line 6 where reference is made to administration of MASC or their progeny to a patient to alter their immune system to resist viral, bacterial or fungal infection. There is no reference or suggest to immune cells.
>
> Alternatively, on page 13, line 13-18, D8 proposes modification of MHC antigen to inhibit rejection of transplanted MASC themselves. Applicant submits that, absent impermissible hindsight, a POSITA would not be led beyond the manipulation and preservation of the MASC cells to further extend this possibility to general natural killer cell function.
>
> Applicant submits that, a POSITA reviewing D8 at the claim date, would not have envisioned using or been led to use MAPCs to modify natural killer cell function. The POSITA would have understood from D8 that MASC were being used for cell replacement and/or were being modified for the purposes of avoiding natural killer cell rejection, and would have known that this would not have been something that would have been relevant to broadly inhibiting natural killer cell function. And a POSITA surely would not have had any kind of reasonable expectation that MAPCs could do that. Absent impermissible hindsight, a POSITA reviewing D8 at the claim date would have made no connection between MASC cells or secreted factors demonstrated to impact natural killer cells themselves. So a POSITA would have had no reason to believe from the teachings of D8 that MAPCs could treat disease/injury by these means.

[59] We understand that the Applicant's submissions with regard to D8 and its disclosure, or lack thereof, are the following.

[60] It is submitted that the POSITA would have understood from D8 that MASCs were going to be transplanted in order to differentiate into functional cells that could replace those that were injured or diseased. We agree and such disclosure has been part of the Panel's summary of D8 disclosure.

[61] It is submitted that D8 proposes modification of MHC antigen to inhibit rejection of transplanted MASCs themselves. We agree.

[62] It is submitted that there is nothing in D8 that would have led a POSITA to envision using the cell therapy with MASCs for inhibiting NK cell function beyond the effects of NK cells on the MASCs themselves and the POSITA would not have been led to use MASCs to modify NK cell function. We agree that the POSITA would understand that D8 teaches to modify MASCs so that MASCs express a MHC antigen at a level sufficient to inhibit the rejection of the transplanted MASCs by NK cells and also agree that D8 does not disclose that transplanted MASCs could

be used to more generally inhibit NK cell functions. However, and this point will be further developed below, we note that the claims on file and their inventive concept identified above do not include an embodiment wherein the MAPCs recited in the claims are also the agent for inhibiting NK cell functions.

[63] With regard to the differences between D8 and the inventive concept of the independent claims, the response to the Preliminary Review letter submits on page 11 that D8 fails to teach or suggest the use of an agent that inhibits NK cell function for the treatment of an adverse immune response or for increasing the engraftment and/or persistence of cells that are phenotypically equivalent to MAPCs (identified as elements (a)(2) and (b) in the response to the Preliminary Review letter).

[64] In view of the above, it is our view that the main differences between the cited prior art disclosure and the inventive concept of the independent claims is that D8 does not teach that increasing the engraftment and/or persistence of cells that are phenotypically equivalent to MAPCs can be achieved with an agent that inhibits NK cell function (independent claims 2 to 6) and does not teach that an agent that inhibits NK cell function could be combined with transplanted cells that are phenotypically equivalent to MAPCs for the treatment of a renal, pancreatic, cardiac, hepatic, neurological, vascular, cancer, autoimmune, genetic or hematological disease.

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] We understand that the response to the Preliminary Review letter submits that:

i) the Preliminary Review letter fails to explain why, without using impermissible hindsight, a POSITA seeking to improve on D8 by preventing an adverse immune response or increase the engraftment and/or persistence of cells that are phenotypically equivalent to MAPCs would come directly and without difficulty to combine D8 with an agent that inhibits NK cell function;

ii) the Preliminary Review letter does not explain why a POSITA would: (i) focus on transplant rejection to the exclusion of other conditions in which cell therapy or

genetically transformed cells could be used, and (ii) be led to combine D8 with any other teaching to prevent an adverse immune response or increase the engraftment and/or persistence of cells that are phenotypically equivalent to MAPCs. D8 on its face appears to instruct the POSITA to follow its teachings without the need to include another agent, let alone an agent for inhibiting NK cell function;

iii) there is nothing in D8 that would have led a POSITA to envision using the cell therapy for inhibiting NK cell function beyond the effects of NK cells on the MASCs themselves and would not have envisioned using or been led to use MAPCs to modify NK cell function through direct contact and secreted factors. Rather, a POSITA would have believed that the MASCs were going to be used as a vehicle to deliver a gene product or as a vehicle to differentiate into functional cells that could replace those that were injured or diseased; and

iv) the specific technical effect of combining MAPC/cell therapy with an agent for inhibiting NK cell function could not be predicted in advance.

[66] First of all, in view of the inventive concept identified above, the two separate relevant inquiries are: i) whether it would have been obvious to use an agent for inhibiting NK cell function to increase the engraftment and/or persistence of cells that are phenotypically equivalent to MAPCs (independent claims 2 to 6) and; ii) whether it would have been obvious to use cells that are phenotypically equivalent to MAPCs in combination with an agent for inhibiting NK cell function for the treatment of an adverse immune response defined as a renal, pancreatic, cardiac, hepatic, neurological, vascular, cancer, autoimmune, genetic or hematological disease (independent claim 1). Therefore, whether it would have been obvious to use MAPCs to directly modify NK cell function is not, in our view, the relevant inquiry as suggested by the submissions found in the response to the Preliminary Review letter.

[67] As described above, D8 is primarily focused on the use of non-embryonic, non-germ, multipotent adult stem cells (MASCs), which are phenotypically equivalent to the MAPCs described in the instant application and the non-ES, non-EG, non-germ cells recited in the claims, for repopulating tissues upon transplantation and differentiation into functional cells that could replace those that were injured or

diseased. We therefore consider that the POSITA would understand from D8 that engraftment and/or persistence of the transplanted MASCs, i.e., non-rejection of the transplanted MASCs, is important to their intended usage.

[68] D8 also disclosed that the transplanted MASCs could be used as a therapeutic treatment of a variety of diseases and conditions such as cancer, cardiovascular disease, liver disease, diabetes, hepatitis, hemophilia, degenerative or traumatic neurological conditions, autoimmune disease, genetic deficiency and anemia. These diseases and conditions are defined as adverse immune responses in independent claim 1.

[69] As established above in the section titled “The relevant common general knowledge”, it is our view that it was CGK at the claim date that MHC-I negative cells are susceptible to the host NK cells killing activity. It is also our view that means and methods to inhibit NK cell activity, including anti-NK cells antibodies, were CGK at the claim date in the context of transplantation of cells that do not express the proper inhibitory MHC-I molecules at their surface.

[70] We stated above that D8 does not teach that increasing the engraftment and/or persistence of cells that are phenotypically equivalent to MAPCs can be achieved with an agent that inhibits NK cell function (independent claims 2 to 6) and does not teach that an agent that inhibits NK cell function could be combined with transplanted cells that are phenotypically equivalent to MAPCs for the treatment of a renal, pancreatic, cardiac, hepatic, neurological, vascular, cancer, autoimmune, genetic or hematological disease. Therefore, for a finding of obviousness, the gap between the prior art and the subject-matter of the claims must be supplied by the relevant CGK and the CGK must have led the POSITA having been taught by D8 to come directly and without difficulty to the claimed subject-matter.

[71] D8 disclosed the use of MASCs for repopulating tissues upon transplantation in an established NOD-SCID mouse model with impaired T and B cell lymphocyte development and deficient NK cell function (Example 6) and further discloses that MASCs are MHC-I negative cells. We consider that rejection of transplanted cells was a primary concern in the fields of cellular therapy and cellular engraftments/transplants at the claim date and such concern would have motivated the POSITA to use their CGK to reduce the probability of rejection and

promote the engraftment of the MASCs disclosed in D8. It was CGK to the POSITA that MHC-I negative cells are susceptible to the host NK cells killing activity and it is our view that such CGK would have led/motivated the POSITA to inhibit host NK cells killing activity in contexts wherein MHC-I negative cells, such as the MASCs disclosed in D8, are to be transplanted.

[72] It is therefore our view that it would have been obvious to the POSITA that inhibition of NK cell activity with CGK means such as anti-NK cells antibodies, concomitantly or prior to transplanting MASCs, would reduce the probability of rejection of the transplanted MASCs by host NK cells and therefore promote the engraftment and/or persistence of the transplanted MASCs, a clearly desirable outcome in the context of D8. The transplanted MASCs of D8 are cells that are phenotypically equivalent to MAPCs and fall within the scope of the non-embryonal stem, non-embryonal germ, non-germ cells phenotypically defined in independent claims 2 to 6.

[73] The POSITA would have also understood from D8 that promoting engraftment and/or persistence of the transplanted MASCs would positively impact the intended therapeutic usages of the transplanted MASCs disclosed in D8 (i.e., therapeutic treatment of a variety of diseases and conditions such as cancer, cardiovascular disease, liver disease, diabetes, hepatitis, hemophilia, degenerative or traumatic neurological conditions, autoimmune disease, genetic deficiency and anemia). Therefore, and with respect to independent claim 1, it is our view that it would have been obvious to the POSITA to combine inhibition of NK cell activity through CGK means such as anti-NK cells antibodies, concomitantly or prior to transplanting MASCs, with the use of transplanted MASCs for the disclosed treatments of diseases that fall into the scope of adverse immune responses as defined in claim 1. As mentioned above, transplanted MASCs cells are phenotypically equivalent to MAPCs and fall within the scope of the non-embryonal stem, non-embryonal germ, non-germ cells phenotypically defined in claim 1.

[74] In the Preliminary Review letter we stated that given that the subject-matter of the present claims relates to particular fields of cellular therapy and cellular engraftments/transplants, fields which could be considered areas of endeavour “where advances are often won by experimentation” (*Sanofi* at para 68), and given that the Applicant provided submissions in the Response to the Final Action dated

June 10, 2019 in which it is stated that “the inventive concept underlying the presently claimed invention would not be apparent or self-evident at the claim date to a person of ordinary skill in the art” [Emphasis added], an “obvious to try” analysis was also considered.

Self-Evident Factor

[75] Within the context of the claimed subject-matter and the Self-Evident Factor, we considered in the Preliminary Review letter on page 15 that the relevant question is whether it would have been more or less self-evident to the POSITA, on the basis of the disclosure of D8 and the relevant CGK, that using an agent for inhibiting NK cell function prior to or in combination with transplanted cells that are phenotypically equivalent to the MAPCs ought to be effective in reducing the probability of rejection of the transplanted cells thereby increasing the engraftment and/or persistence of said transplanted cells or for the treatment of an adverse immune response, a disease or an injury.

[76] Said question encapsulates two separate inquiries that are aligned with those laid out above at para 66: i) whether it would have been more or less self-evident to the POSITA that using an agent for inhibiting NK cell function prior to or in combination with transplanted cells that are phenotypically equivalent to the MAPCs ought to be effective in reducing the probability of rejection of said transplanted cells thereby increasing the engraftment and/or persistence of said transplanted cells (independent claims 2 to 6) and; ii) whether it would have been more or less self-evident to the POSITA that using an agent for inhibiting NK cell function prior to or in combination with transplanted cells that are phenotypically equivalent to the MAPCs ought to be effective for the treatment of an adverse immune response defined as a renal, pancreatic, cardiac, hepatic, neurological, vascular, cancer, autoimmune, genetic or hematological disease (independent claim 1).

[77] As explained above at paras 53 and 62, we consider that the scope of the claims on file excludes the transplanted MAPCs themselves as the recited agent inhibiting NK cell function or alternatively, if not excluded, the recited agent inhibiting NK cell function is otherwise not limited in any manner to MAPCs and encompass CGK means for inhibiting NK cell function.

[78] Once again but this time in the context of an “obvious to try” analysis, we therefore consider that whether the POSITA would have “been led to use MAPCs to modify natural killer cell function”, as submitted by the Response to the Preliminary Review letter on page13, is not the relevant inquiry for the claims on file.

[79] The mere possibility that something might work is not sufficient but an amount of uncertainty is allowed in the “obvious to try” analysis (see *Les Laboratoires Servier v Apotex Inc*, 2019 FC 616 at para 269 and *Janssen Inc v Apotex Inc*, 2021 FC 7, at para 135).

[80] Given that it was CGK at the claim date that MHC-I negative cells are susceptible to the host NK cells killing activity and given that D8 discloses that MASCs are MHC-I negative cells, it would have been self-evident to the POSITA that inhibition of host NK cell function ought to be effective in reducing the probability of rejection of the transplanted cells and therefore promote their engraftment/persistence (independent claims 2 to 6).

[81] As mentioned above, an amount of uncertainty (or unpredictability, in reference to Applicant’s submissions) is allowed in the “obvious to try” analysis and we consider that the effect of inhibiting host NK cell function on the engraftment/persistence of transplanted MHC-I negative cells, such as cells that are phenotypically equivalent to the MAPCs, was a predictable one on the basis of the CGK.

[82] It is also our view that it would have been self-evident to the POSITA that using an agent for inhibiting NK cell function prior to or in combination with transplanted cells that are phenotypically equivalent to the MAPCs ought to be effective for the treatment of an adverse immune response defined as a renal, pancreatic, cardiac, hepatic, neurological, vascular, cancer, autoimmune, genetic or hematological disease (independent claim 1) as the transplanted cells would be more likely to achieve the therapeutic treatments disclosed in D8 if their engraftment/persistence is promoted by inhibiting NK cell function. According to D8, the MASCs could be used to replace damaged, diseased, dysfunctional or dead cells in the body of a mammal as well as in the therapeutic treatment of a variety of diseases and conditions such as cancer, cardiovascular disease, metabolic disease, liver disease, diabetes, hepatitis, hemophilia, degenerative or traumatic neurological conditions, autoimmune disease, genetic deficiency, connective tissue disorders,

anemia and infectious disease.

[83] As expressed in the Preliminary Review letter, we consider that the above assessment is largely determinative of the “obvious to try” inquiry in this case. Nevertheless, we make the following observations with regard to other non-exhaustive factors to be considered in an “obvious to try” analysis.

Motive Factor

[84] With respect to the Motive Factor, which includes considerations provided in the prior art to find the solution the patent addresses, we offered the following in the Preliminary Review letter on page 16. We considered that rejection of transplanted cells was a primary concern in the fields of cellular therapy and cellular engraftments/transplants at the claim date and would have motivated the POSITA to use their CGK to reduce the probability of rejection of the MASCs disclosed in D8. Given the teaching of D8 with regard to the lack of expression of MHC-I molecules, it is our view that the well-known potential detrimental role of host NK cells to MHC-I negative cells would have motivated the POSITA to prevent expected NK cells killing activity toward the transplanted MHC-I negative cells disclosed in D8 (i.e., transplanted MASCs that are phenotypically equivalent to the MAPCs of the instant application) by inhibiting host NK cell function.

Extent and Effort Factor

[85] In the Preliminary Review letter on page 16, we considered that the extent, nature, and amount of effort required to inhibit host NK cells activity with CGK means in the context of MASCs derived treatments as taught by D8 would have been within the POSITA’s capabilities as of the claim date.

Conclusion on obvious to try

[86] Therefore, and taking into account the foregoing consideration of the relevant factors pertaining to an “obvious to try” analysis, we are of the view that it was obvious to try to obtain the subject-matter of the independent claims.

Conclusion on obviousness

[87] In view of the foregoing, it is our view that the claims on file define subject-matter that would have been obvious to the POSITA, as of the claim date, in view of D8 and their CGK, contrary to section 28.3 of the *Patent Act*.

[88] With regard to the dependent claims and their additional limitations and further characterization of the subject-matter encompassed by the independent claims, it is our view that the addition of a physiologically acceptable carrier, the characterization of the subject as suffering from a disease or injury, the characterization of the nature of the injury, the characterization of the non-ES, non-EG as autologous, allogeneic or xenogeneic, and the further limitations with regard to the agent that inhibits NK cell, do not denote any degree of invention under any of our obviousness analyses presented above.

REFERENCES TO FOREIGN PRACTICE OR LAW

[89] The Final Action on pages 6 and 7 expresses the view that a statement found at page 1, lines 21 to 24 regarding the rights of foreign governments to the invention and another statement found at page 13, lines 13 to 15 which depends on foreign practice or law may be misleading and cause confusion in the context of Canadian law and should be removed. According to the *Manual of Office Practice* section 14.05.07 (CIPO, December 2010) such statements may be viewed as being "incorrect", and therefore a defect under subsection 27(3) of the *Patent Act*.

[90] The statement found at page 1, lines 21 to 24 read as follows:

> This work was funded by United States Grant Nos. RO1-HL49997 and RO1-DK58295 from the National Institutes of Health. The government may have certain rights to this invention.

[91] The statement found at page 13, lines 13 to 15 read as follows:

> The terms "comprises", "comprising", and the like can have the meaning ascribed to them in U.S. Patent Law and can mean "includes", "including" and the like.

[92] In the Preliminary Review letter we agreed with the characterizations of these statements as presented in the Final Action and expressed the preliminary view that both statements should be removed.

[93] The response to the Preliminary Review letter proposed new pages 1 and 13 addressing both statements.

[94] Therefore, we consider that the statement found at page 1, lines 21 to 24 regarding the rights of foreign governments to the invention and the statement found at page 13, lines 13 to 15 which depends on foreign practice or law may be misleading and cause confusion in the context of Canadian law, a defect under subsection 27(3) of the *Patent Act*.

ANALYSIS OF THE PROPOSED AMENDMENTS

[95] During the review, the Panel may consider proposed amendments. With the response to the Final Action, the Applicant submitted a proposed claims set

comprising new dependent claim 16 in addition to the claims on file.

[96] Proposed dependent claim 16 further specifies that the recited medicament is a formulation for sequential administration of the agent for inhibiting natural killer cell function followed by administration of the non-ES, non-EG, non-germ cells.

[97] In the Preliminary Review letter, we stated that the subject-matter of proposed claim 16 had been already considered within the obviousness analysis of claims 2, 3 and 5 on file and that, accordingly, said analysis and associated preliminary conclusions also apply to proposed claim 16.

[98] The response to the Preliminary Review letter did not specifically address or comment on proposed claim 16.

[99] We consider that our above final obviousness analysis of claims 2, 3 and 5 on file already considered the subject-matter of proposed claim 16 and that said analysis and associated conclusions also apply to proposed claim 16.

[100] Therefore, it is our view that the proposed amendment does not meet the requirements of a necessary amendment under subsection 86(11) of the *Patent Rules*.

[101] Further, the response to the Preliminary Review letter proposed new pages 1 and 13 addressing the references to foreign practice or law issue.

[102] Proposed page 1 of the description has been amended to remove the text appearing at lines 21 to 24.

[103] Proposed page 13 of the description has been amended to reword lines 13 to 15 to read:

> The terms “comprises”, “comprising”, and the like can mean “includes”, “including” and the like.

[104] We are of the view that the proposed amended pages 1 and 13 would address the issue.

[105] However, as discussed in previous sections above, it is our view that all the claims

on file, as well as the new proposed claim 16, are obvious and do not comply with section 28.3 of the *Patent Act*. The proposed amendments to description pages 1 and 13 would not alter the outcome of the above reasoning with respect to the obviousness defect for these claims and therefore conclude that they are not considered necessary amendments in accordance with subsection 86(11) of the *Patent Rules*.

RECOMMENDATION OF THE BOARD

[106] In view of the above, the Panel recommends that the application be refused on the basis that:

- Claims 1 to 15 are obvious and do not comply with section 28.3 of the *Patent Act*.
- The specification is non-compliant with subsection 27(3) of the *Patent Act* because it contains a statement regarding the rights of foreign governments to the invention and a statement regarding foreign practice or law that may be misleading and cause confusion in the context of Canadian law, statements that fail to correctly and fully describe the invention.

Marcel Brisebois	Ryan Jaecques	Christine Teixeira
Member	Member	Member

DECISION OF THE COMMISSIONER

[107] I concur with the findings of the Board and its recommendation to refuse the application because the claims on file do not comply with section 28.3 of the *Patent Act* and the specification is non-compliant with subsection 27(3) of the *Patent Act*.

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

Virginie Ethier
Assistant Commissioner of Patents

Dated at Gatineau, Quebec

this 16th day of August, 2022.