Commissioner=s Decision #1329
Décision du Commissaire #1329

TOPIC: F00, O00, B00, B22, C00
SUJET: F00, O00, B00, B22, C00

Application No. : 2,388,807
Demande n^{o}. : 2,388,807

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,388,807 having been rejected under subsection 30(3) of the *Patent Rules*, has consequently been reviewed in accordance with subsection 30(6) of the *Patent Rules* by the Patent Appeal Board and the Commissioner of Patents. The findings of the Board and the decision of the Commissioner are as follows:

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INTRODUCTION

[1] This decision deals with a review of the rejection of patent application No. 2,388,807.

[2] The Applicant is Oncolytics Biotech, Inc., the inventors are Matthew C. Coffey and Bradley G. Thompson and the invention is entitled AVIRUSES FOR THE TREATMENT OF CELLULAR PROLIFERATIVE DISORDERS@.

BACKGROUND

[3] The application is concerned with the use of engineered viruses for treating tumors (i.e., cell proliferative disorders) in mammals. In particular, it is concerned with treating ARas-mediated@ cell proliferative disorders wherein the proliferating cells are unable to activate a Protein Kinase R (PKR) response.

[4] A virus is a small infectious agent that can replicate only inside the cells of an organism. The viruses can be released from the host cell by lysis, a process that burts the cell membrance and kills the host cell. Viral infections in animals provoke an immune response that usually eliminates the infecting virus.

[5] PKR is a component of host anti-viral defense mechanisms. Once activated, PKR prevents viral replication in the host cell through inhibition of protein synthesis.

[6] The Ras protein is involved in intracellular signaling networks. Ras protein signaling activation causes cell growth, differentiation and survival. Inappropriate or dysregulated activation of Ras can lead to cell proliferative disorders such as cancer. According to the application=s description, improper Ras signaling may contribute to approximately 30% of all human tumors.

[7] Importantly, the instant description teaches another cellular event driven by Ras: the activation of PKR is blocked in cells in which Ras is activated, such as Ras-mediated tumor cells.

[8] Certain viruses still replicate effectively in cells in spite of the PKR activity because they produce products that can counteract the activity of PKR: adenoviruses produce a VAI RNA element that acts as a competitive inhibitor of PKR; vaccinia viruses produce K3L and E3L proteins that down-regulate PKR; herpes simplex viruses produce infected-cell protein 34.5 (ICP34.5) that prevents the antiviral effects of PKR; and parapoxviruses encode the gene OV20.0L that is involved in blocking PKR activity. Such viruses would indiscriminately kill both normal and tumor cells.

[9] However, if the PKR antagonizing genes of the viruses are rendered nonfunctional through mutations, these mutant viruses cannot replicate in normal cells due to the antiviral activity of PKR.

[10] In the case of cells having Ras inappropriately or constitutively activated (e.g. tumor cells), the same mutant viruses can effectively replicate and cause cell death because PKR is unable to perform its anti-viral functions.

[11] It follows that mutant viruses which do not produce anti-PKR products can specifically kill the tumor cells while sparing the normal cells.

PROSECUTION HISTORY

[12] The subject application was filed on November 8, 2000 and the Examiner in charge of the application issued a Final Action on May 24, 2006. In the Final Action, the Examiner rejected the application on the grounds that all the claims were anticipated, obvious, not adequately supported by the description and/or indefinite.

[13] In its response to the Final Action, the Applicant argued against these conclusions. The Examiner was not persuaded by the Applicant=s arguments and maintained the rejection. Subsequently, a Summary of Reasons was forwarded to the Patent Appeal Board, a copy of which was sent to the Applicant on August 22, 2007. A first supplemental analysis from the Examiner addressing the question of obviousness with respect to then pending claims in accordance with the direction provided in *Apotex Inc. v. Sanofi-Synthelabo Canada Inc.*, 2008 SCC 61 was sent to the Applicant on June 4, 2010.

[14] In a letter dated October 28, 2010, the Applicant voluntarily proposed the deletion of a number of claims in order to reduce the number of issues to be addressed at the November 3, 2010 hearing. The Board agreed to conduct the review on the basis of the proposed claim set, which contains 30 claims that correspond to claims 52 to 73 and 75 to 82 of the rejected application. Unless otherwise noted, all references to the claims will be to the proposed claims.

[15] At the hearing, the Board indicated to the Applicant that if a new question of obviousness arose during the review it would be dealt with at the Board. Following the hearing, the Board requested a second supplemental analysis from the Examiner with regard to the inventiveness of the claims. The analysis was sent to the Applicant on March 14, 2011. The Applicant=s response was received on June 14, 2011.

THE ISSUES

[16] In the Final Action, the subject matter of proposed claims 1 to 6 and 8 to 30 was found not compliant with paragraph 28.2(1)(*b*) of the *Patent Act* as being anticipated by the prior art document Roberts et al. The Examiner also found the subject matter of proposed claims 3 and 28 anticipated by the prior art documents Molnar-Kimber et al., Toda et al. and Chahlavi et al. Independent claim 7 was not found to be anticipated by any of the cited prior art documents.

[17] The Examiner also considered the application to be defective on the grounds that the subject matter of proposed claims 1 to 30 was not compliant with section 84 of the *Patent Rules* and that the specification was not compliant with subsection 27(3) of the *Patent Act* with respect to the use of the recited mutant viruses for the contemplated purposes.

[18] Finally, the Examiner found the subject matter of claims 1 to 30 not compliant with subsection 27(4) of the *Patent Act* for being indefinite with respect to the viruses and their mutations set forth in these claims.

[19] Based on the above, the Patent Appeal Board is faced with 4 questions:

(1) Is the subject matter of claims 1 to 6 and 8 to 30 anticipated by the cited prior art?
(2) Is the subject matter of claims 1 to 6 and 8 to 30 obvious in view of the cited prior art?

(3) Does the instant specification provide proper and sufficient disclosure for the use of the viruses encompassed by the scope of the claims?

(4) Are the viruses encompassed by the scope of the claims adequately defined?

CLAIMS AT ISSUE

[20] The foregoing questions require a consideration of all of the claims, except that the novelty and inventiveness of claim 7 are not in question. The independent claims read as follows:

> 1. The use of a pharmaceutical composition to treat a Ras-mediated cell proliferative disorder in a mammal that has been tested as having a Ras-mediated cell proliferative disorder wherein the proliferating cells are unable to activate a PKR response and wherein the pharmaceutical composition comprises an effective amount of one or more adenoviruses having a mutation in the gene encoding VAI RNA, wherein VAI RNA is not transcribed due to the mutation.
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> 3. The use of a pharmaceutical composition to treat a Ras-mediated cell proliferative disorder in a mammal that has been tested as having a Ras-mediated cell proliferative disorder wherein the proliferating cells are unable to activate a PKR response and wherein the pharmaceutical composition comprises an effective amount of one or more HSV having a mutation in the $_{\gamma 1}$34.5 gene, wherein the $_{\gamma 1}$34.5 gene is not transcribed due to the mutation.
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> 4. The use of a pharmaceutical composition to treat a Ras-mediated cell proliferative disorder in a mammal that has been tested as having a Ras-mediated cell proliferative disorder wherein the proliferating cells are unable to activate a PKR response and wherein the pharmaceutical composition comprises an effective amount of one or more vaccinia viruses comprising a mutant gene selected from the group consisting of E3L and K3L, wherein said mutant gene is not transcribed due to the mutation.
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> 7. The use of a pharmaceutical composition to treat a Ras-mediated cell proliferative disorder in a mammal that has been tested as having a Ras-mediated cell proliferative disorder wherein the proliferating cells are unable to activate a PKR response and wherein the pharmaceutical composition comprises an effective amount of one or more parapoxvirus orf viruses having a mutation in the OV20.0L gene, wherein the OV20.0L gene is not transcribed due to the mutation.
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> 28. The use of a pharmaceutical composition to inhibit metastasis of a neoplasm having an activated Ras-pathway in a mammal that has been tested as having a Ras-mediated cell proliferative disorder, wherein the neoplastic cells are unable to activate a PKR response and wherein the pharmaceutical composition comprises an effective amount of one or more viruses selected from the group consisting of modified adenovirus, modified HSV, modified vaccinia virus and modified parapoxvirus orf virus wherein the modified adenovirus has a mutation in the gene encoding VAI RNA, the modified HSV has a mutation in the $_{\gamma 1}$34.5 gene, the modified vaccinia virus has a mutation in the E3L or K3L gene, and the modified parapoxvirus orf virus has a mutation in the OV20.0L gene, wherein said gene is not transcribed due to the mutation.

CLAIM CONSTRUCTION

[21] Having reviewed the prosecution, we identified the following points of disagreement between the Examiner and the Applicant with respect to the meaning of certain phrases in the claims:

i) What is actually encompassed by the phrase ARas-mediated cell proliferative disorder@?

ii) How should the prior Atesting@ step be construed?

iii) Are the pharmaceutical compositions defined in the claims limited to contain virus(es) alone?

The conclusions of the Board with respect to the meaning of the above phrases will be applied, as required, in the following analyses and findings.

[22] The principles of construction are well established in the Canadian jurisprudence, notably in *Free World Trust v. Electro Santé Inc.*, 2000 SCC 66 (*Free World Trust*), and *Whirlpool Corp. v. Camco Inc.*, 2000 SCC 67 (*Whirlpool*). Through a purposive construction, a fair and knowledgeable interpretation is given to the technical meaning of the terms and concepts used in the claims (*Free World Trust*, at para. 51).

[23] Claim construction is done from the perspective of the person skilled in the art (POSITA) in light of the ordinary skill and knowledge of the particular art to which the invention relates and reading each claim in the context of the rest of the specification.

Applying the Legal Principles

[24] In view of the principles introduced above, we first need to identify the POSITA. The Examiner stated in the first supplemental analysis that the POSITA is a medical virologist with experience in the field of oncolytic viruses. The applicant did not contest the identity of the POSITA. We agree with the identity of the POSITA as proposed by the Examiner.

i) What is actually encompassed by the phrase ARas-mediated cell proliferative disorder@?

[25] Globally, the Examiner considers that an activated Ras-pathway is a known and inherent feature of many neoplasms and that many types of tumors susceptible to the treatments disclosed in the cited prior art references, although not necessarily explicitly characterized as Ras-mediated cell proliferative disorders, fall within the definition of a ARas-mediated cell proliferative disorder@.

[26] On the other hand, the Applicant=s submissions presented in its response to the Final Action and at the hearing indicate that the Ras-mediated cell proliferative disorder recited in the proposed claims should not be construed as encompassing the tumors of the cited prior art references.

[27] To assist in understanding the exact nature of the contemplated disorder, we had recourse to the description portion of the specification. According to page 19, lines 26 to 29 of the description, a Ras-mediated cell proliferative disorder results:

> at least in part, by the activation of Ras, an upstream element of Ras, or an element in the Ras signalling pathway...

[28] In the AState of the Art@ portion of the instant description, the following is found on page 3, lines 14 to 25:

> Genetic alteration of the proto-oncogene Ras is believed to contribute to approximately 30% of all human tumors. The role that Ras plays in the pathogenesis of human tumors is specific to the type of tumor. Activating mutations in Ras itself are found in most types of human malignancies, and are highly represented in pancreatic cancer (80%), sporadic colorectal carcinomas (40-50%), human lung adenocarcinomas (15-24%), thyroid tumors (50%) and myeloid leukemia (30 %). Ras activation is also demonstrated by upstream mitogenic signaling elements, notably by tyrosine receptor kinases (RTKs). These upstream elements, if amplified or overexpressed, ultimately result in elevated Ras activity by the signal transduction activity of Ras. Examples of this include overexpression of PDGFR in certain forms of glioblastomas, as well as in c-erbB- 2/neu in breast cancer. [Citations omitted]

[29] These two particular passages are mutually consonant and the Board finds that the expression ARas-mediated cell proliferative disorder@ would have been read and understood by the POSITA as including tumors and neoplasms having an elevated Ras activity as a result of a mutation or the activation of an upstream signaling element. The POSITA would have also understood that the presence of an elevated Ras activity was an inherent characteristic of a relatively high proportion of many types of human tumors.

ii) How should the prior Atesting@ step be construed?

[30] It is clear from the Final Action, the Applicant=s response to the Final action and the Applicant=s oral submissions at the hearing that the prior step of Atesting@ for the presence of a ARas-mediated cell proliferative disorder wherein the proliferating cells are unable to activate a PKR response@ constitutes another matter of contention.

[31] According to the specification, different types of tumors should be particularly susceptible to the disclosed treatment because of the prevalence of the activation of the Ras pathway in these tumors.

[32] It is also apparent from different passages of the instant description and from the nature of the selected viruses (i.e., viruses having their mechanisms of preventing PKR activation disrupted) that the successful use of the recited pharmaceutical composition depends on the inability of the targeted tumors to activate the antiviral response mediated through PKR and not whether Ras is activated. The following passage found on page 6 lines 20 to 24 of the description is relevant in this regard:

> However, if infected cells are unable to activate the antiviral response mediated through PKR (i.e., Ras-mediated tumor cells), then these mutant viruses should replicate unheeded and cause cell death. Therefore, these mutant viruses can replicate preferentially in Ras-transformed cells where it is determined that PKR is unable to function.

[33] It follows that any cell proliferative disorder wherein the proliferative cells are unable to

activate a PKR response should be susceptible to the use of the recited mutated viruses, not only Ras-mediated cell proliferative disorders.

[34] Based on the wording of the claims and in the context of the entire specification, the step of testing could encompass testing the tumor cells for Ras and PKR activation before the use of the defined virus.

[35] However, the only specific references to a test of some sort are found in the portion of the description entitled AEXAMPLES@ on pages 32 to 39. This relevant passage of the description teaches that different tumor cell lines of different cancer types should be tested to determine their susceptibility to virus oncolysis, the sought-after therapeutic effect. Importantly, the different cell lines were not specifically tested for activated Ras or specifically tested for their capacity to activate a PKR response and it is not suggested to do so.

[36] Therefore, it appears that there is no basis for limiting the scope of the expression Ahas been tested as having a Ras-mediated cell proliferative disorder wherein the proliferating cells are unable to activate PKR@ to the determination of Ras and PKR activation status.

[37] In our view, having reviewed the specification and how the inventors themselves suggest to identify the suitable tumors for the treatment, the expression Ahas been tested as having a Ras-mediated cell proliferative disorder wherein the proliferating cells are unable to activate PKR@ not only encompasses testing for tumors and neoplasms having an elevated Ras activity and a PKR that is unable to function, but also encompasses directly testing the susceptibility of tumor and neoplastic cells to the oncolytic activity of the recited viruses.

iii) Are the pharmaceutical compositions defined in the claims limited to contain virus(es) alone?

[38] The Applicant considers that the pharmaceutical composition defined in the claims should be construed as being limited to a pharmaceutical composition comprising a modified virus alone.

[39] The Federal Court of Appeal in *Novopharm Limited v. Abbott Laboratories Limited*, 2007 FCA 251, considering a similar argument, cautioned against construing a claim to the use of a drug as excluding the simultaneous use of other compounds, by importing limitations from the description:

> Thus, even if there was a limitation implicit or explicit in the disclosure, it could not be imported into the claims. Drugs often are not administered in a pure state but mixed with an excipient or other drugs and the use of such drugs would be highly restricted if the mention of a use of a drug would be read as implying it has to be used alone. Unless the use claimed specifically employs such words as Aalone@ or Anot in conjunction with other compounds@ it would be improper to read such a limitation into the claimY

[40] There are no such words as Aalone@ or Anot in conjunction with other compounds@ in the proposed independent claims and the plain meaning of the words Awherein the pharmaceutical composition comprises an effective amount of@ does not preclude the presence of additional elements or constituents.

[41] Moreover, several passages of the instant description describe the contemplated

pharmaceutical compositions as containing more than a virus alone. This is illustrated by the following passage found on page 25, lines 1 to 6 of the description:

> This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the viruses associated with Apharmaceutically acceptable carriers or excipients.@ This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more immunosuppressants or immunoinhibitors and one or more of the viruses associated with Apharmaceutically acceptable carriers or excipients.@

[42] Therefore, the Board finds that there is no basis for construing the claims as being limited to the use of a pharmaceutical composition comprising viruses alone.

QUESTION (1): IS THE SUBJECT MATTER OF CLAIMS 1 TO 6 AND 8 TO 30 ANTICIPATED BY THE CITED PRIOR ART?

Legal Authorities and Principles

[43] The statutory provision relevant to the rejection under anticipation is found in subsection 28.2(1) of the *Patent Act* that states:

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

[44] The Supreme Court of Canada in *Sanofi*, reviewed the law on anticipation at paragraphs 23 to 37. The Court held that two separate requirements must be established in order for there to be anticipation: disclosure and enablement.

[45] In *Abbott Laboratories v. Canada (Minister of Health)*, 2008 FC 1359 (*Abbott*), Justice Hughes summarized the relevant requirements of anticipation as follows:

> 1. For there to be anticipation there must be both disclosure and enablement of the claimed invention.
>
> 2. The disclosure does not have to be an Aexact description@ of the claimed invention. The disclosure must be sufficient so that when read by a person skilled in the art willing to understand what is being said, it can be understood without trial and error.
>
> 3. If there is sufficient disclosure, what is disclosed must enable a person skilled in the art to carry out what is disclosed. A certain amount of trial and error experimentation of a kind normally expected may be carried out.
>
> 4. The disclosure when carried out may be done without a person necessarily recognizing what is present or what is happening.

> 5. If the claimed invention is directed to a use different from that previously disclosed and enabled then such claimed use is not anticipated. However if the claimed use is the same as the previously disclosed and enabled use, then there is anticipation.
> 6. The Court is required to make its determinations as to disclosure and enablement on the usual civil burden of balance and probabilities, and not to any more exacting standard such as quasi-criminal.
>
> 7. If a person carrying out the prior disclosure would infringe the claim then the claim is anticipated.

Analysis

[46] The Applicant submitted at the hearing that the inventors discovered that Ras-mediated cell proliferative disorders are susceptible to the oncolytic activity of the recited viruses because of their inability to activate a PKR response. This discovery allows the screening of good cancer patient candidates for the disclosed therapy based on the detection of Ras activity. According to the Applicant, such screening is necessarily novel since the role played by Ras in PKR inactivation was unknown before.

[47] However, the subject matter of the claims is a therapeutic use, and not a method of screening patients to identify good candidates for the therapeutic use of a pharmaceutical composition. It is this therapeutic use, and not a method of screening, that must be compared to the prior art.

[48] The Board acknowledges that the discovery of the mechanism of action of an old compound could lead to new uses for the old compound. However, restricting the scope of a claim according to the mere discovery of a scientific explanation for the prior art=s performance or to the mechanism of action which underlies a use already described in the prior art cannot, without more, give rise to novelty (see *Biovail Corporation v. Canada (Health)*, 2010 FC 46 at para. 99). If the mechanism of action is inherent to the compound and the susceptible tumor, it is irrelevant whether the mechanism was precisely disclosed in the prior art.

[49] Considering the requirements of anticipation and the claims construction above, an anticipatory prior art document must disclose and enable the use of the mutated viruses recited in the claims for treating a mammal suffering from a disorder that falls into the scope of tumors and neoplasms having an elevated Ras activity or tumor and neoplastic cells susceptible to the oncolytic activity of the recited viruses.

Roberts et al.

[50] The first of the prior art references relied upon by the Examiner is Roberts et al., a PCT application (WO 99/18799) published on April 22, 1999. The reference was published before the application priority date of November 12, 1999 and is citable under paragraph 28.2(1)(*b*) of the *Patent Act*.

[51] In the response to the Final Action, the Applicant submitted, in part, the following with respect to the publication of Roberts et al.:

> Roberts describes the use of interferon-sensitive viruses for treatment of neoplastic cells. Roberts describes the use of these viruses for treating cells deficient in an IFN-mediated antiviral response. Roberts does not disclose or suggest testing a mammal to determine whether the mammal has a Ras-mediated cell proliferative

disorder.

> As evidenced by the following abstract, Malmgaard, *J. Interferon Cytokine Res*. **24**(8):439-54 (2004) (abstract enclosed) (AMalmgaard@), in response to viral infections, IFN activates numerous intrinsic antiviral factors including PKR, 2-5A system, Mx proteins and apoptotic pathways. Thus, cells deficient in mediating an IFN antiviral response do not activate these factors. As described in the present application at least at page 5, in Ras-mediated tumor cells, PKR is induced in the presence of IFN. However, activated Ras inhibits PKR. Therefore, Ras-mediated tumor cells are not inherently cells deficient in IFN-mediated antiviral activity. Furthermore, Roberts does not enable one of ordinary skill in the art to make and use adenoviruses, HSV, vaccinia viruses and parapoxviruses for use in treating Ras-mediated proliferative disorders. Roberts provides sufficient guidance to one of skill in the art only for the use of Newcastle disease virus to treat cells deficient in an IFN-mediated antiviral response. In addition, Roberts does not enable one of ordinary skill in the art to make and use an effective amount of a virus for use in treating a Ras-mediated cell proliferative disorder. This is because Roberts does not recognize that all cells deficient in an IFN-mediated antiviral response are not necessarily Ras-mediated tumor cells. Therefore, Roberts does not anticipate nor does Roberts make obvious the claims of the present application. [Emphasis in original]

[52] At the hearing, the Applicant admitted that the engineered viruses disclosed in Table 2 of Roberts et al. are old viruses that are encompassed by the scope of some of the Applicant=s claims. Furthermore, the Applicant agreed that some of the tumor cell lines found to be susceptible to the treatment of Roberts et al. are Ras-mediated but others are not. The Applicant also submitted that since Roberts et al. did not recognize the role played by Ras and PKR in their treatment, the disclosure of Roberts et al. would not necessarily and inevitably lead the POSITA to the use of the mutated viruses mentioned in Roberts et al. for the treatment of a Ras-mediated cell proliferative disorder without the possibility of failure. According to the Applicant, since Roberts et al. does not mention Ras at all, there is no way that it can disclose that mutated viruses should be used for Ras-mediated cell proliferative disorders and hence, the step of identifying a proliferative disorder as Ras-mediated that is present in their invention cannot have been disclosed by Roberts et al.

[53] Finally, the Applicant submitted at the hearing that the disclosure of Roberts et al. is not enabled for the use of the mutated adenoviruses because corresponding claims prosecuted in Canada were objected for lack of enablement by the Canadian Intellectual Property Office and cancelled thereafter by Roberts et al.

Disclosure

[54] Roberts et al. discloses the use of an effective amount of an adenovirus having a mutation in the gene encoding VAI RNA, a HSV having a mutation in the gamma 34.5 gene or a vaccinia virus having a mutation in the E3L or K3L gene viruses to selectively kill neoplastic cells deficient in an IFN-mediated anti-viral response. These mutant viruses are known engineered viruses and are listed in Table 2 on page 27.

[55] The disclosed therapy is based on the fact that normal cells, which possess an intact IFN-mediated anti-viral response, limit the replication of the engineered viruses and are not killed. On the other hand, neoplastic cells deficient in an IFN-mediated anti-viral response are susceptible to the treatment.

[56] On pages 23 to 27, Roberts et al. discloses how to determine the susceptibility of a given neoplasm to the proposed viral therapy. On pages 30 to 35, Roberts et al. discloses the various types of treatable neoplasms, how to formulate a therapeutically effective dose of the virus, how to administer the therapeutical composition comprising the virus and the different additional therapies that can be optionally combined with the viral therapy.

[57] IFN anti-viral activity in a cell is the result of many biological pathways, not necessarily one using PKR. Therefore, the Board agrees with the Applicant that tumor cells could be deficient in their overall IFN-mediated anti-viral response but nevertheless have an adequate PKR activation. However, the Board also finds that tumor cells selectively susceptible to the oncolytic activity of the engineered viruses disclosed in Roberts et al. are deficient in their overall IFN-mediated anti-viral response because they are unable to activate PKR, whether the result of Ras activity or otherwise.

[58] This finding is based on the nature of the genes altered in the engineered viruses of Table 2, in the Roberts et al. disclosure on page 14, second paragraph, and on page 5, lines 7 to 14 of the instant description. If, as submitted by the applicant, tumor cells are deficient in their overall IFN-mediated anti-viral response but nevertheless have an adequate PKR activation, such tumor cells would not be susceptible to the engineered viruses of Table 2 which lack PKR antagonizing functions.

[59] Whether Ras-mediated tumor cells are cells inherently deficient in IFN-mediated antiviral activity or not is inconsequential for the POSITA reading the disclosure of Roberts et al. Any tumor cells that are unable to activate a PKR response would ultimately fail to reduce the replication of the engineered viruses of Table 2 and thus, such tumors would be screened in by the POSITA as a good candidate for the viral therapy disclosed in Roberts et al.

[60] The Applicant contends that the scope of what is described as tumor cells deficient in IFN-mediated anti-viral response in Roberts et al. is broader than a Ras-mediated cell proliferative disorder wherein the proliferating cells are unable to activate a PKR response. However, that does not change the fact that treatment with the engineered viruses disclosed by Roberts et al. effectively covers any cell proliferative disorder wherein the proliferating cells are unable to activate a PKR response. In light of the instant description, the group of tumors susceptible to the engineered viruses of Table 2 necessarily includes Ras-mediated cell proliferative disorders wherein the proliferating cells are unable to activate a PKR response.

[61] Roberts et al. discloses on page 23, last paragraph, specific guidance as how to test whether a given tumor found in a patient is susceptible to the disclosed treatment. It follows that it would be apparent to the POSITA, having a mind willing to understand, that testing the susceptibility of primary tumor tissue or cells obtained from patient biopsies to the oncolytic activity of the engineered viruses disclosed in Table 2 precedes any treatment. Again, we reiterate that since the viruses of Table 2 lack PKR antagonizing function, only tumor cells having the inherent inability to activate a PKR response would be susceptible to the treatment of Roberts et al., which includes, as a subset, all Ras-mediated cell proliferative disorders wherein the proliferating cells are unable to activate a PKR response.

[62] The Applicant further submitted that the disclosure of Roberts et al. would not necessarily

and inevitably lead the POSITA to the use of the mutated viruses mentioned in Roberts et al. for the treatment of a Ras-mediated cell proliferative disorder without the possibility of failure. In *Sanofi* at paras. 23 and 25, Justice Rothstein observed that one should not overstate the stringency of the test for anticipation.

[63] To meet the disclosure requirement, the Roberts et al. disclosure does not have to be an Aexact description@ of the proposed claimed invention but needs to disclose subject matter which, if performed, would necessarily result in an infringement of the proposed claims if the instant application subsequently issued to patent. The disclosure of Roberts et al. would lead the POSITA to the use of the mutated viruses mentioned in the Table 2 of Roberts et al. for the treatment of any cell proliferative disorder tested as susceptible to the oncolytic activity of said viruses, which necessarily includes, but is not limited to, a Ras-mediated cell proliferative disorder wherein the proliferating cells are unable to activate a PKR response.

[64] Therefore, we find that Roberts et al. discloses subject matter which, if performed by the POSITA, would necessarily result in infringement of the claims 1 to 6, 8 to 10, 12 to 15, 17 to 20, 23, 24, 26 and 28 to 30 if a patent were to issue for the claimed subject matter, and that the disclosure requirement of anticipation has been met.

Enablement

[65] With regard to the enablement requirement, the Applicant argues that the disclosure of Roberts et al. does not enable the use of the mutated adenoviruses because such subject matter was considered to lack enablement by the Canadian Intellectual Property Office and cancelled thereafter by Roberts et al.

[66] The mere fact that a possible defect was identified during the examination of another case, without more, cannot be considered conclusive as to whether or not the application was defective. We consider below whether or not the disclosure in Roberts et al. meets the enablement requirement of anticipation.

[67] In the analysis of the enablement requirement in the context of anticipation, one must consider whether the skilled person would have been able to perform what was disclosed in the prior art publication, with some trial and error or experimentation but without undue burden. Roberts et al. provides the identity of old and known engineered viruses (e.g. see Table 2) that can be used in the disclosed viral therapy, provides clear teachings and specific guidance as to how to determine the susceptibility of a given neoplasm to the proposed viral therapy and provides specific guidance to the POSITA as to how to formulate and administer the compositions comprising the viruses and how additional therapies can be optionally combined with the viral therapy.

[68] With respect to the Applicant=s submission that Roberts et al. does not enable one of ordinary skill in the art to make and use an effective amount of a virus for use in treating a Ras-mediated cell proliferative disorder principally because Roberts et al. does not recognize that all cells deficient in an IFN-mediated antiviral response are not necessarily Ras-mediated tumor cells, such an argument cannot be sustained. In *Abbott*, the Federal Court determined that the prior disclosure when carried out may be done without a person necessarily recognizing what is present or what is happening (see point 4 at paragraph 45 of this recommendation).

[69] In view of the above, the Board finds that Roberts et al. discloses and enables the use of the

recited mutated viruses for treating a mammal suffering from a disorder that falls into the scope of tumors and neoplasms having an elevated Ras activity or tumors and neoplastic cells susceptible to the oncolytic activity of the recited viruses and thus, anticipates claims 1 to 6, 8 to 10, 12 to 15, 17 to 20, 23, 24, 26 and 28 to 30.

[70] The Board finds that Roberts et al. does not specifically disclose that neurofibromatosis, hematopoietic neoplasms and metastases are treatable using the engineered viruses recited in the claims; does not disclose the immunoprotection of the engineered viruses; and does not disclose the pre-treatment of the viruses with a protease. Therefore, claims 11, 16, 21, 22, 25 and 27 recite novel subject matter in view of Roberts et al.

Molnar-Kimber et al.

[71] The second reference cited by the Examiner for anticipation against the subject matter of claims 3 and 28 is Molnar-Kimber et al., a PCT application (WO 99/45783) published on September 16, 1999, a date that precedes the application priority date of November 12, 1999. Molnar-Kimber et al. is citable under paragraph 28.2(1)(*b*) of the *Patent Act*.

[72] The Applicant stated, in part, the following in the response to the Final Action with respect to the disclosure of Molnar-Kimber et al.:

> Molnar-Kimber describes administration of producer cells to a subject for treatment of tumor cells, wherein the producer cell contains an oncolytic virus. Therefore, Molnar-Kimber does not disclose or suggest pharmaceutical compositions comprising only *virus*. In addition, Molnar-Kimber does not disclose or suggest administration of an effective amount of a modified virus *alone* for use in treating a Ras-mediated cell proliferative disorder. Since Molnar-Kimber describes administering *producer cells*, it does not enable one of ordinary skill in the art to administer virus alone. In addition, Molnar-Kimber does not recognize the difference between Ras-mediated tumor cells and other types of tumor cells. Therefore, Molnar-Kimber does not enable one of skill in the art as to how to make and use an effective amount of a modified virus for use in treating Ras-mediated cell proliferative disorders. Therefore, Molnar-Kimber does not anticipate or render obvious claims 3, 29, 54 and 80. [Emphasis in the original]

[73] In summary, the Applicant submits that Molnar-Kimber et al. does not disclose and enable the use of a virus alone (i.e., without producer cells), and does not disclose and enable the use of a modified virus as recited in the claims for the treatment of Ras-mediated cell proliferative disorders because Molnar-Kimber et al. does not recognize the difference between Ras-mediated tumor cells and other types of tumor cells.

Disclosure

[74] Molnar-Kimber et al. discloses an engineered herpes simplex type 1 virus (HSV-1) having the gamma 34.5 gene mutated so said gene is not transcribed. According to its specification on page 4, lines 20 to 23, such HSV-1 mutants have been shown to replicate preferentially in tumor cells, causing a direct oncolytic effect while sparing normal cells. Moreover, the disclosure of Molnar-Kimber et al. exemplifies the use of one of said HSV-1 mutants for treating mice bearing a Ras-mutated murine fibroblast tumor (i.e., the EJ-62 cell line) in their peritoneum. Established intraperitoneal tumors were treated with single or multiple virus injections and prolonged survival was observed in all treated groups.

[75] When specifically directed to Example 3 of Molnar-Kimber et al. at the hearing, the Applicant recognized that Molnar-Kimber et al. discloses the treatment of a Ras-mutated tumor cell line but submitted that the chosen virus had been also used against other cell lines without necessarily selecting for Ras-mediated tumor cell lines and thus, the use of that particular cell line is part of a Alet=s try@ approach as opposed to knowingly selecting Ras-mediated proliferating cells as targets for the virus.

[76] It is true that the description of Molnar-Kimber et al. discloses on pages 33 to 36 that the same virus exerts an *in vivo* oncolytic effect on the A2780 cell line (i.e., a well- known Ras-mutated cell line) but also on the SKOV3 cell line (i.e., a cell line wherein Ras was not known to be mutated or constitutively activated). In view of the nature of the virus used in the assays (i.e., a mutant HSV which lacks PKR antagonizing function), these results are not conflicting but rather in line with the passage found on page 6, lines 20 to 24 of the Applicant=s own description. A given tumor unable to activate a PKR response would be susceptible to such a virus, independently of the signaling pathway leading to this incapacity (i.e., Ras-mediated or not).

[77] The Applicant has allegedly discovered that the Ras signaling pathway is one pathway capable of inhibiting a PKR response and accordingly, has chosen to restrict the scope of the claims to Ras-mediated cell proliferative disorders. However, the demonstration by Molnar-Kimber et al. of the successful use of the same old and known mutant HSV in the treatment of a broader genus of tumors clearly does not disqualify the reference from consideration as an anticipatory document, especially if the mechanism of action behind all the treatments is the preferential replication of an engineered virus lacking PKR antagonizing function within tumor proliferating cells that are unable to activate a PKR response.

[78] Once again, to meet the disclosure requirement, Molnar-Kimber et al. does not have to provide an Aexact description@ of the claimed invention but need to disclose subject matter which, if performed, would necessarily result in an infringement of the claims if the instant application subsequently issued to patent. Moreover, the POSITA could carry out the prior disclosure of Molnar-Kimber et al. without necessarily recognizing what is present or what is happening. Inherent features of a prior known treatment (i.e., the mechanism of action) are not patentable (See *Biovail*, points 2, 4 and 7 at paragraph 45 and paragraph 48 of this recommendation).

[79] The Board finds that the disclosure of Molnar-Kimber et al. would have led the POSITA to the use of an engineered HSV having a mutation in the gamma 34.5 gene alone for the treatment of any cell proliferative disorder susceptible to the oncolytic activity of said virus which necessarily includes, but is not limited to, the proven Ras-mutated tumor of Example 3. Although the POSITA would not necessarily recognize why the mutant virus used in Molnar-Kimber et al. demonstrates oncolytic activity, the proliferating cells of the tumor are inevitably unable to activate a PKR response as they are specifically sensitive to the mutant HSV which lacks PKR antagonizing function.

[80] In view of the above, Molnar-Kimber et al. discloses subject matter which, if performed, would necessarily result in infringement if a patent were to issue for the claimed subject matter and the Board finds that the disclosure requirement of anticipation has been met.

Enablement

[81] The disclosure of Molnar-Kimber et al. must enable a POSITA to carry out what is disclosed without undue burden.

[82] Molnar-Kimber et al. discloses the identity of an old and known mutant HSV having a mutation in the gamma 34.5 gene that is used in the disclosed viral therapy, provides clear teachings and specific guidance as to how to determine the susceptibility of a given tumor to the disclosed viral therapy (see pages 30 to 36 and pages 45 to 46) and provides specific guidance to the POSITA as to how to formulate and administer the compositions comprising the mutant HSV. Therefore, the Board finds that the skilled person would have been able to perform what has been disclosed in Molnar-Kimber et al. with some trial and error or routine experimentation but without undue burden.

[83] Therefore, the Board finds that Molnar-Kimber et al. discloses and enables the use of a mutant HSV for treating a mammal suffering from a disorder that falls into the scope of tumors and neoplasms having an elevated Ras activity or tumor and neoplastic cells susceptible to the oncolytic activity of the recited viruses and, thus, anticipates claims 3 and 28.

Toda et al. and Chahlavi et al.

[84] Toda et al. (*Hum Gene Ther* 9(15):217-2185) and Chahlavi et al. (*Neoplasia* 1(2):162-169) were respectively published on October 10, 1998 and June, 1999 and hence, were publicly available before the claim date and are citable under paragraph 28.2(1)(*b*) of the *Patent Act*. Both references disclose the use of G207, an engineered HSV-1 having the gamma 34.5 gene mutated so said gene is not transcribed, for killing human malignant cell lines *in vitro* and *in vivo*.

[85] With respect to the disclosure of Toda et al. and Chahlavi et al., the Applicant submits that the references do not disclose an effective amount of a pharmaceutical composition comprising a modified virus for use in treating Ras-mediated cell proliferative disorders and that the malignant cell lines disclosed are not inherently Ras-mediated cell proliferative disorders.

Disclosure

[86] Both references disclose the use of a mutant HSV-1 which falls within the scope of the proposed independent claims 3 and 28 to treat a cell proliferative disorder. However, there is no evidence in these references or on record that the particular tumor cell lines used in the killing assays were Ras-mediated tumor cell lines. This constitutes the principal difference between the disclosures of Toda et al. and Chahlavi et al. and the disclosure of Molnar-Kimber et al. presented above.

[87] The Board finds that the disclosure of Toda et al. or Chahlavi et al. would independently lead the POSITA to the use of an engineered HSV having a mutation in the gamma 34.5 gene for the clinical treatment of any human malignant mammary tumor or any human squamous cell carcinoma found to be susceptible to the oncolytic virus when tested *ex vivo*. According to the Applicant=s submissions and the instant description, only cells unable to activate a PKR response would be affected by an engineered HSV having a mutation in the gamma 34.5 gene which lacks PKR antagonizing function.

[88] Once again, the POSITA would not necessarily recognize why the mutant virus used in Toda

et al. and Chahlavi et al. demonstrates oncolytic activity. However, the proliferating cells of the tumors susceptible to the treatment of Toda et al. and Chahlavi et al. are inevitably unable to activate a PKR response as they are specifically sensitive to the mutant HSV G207 which lacks PKR antagonizing function. The POSITA taught by either Toda et al. or Chahlavi et al. would have understood that any human malignant mammary tumor or any human squamous cell carcinoma found susceptible to the G207 *ex vivo* could be treated and this, independently of any test result regarding the activation status of Ras in the cell proliferative disorder to be treated.

[89] However and unlike Roberts et al., the disclosures of Toda et al. and Chahlavi et al. are very specific with respect to the group of tumors treatable with the virus and there is no evidence that this specific group necessarily includes, as a subset, Ras-mediated cell proliferative disorders.

[90] Therefore, we cannot conclude that either Toda et al. and Chahlavi et al. independently discloses subject matter which, if performed, would necessarily result in infringement of the claims 3 and 28 if a patent were to issue for the claimed subject matter.

[91] In view of the above, the Board finds that Toda et al. and Chahlavi et al. do not anticipate claims 3 and 28.

Conclusions on Anticipation

[92] In view of the above analyses, we find claims 1 to 6, 8 to 10, 12 to 15, 17 to 20, 23, 24, 26 and 28 to 30 to be anticipated by the cited prior art. Claim 7, which was not in issue, and claims 11, 16, 21, 22, 25 and 27 are not anticipated.

QUESTION (2): IS THE SUBJECT MATTER OF CLAIMS 1 TO 6 AND 8 TO 30 OBVIOUS IN VIEW OF THE CITED PRIOR ART?

[93] In the event we are wrong on the issue of anticipation and because the prior art was a serious point of contention, we found it appropriate for the sake of completeness to consider whether the cited prior art, if not anticipatory, renders obvious the subject matter of the claims.

[94] In the second supplemental analysis, the Examiner considered that the subject matter of claims 1 to 6 and 8 to 30 would have been obvious on the claim date to a POSITA having regard to Roberts et al. and the common general knowledge in the art. Further, the Examiner considered that the subject matter of claims 3 and 8 to 30 would have been obvious on the claim date to a POSITA having regard to Molnar-Kimber et al. and the common general knowledge in the art.

[95] In response to the supplemental analysis, the Applicant submitted that the subject matter of the claims is inventive in view of the cited prior art.

Relevant Legal Authorities and Principles of Obviousness

[96] The statutory provision relevant to obviousness is found in section 28.3 of the *Patent Act* that states:

> The subject-matter defined by a claim in an application for a patent in Canada must be subject-matter that would not have been obvious on the claim date to a person skilled in the art or science to which it pertains, having regard to

> (a) information disclosed more than one year before the filing date by the applicant, or by a person who obtained knowledge, directly or indirectly, from the applicant in such a manner that the information became available to the public in Canada or elsewhere; and
>
> (b) information disclosed before the claim date by a person not mentioned in paragraph (a) in such a manner that the information became available to the public in Canada or elsewhere.

[97] In *Sanofi*, the Supreme Court of Canada set out a useful approach to follow in assessing obviousness:

> (1) (a) Identify the notional Aperson 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 Astate 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?

Applying the Legal Principles to the Facts of this Case

The Aperson skilled in the art@ and the relevant common general knowledge of that person as of November 12, 1999, the priority date of the instant application

[98] As previously found in paragraph 24 above, the POSITA is a medical virologist with experience in the field of oncolytic viruses.

[99] Regarding the relevant common general knowledge of that POSITA, the Applicant stated the following in the response to the second supplemental analysis:

> As a preliminary note, Applicant points out that the Examiner has not set out the common general knowledge that a person in this field would possess. Nor does the Examiner provide any documents to support her position on what the common general knowledge would be. Without this information it is impossible for Applicant to determine if there is a dispute between what the Examiner believes the common general knowledge to be and what Applicant believes the common general knowledge to be. Accordingly, Applicant cannot agree with the Examiner=s position regarding the relevant common general knowledge of the person skilled in the art.

[100] The following passages of the second supplemental analysis relate to what is considered common general knowledge by the Examiner:

> Notably, Roberts et al. do not specifically disclose that the virus is immunoprotected (claim 21), encapsulated in a micelle (claim 22) or pre-treated with a protease (claim 27). However, drawing upon the common general knowledge these features are considered to be well known options to the skilled person regarding method of administration of the virus. Furthermore, the entire specification is devoid of any working examples and the text is presented in a manner to indicate that the features of the claims are merely contemplated, desired elements drawn from the prior art.
>
> ...
>
> Molnar-Kimber et al. do not specifically disclose pharmaceutical formulations which comprise more than one type of virus (claim 8), more than two strains of virus (claim 9), an effective amount of a chemotherapeutic agent (claim 26 and 30), or wherein the virus has been pre-treated with a protease (claim 27). However, a skilled person would appreciate that such modifications of said pharmaceutical compositions fall within the scope of common general knowledge.

[101] Some of the features identified by the Examiner as common knowledge in the supplemental analysis are mentioned in the instant description in the following passages:

> The virus may be modified such that the virion is packaged in a liposome or micelle, or the proteins of the outer capsid have been mutated. [see page 7, lines 16 to 17]
>
> ...
>
> The virus may be a recombinant virus from two or more types of viruses with differing pathogenic phenotypes such that it contains different antigenic determinants thereby reducing or preventing an immune response by a mammal previously exposed to a virus subtype. Such recombinant virions can be generated by co-infection of mammalian cells with different subtypes of virus with the resulting resorting and incorporation of different subtype coat proteins into the resulting virion capsids. [see page 18, line 24 to page 19 line 2]
>
> ...
>
> The virus is preferably a virus modified to reduce or eliminate an immune reaction to the virus. Such modified virus are termed Aimmunoprotected virus@. Such modifications could include packaging of the virus in a liposome, a micelle or other vehicle to mask the virus from the mammals immune system. [see page 19, lines 16 to 19]
>
> ...
>
> When the virus is administered systemically to immunocompetent mammals, the mammals may produce an immune response to the virus. Such an immune response may be avoided if the virus is of a subtype to which the mammal has not developed immunity, or the virus has been modified as previously described herein such that it is immunoprotected, for example, by protease digestion of the outer capsid or packaging in a micelle. [see page 21, lines 16 to 21]
>
> ...
>
> It is further contemplated that the virus of the present invention may be administered in conjunction with or in addition to known anti-cancer compounds or chemotherapeutic agents. [see page 29, lines 24 to 26]

[102] The description disclosed, at least in part, the contemplated routes of administration and dosing requirements as follows:

> The route by which the virus is administered, as well as the formulation, carrier or vehicle, will depend on the location as well as the type of the neoplasm. A wide variety

> of administration routes can be employed. [see page 20, lines 14 to 16]
> ...
> Preferably, the effective amount is that amount able to inhibit tumor cell growth. Preferably the effective amount is from about 1.0 pfu/kg body weight to about 10^{15} pfu/kg body weight, more preferably from about 10^{2} pfu/kg body weight to about 10^{13} pfu/kg body weight. For example, for treatment of a human, approximately 10^{2} to 10^{17} plaque forming units (PFU) of virus can be used, depending on the type, size and number of tumors present. The effective amount will be determined on an individual basis and may be based, at least in part, on consideration of the type of virus; the chosen route of administration; the individual=s size, age, gender; the severity of the patient=s symptoms; the size and other characteristics of the neoplasm; and the like. [see page 28, lines 16 to 25]

[103] It is clear from page 3, lines 14 to 25 of the description that it was generally known that activated Ras plays a role in a significant proportion of all human tumors. Moreover, the Applicant made it clear at the hearing and in the response to the second supplemental analysis that it was a matter of routine experimentation to determine if the Ras pathway is activated in any particular neoplasm.

[104] Given the very brief and generic guidance provided by the instant description with regard to some of the features and elements found in the claims, the Board finds the following with respect to the common general knowledge as it relates to cell proliferative disorders, Ras activity in tumors and oncolytic viruses and their uses as of November 12, 1999, the claim date of the instant application:

- The POSITA knows the routinely used therapies, therapeutic agents and combinations thereof for treating cell proliferative disorders.

- The POSITA knows that the presence of an elevated Ras activity, as a result of a mutation or the activation of an upstream signaling element, is an inherent characteristic of a relatively high proportion of many types of human tumors and also knows how to test for Ras activity in any particular neoplasm.

- The POSITA knows the advantages of masking an oncolytic virus from the recipient immune system and the common techniques to achieve it.

- The POSITA knows how to formulate compositions comprising oncolytic viruses and how to choose between the different routes of administration.

- The POSITA knows that the dosing requirements of an oncolytic virus are determined on an individual basis and may be based on different considerations such as the type of virus; the type, size and numbers of tumors present; the chosen route of administration and the individual=s size, age and gender. The dosing requirements are also routinely assessed in clinical trials.

The inventive concept of the claims in question

[110] The Examiner identified the following as the inventive concept of the claims 1 to 6 and 8 to 30:

> The single general inventive concept which links the above claims is the use of a

> selected oncolytic virus to treat a Ras-mediated cell proliferative disorder/inhibit metastasis of a neoplasm having an activated Ras-pathway in a mammal that has been tested as having a Ras-mediated cell proliferative disorder prior to use of the selected oncolytic virus. [Emphasis in the original]

[111] The Applicant agreed with the Examiner=s assessment of the inventive concept of the claims in question.

[112] Bearing in mind our previous construction of the testing step, we find that the inventive concept of the claims is the use of a selected oncolytic virus to treat a Ras-mediated cell proliferative disorder or to inhibit metastasis of a neoplasm having an activated Ras-pathway in a mammal that has been tested as having a tumor or neoplasm showing an elevated Ras activity and a PKR that is unable to function or as having tumor or neoplastic cells susceptible to the oncolytic activity of the recited viruses prior to use of the selected oncolytic virus.

The differences between the Astate of the art@ and the inventive concept of the claims 1 to 6 and 8 to 30

[113] This necessarily requires a determination of what has been disclosed and taught in the cited prior art.

[114] For the purpose of anticipation, the Board already determined what has been disclosed and taught by Roberts et al. (paragraphs 54-61) and Molnar-Kimber et al. (paragraph 74).

[115] The Examiner acknowledged that Roberts et al. and Molnar-Kimber et al. do not disclose testing the neoplastic cells for Ras activation prior to the use of the known oncolytic viruses and that Roberts et al. does not explicitly identify Ras-mediated cell proliferative disorders as a subgroup of cell proliferative disorders susceptible to the treatment with the known oncolytic viruses.

[116] According to the Applicant, the specific treatment of a Ras-mediated proliferative disorder once it has been confirmed that a neoplasm is Ras-mediated, rather than the treatment of any cell proliferative disorder susceptible to the recited known oncolytic viruses, constitutes the difference between the matter cited as forming part of the Astate of the art@.

[117] In our view, the main difference resides in choosing, in the present claims, to define the proliferative disorder to be treated in terms of the discovery of a mechanism of action that rationalizes the known oncolytic activity of the known viruses.

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?

[118] Given that the discovery of the mechanism of action underlying the oncolytic activity of the known mutated viruses against tumors and neoplasms having an elevated Ras activity is not, by itself, patentable, the question is whether it was obvious as of November 12, 1999 that the recited mutant oncolytic viruses could be useful in treating Ras-mediated cell proliferative disorders/inhibiting metastasis of a neoplasm having an activated Ras-pathway in a mammal.

[119] According to the Applicant, the claims 1 to 6 and 8 to 30 are inventive over Roberts et al. and

the claims 3 and 8 to 30 are inventive over Molnar-Kimber et al. The Applicant provided the following arguments:

- There are advantages of confirming the presence of Ras activation in a neoplasm. Treatment options can be tailored by confirming the presence of Ras activation to specifically select an oncolytic virus that is known to act as an anti-neoplastic agent in Ras-activated cells. Tailoring treatment of a patient with a neoplasm saves time and money that can be squandered when a generalized treatment is utilized.

- Although susceptible tumor cells disclosed in Roberts et al. or Molnar-Kimber et al. may fall within Applicant=s definition of a Ras-mediated cell proliferative disorder, not all tumor cells disclosed in the prior art are Ras-activated tumor cells and neither Roberts et al. nor Molnar-Kimber et al. discloses or suggests testing the cells for Ras activation as is required by the claims.

- Roberts et al. encourages the use of any oncolytic virus to treat any cell proliferative disorder but fails to motivate one skilled in the art to confirm Ras activation prior to administration of the oncolytic virus that is selected to treat Ras-activated neoplastic cells.

- In contrast to the cells that are the subject matter of the claims 1 to 6 and 8 to 30, the tumor cells of Roberts et al. were treated with oncolytic viruses without regard for whether Ras was involved in tumorigenicity. Simply providing a list of tumor cells that can be killed with neoplastic viruses does not allow one of skill in the art to administer an oncolytic virus specifically selected for the treatment of a Ras-activated neoplasm as provided by the claims.

- Roberts et al. and Molnar-Kimber et al. encourage the use of mutant viruses to treat any cell proliferative disorder but fail to specifically describe the use of an oncolytic virus that kills the specific subset of Ras-activated neoplasms, in order to provide a personalized treatment for such a specific type of neoplasm.

- While it may be a matter of routine experimentation to determine if the Ras pathway was activated in any particular neoplasm, there is nothing in Roberts et al. or Molnar-Kimber et al. that suggests testing for Ras activation, much less testing for Ras activation in order to administer an oncolytic virus that will kill Ras-activated cells.

[126] We begin by addressing the ASetting the Stage for the Present Invention@ section of the Applicant=s submission in response to the second supplemental analysis. In this section, the Applicant put emphasis on the advantages noted above of selecting the candidates for the disclosed viral therapy based on the detection of Ras activity in the tumor present in the patient. In a nutshell, such a method of selecting candidates would advantageously spare precious time and resources by not using the recited mutant viruses with patients having a tumor previously tested as not mediated by Ras. However, what is claimed is the actual use of the known mutant viruses for the treatment of a subgenus of cell proliferative disorders. Moreover, at paragraph 37, we construed that the scope of the defined testing step is not limited to the detection of Ras activity but rather encompasses testing for tumors and neoplasms having an elevated Ras activity and a PKR that is unable to function, and also directly testing the susceptibility of tumor and neoplastic cells to the oncolytic activity of the recited viruses..

[127] It also appears that the Applicant considers that the recognition of specifically testing for a

Ras-mediated disease in order to provide personalized treatment for a specific type of neoplasm makes claims 1 to 6 and 8 to 30 inventive over the cited prior art since not all neoplasms are Ras-mediated. Again, what is claimed is not a method of selecting suitable patients for a given therapy but the use of compounds to treat a subgenus of cell proliferative disorders. It is not clear how the recognition of a subgroup of neoplasms among a broader group of neoplasms that are all susceptible to a given treatment is inventive simply because not all neoplasms are part of that subgroup. It is important to reiterate that the mere discovery of an inherent mechanism of action of a known therapy does not render the use of the known therapy inventive and it is not patentable.

[128] According to the Applicant=s argumentation, the step of confirming the presence of Ras activation confers advantages because if an oncolytic virus specific for Ras-activated neoplasms is administered to a patient that does not have a Ras-activated neoplasm, precious time and resources will be wasted. However, it is clear from the instant specification that the mutated viruses recited in the claims would show specific oncolytic activity against not only Ras-activated neoplasms but against any neoplasm unable to activate a PKR response. It appears that candidates susceptible to the oncolytic activity of the viruses would have been excluded by such a selecting step. Having that in mind, it is not apparent how the administration of the recited viruses to a patient who does not suffer from a Ras-activated neoplasm but who, nonetheless, suffers from a neoplasm unable to activate a PKR response that is susceptible to said viruses would translate into a waste of precious time and resources.

Roberts et al.

[129] The POSITA is aware that the characterization and identification of a given tumor precedes any treatment.

[130] Moreover, tumors or neoplasms previously tested for Ras activity or known as being Ras-mediated are not excluded from the treatment disclosed by Roberts et al.

[131] Therefore, it would have been obvious to use one or more of the mutated oncolytic viruses disclosed in Roberts et al. to treat a cell proliferative disorder or to inhibit a metastasis of a neoplasm in a mammal that has been tested as having a tumor or neoplastic cells susceptible to the oncolytic activity of the recited viruses, prior to the use of the selected oncolytic virus, including tumors characterized as Ras-mediated cell proliferative disorders.

Molnar-Kimber et al.

[132] Molnar-Kimber et al. exemplifies the use of a known engineered HSV-1 having the gamma 34.5 gene mutated for treating mice bearing a Ras-mutated murine fibroblast tumor in their peritoneum.

[133] Given the successful treatment of mice bearing Ras-mediated tumor cells disclosed in Molnar-Kimber et al., there is further motivation for the POSITA to test whether a given tumor is a Ras-mediated cell proliferative disorder prior to using the treatment disclosed in Molnar-Kimber et al.

[134] Therefore, we find that viewed without any knowledge of the alleged invention as claimed, it would have been obvious for the POSITA to use one or more known oncolytic HSV-1 viruses having a mutation in the gamma 34.5 gene to treat a Ras-mediated cell proliferative disorder or

to inhibit metastasis of a neoplasm having an activated Ras-pathway in a mammal that has been tested or known as having a tumor or neoplasm showing an elevated Ras activity or as having tumor or neoplastic cells susceptible to the oncolytic activity of the known oncolytic HSV-1 prior to use of the selected oncolytic virus.

[135] The features and elements that are found in the dependent claims but that are not specified in the inventive concept defined above are considered not inventive. These features and elements comprise the use of more than one strain of virus, the route of administration, the immunoprotection and the encapsulation of the virus, the dosing requirement, the pre-treatment of the virus with a protease, the addition of a chemotherapeutic agent. This is consistent with the generic guidance provided by the instant description with regard to such features and elements.

Conclusions on Obviousness

[136] Therefore we find the claims 1 to 6 and 8 to 30 obvious in view of Roberts et al. and the common general knowledge in the art and we independently find the claims 3 and 8 to 30 obvious in view of Molnar-Kimber et al. and the common general knowledge in the art. The obviousness of claim 7 was never in issue. It is worth noting that claim 7 is therefore the only claim that has not been found to be either anticipated or obvious.

QUESTION (3): DOES THE INSTANT SPECIFICATION PROVIDE PROPER AND SUFFICIENT DISCLOSURE FOR THE USE OF THE VIRUSES ENCOMPASSED BY THE SCOPE OF THE CLAIMS?

[137] The Examiner found that the claimed use is not soundly predicted because there is no demonstration of the use of any of the specific viruses recited in the proposed claims to selectively treat a Ras-mediated cell proliferative disorder and because there is no factual basis to support such use. Moreover, the Examiner found that the specification is not enabling as undue experimentation would have been required to practice the invention.

[138] To contextualize the Examiner=s above noted points, which apply to all of the claims, we point to the language of claim 7 since no prior art was cited against it. In claim 7, the Examiner considers that the viruses encompassed by the phrase Aone or more parapoxvirus orf viruses having a mutation in the OV20.0L gene, wherein the OV20.0L gene is not transcribed due to the mutation@ are not enabled and that there no factual basis to support their desired oncolytic activity.

Sound Prediction

[139] The Board finds that there is enough information in the specification to infer that the recited modified viruses would have the desired specific oncolytic activity. Further, the factual basis would lead the POSITA to conclude that said modified viruses would be useful for the treatment of Ras-mediated cell proliferative disorders wherein the proliferating cells are unable to activate a PKR response. The factual basis and reasoning that lead to this conclusion are as follows.

[140] Generally, as a factual basis, the specification discloses that:

$ PKR is inhibited in Ras-mediated cells;

$ PKR functions in normal cells to defend against viral infection; and,

$ viruses mutated to render them susceptible to PKR activity were known.

[4] Based on the factual basis, the specification discloses a line of reasoning that the mutated viruses would replicate unheeded in Ras-mediated tumor cells while sparing normal cells. As

for disclosure, the reasoning is explicitly articulated on page 6, lines 15 to 24 of the description:

> Accordingly, it has been found that viruses which have evolved certain mechanisms of preventing PKR activation are likely rendered replication incompetent when these same mechanisms are prevented or mutated. Mutation or deletion of the genes responsible for antagonizing PKR should prevent viral replication in cells in which the PKR activity is normal (i.e. normal cells). However, if infected cells are unable to activate the antiviral response mediated through PKR (i.e., Ras-mediated tumor cells), then these mutant viruses should replicate unheeded and cause cell death. Therefore, these mutant viruses can replicate preferentially in Ras-transformed cells where it is determined that PKR is unable to function.

Sufficiency of Disclosure

[5] The Board finds that the POSITA would be able to directly come to the claimed subject matter without having recourse to inventive ingenuity or undue experimentation.

[6] With regard to the modified viruses encompassed by the scope of the proposed claims, it is clear from the specification that such viruses were known and available at the publication date. Moreover, the specification identifies, for each type of virus, at least a gene that should be targeted by a mutation to prevent its transcription and hence, inhibits the mechanism of preventing PKR activation of the virus. We find that it is well within the capacity of the POSITA to produce mutated viruses functionally equivalent to those known in the art by targeting the described genes with additional or alternate mutations. The type and nature of mutations leading to the non-transcription of a given gene are well known in the art (e.g., a nonsense mutation that results in a premature stop codon). We also find that the skilled person could use routine techniques to test for a mutated virus= ability to lyse Ras-activated cells.

Conclusions on Disclosure

[7] Accordingly, the present claims are based on a properly supported sound prediction and the disclosure was adequately enabled.

QUESTION (4): ARE THE VIRUSES ENCOMPASSED BY THE SCOPE OF THE CLAIMS ADEQUATELY DEFINED?

[8] The crux of the Examiner=s concern is that the recited viruses are not adequately defined so as to be distinguishable from mutated viruses which have not been disclosed by the Applicant or already known in the art.

[9] The Board agrees with the Applicant=s submission that uses of known viruses are claimed in the instant application, not viruses *per se*. It follows that it is unnecessary to distinguish the mutated viruses from those already known in the art. Rather, the uses must be uniquely and unambiguously distinguished from the prior art. As long as the terms and expressions used to define the contemplated viruses are understood by the POSITA and permit to set clear bounds for the proposed claims, the proposed claims are definite with respect to the viruses.

[10] Each type of virus defined in the proposed claims (i.e., adenovirus, Herpes simplex virus, vaccinia virus and parapoxvirus) is understood by the POSITA. Each recited virus is further defined as having a mutation in a particular gene so the corresponding RNA is not transcribed. The proposed claims identify the target gene and the POSITA can readily comprehend and predict a large number of mutations that would result in the non-transcription of the target gene.

Conclusions on Clarity of Claims

[11] Based on the foregoing, we conclude that the POSITA would have no difficulty understanding and predicting what modified viruses fall within the scope of the proposed claims and thus, the proposed claims are definite and comply with subsection 27(4) of the *Patent Act*.

CONCLUSIONS

[12] The subject matter of proposed claims 1 to 6, 8 to 10, 12 to 15, 17 to 20, 23, 24, 26 and 28 to 30 is anticipated by Roberts et al. The subject matter of proposed claims 3 and 28 is anticipated by Molnar-Kimber et al. but not anticipated by Toda et al. and Chahlavi et al. Therefore, proposed claims 1 to 6, 8 to 10, 12 to 15, 17 to 20, 23, 24, 26 and 28 to 30 do not comply with paragraph 28.2(1)(*b*) of the *Patent Act*.

[13] The subject matter of proposed claims 1 to 6 and 8 to 30 is obvious in view of Roberts et al. and the common general knowledge in the art and the subject matter of proposed claims 3 and 8 to 30 is obvious in view of Molnar-Kimber et al. and the common general knowledge in the art. Therefore, proposed claims 1 to 6 and 8 to 30 do not comply with section 28.3 of the *Patent Act*.

[14] The instant specification provides sufficient support for the uses of the viruses encompassed by the scope of the proposed claims. The proposed claims are compliant with section 84 of the *Patent Rules* and the specification, insofar as it relates to proposed claims 1 to 30, is compliant with subsection 27(3) of the *Patent Act*.

[15] The proposed claims define distinctly and in explicit terms the subject matter of the invention for which an exclusive privilege or property is claimed and thus, proposed claims 1 to 30 comply with subsection 27(4) of the *Patent Act*.

[16] Only claim 7 was not found to be either anticipated or obvious by the examiner. It remains the only independent claim that, in view of the foregoing conclusions, is patentable. The dependent claims, to the extent they refer only to claim 7, are also patentable. Finally, independent claim 28 can be made patentable if limited to the virus of claim 7.

RECOMMENDATIONS

[17] In view of the above conclusions, the Board recommends that the Applicant be informed in accordance with paragraph 31(*c*) of the *Patent Rules*, that the following amendments, and only the following amendments, of the application are necessary for compliance with the *Patent Act* and *Patent Rules*:

Replacement of the claims currently on file with claims 1 to 30 proposed in the Applicant=s correspondence dated October 28, 2010 , wherein:

a) claims 1 to 6 are deleted;

b) claim 28 is restricted so as to limit the scope of the claim to the use of a modified parapoxvirus orf virus that has a mutation in the OV20.0L gene and wherein said gene is not transcribed due to the mutation; and

c) claims 7 to 30 are renumbered 1 to 24, and the claim dependencies are adjusted accordingly.

Marcel Brisebois	Mark Couture	Stephen MacNeil
Member	Member	Member

COMMISSIONER=S DECISION

[18] I concur with the findings and recommendation of the Patent Appeal Board. Accordingly, I invite the Applicant to make the above amendments, and only the above amendments, within three months from the date of this decision, failing which I intend to refuse the application.

Sylvain Laporte
Commissioner of Patents

Dated at Gatineau, Quebec
this 17th day of July, 2012