Commissioner’s Decision #1442

Décision de la Commissaire #1442

TOPIC:	G00 (Utility) O00 (Obviousness) J80 (Professional or Artistic Skill) K11 (Treatment)
SUJET:	G00 (Utilité) O00 (Évidence) J80 (Aptitudes professionnelles (artistiques)) K11 (Traitement)

Application No.: 2,416,408

Demande n°.: 2 416 408

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,416,408, having been rejected under subsection 30(3) of the *Patent Rules*, has subsequently been reviewed in accordance with paragraph 30(6)(*c*) of the *Patent Rules*. The recommendation of the Patent Appeal Board and the decision of the Commissioner are to refuse the application.

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INTRODUCTION

[1] This recommendation concerns the review of rejected patent application number 2,416,408, which is entitled "Methods for therapy of neurodegenerative disease of the brain" and is owned by Regents of the University of California. The outstanding defects to be addressed are whether the subject-matter of the claims on file lack utility, whether the subject-matter of the claims on file would have been obvious and whether the claims on file are directed to subject-matter that lies outside the definition of an invention. A review of the rejected application has been conducted by the Patent Appeal Board pursuant to paragraph 30(6)(*c*) of the *Patent Rules*. As explained in more detail below, our recommendation is that the application be refused.

BACKGROUND

The application

[2] Patent application 2,416,408, based on a previously filed Patent Cooperation Treaty application, was effectively filed in Canada on May 17, 2001 and published on January 31, 2002.

[3] The application relates to methods for chronic delivery of neurotrophins into mammalian brain and the treatment of neurodegenerative diseases. Neurotrophins are a family of proteins that play a positive role in the development, survival and regulation of neurons in mammals.

Prosecution history

[4] On July 22, 2014, a Final Action ("FA") was written pursuant to subsection 30(4) of the *Patent Rules*. The FA explained that the subject-matter of claims 1-11 on file would have been obvious, contrary to section 28.3 of the *Patent Act*; that the subject-

matter of claims 1-11 on file lacks utility, contrary to section 2 of the *Patent Act*, that the subject matter of the claims on file lacks support, contrary to section 84 of the *Patent Rules*; that the specification fails to correctly and fully describe the claimed invention and fails to enable the subject-matter of the claims on file, contrary to subsection 27(3) of the *Patent Act*; and that claims 12-14 on file are directed to subject-matter that lies outside the definition of an invention as defined in section 2 of the *Patent Act.*

[5] In a response to the FA ("R-FA") dated January 22, 2015, the Applicant provided arguments as to why the subject-matter of the claims on file was patentable and not open to objection for the reasons outlined in the FA.

[6] As the Examiner was not persuaded by the Applicant's arguments, the application was forwarded to the Patent Appeal Board ("the Board") for review, along with a Summary of Reasons ("SOR") maintaining the defects identified in the FA for the claims on file.

[7] In a letter dated February 25, 2016 (the "Acknowledgement Letter"), the Board forwarded the Applicant a copy of the SOR and offered the Applicant an opportunity to make further written submissions and/or attend an oral hearing. The Applicant did not respond to the Acknowledgement Letter.

[8] The present Panel was formed to review the application under paragraph 30(6)(*c*) of the *Patent Rules* and make a recommendation to the Commissioner as to its disposition. In a letter dated September 21, 2017 (the "Panel Letter"), we expressed the view that the alleged defects raised under section 84 of the *Patent Rules* (lack of support) and subsection 27(3) of the *Patent Act* (insufficiency of disclosure) do not raise considerations not already presented as a failure to comply with section 2 of the *Patent Act* with respect to claims 1 to 11. Similarly, we expressed the view that the support and sufficiency issues noted with respect to claims 12 to 14 would also be

more appropriately addressed as a possible lack of utility defect under section 2 of the *Patent Act*, given the factual context of the instant case.

[9] In the same letter, we considered whether the instant application does not comply with the *Patent Act* and *Patent Rules* with respect to defects other than those indicated in the FA, pursuant to subsection 30(6.1) of the *Patent Rules*. More specifically, we considered whether claims 12-14 on file lack utility (section 2 of the *Patent Act*), whether claims 12-14 on file would have been obvious in view of prior art cited against claims 1-11 (section 28.3 of the *Patent Act*) and whether claims 1-11 on file encompass a method of medical treatment (subject-matter that lies outside the definition of an invention as defined in section 2 of the *Patent Act*). Further, we set out our preliminary analysis and rationale as to why, based on the record before us, the subject-matter of the claims on file is useful, would have been obvious in view of the cited prior art and that the claims on file are directed to subject-matter that lies outside the definition of an invention as defined in section 2 of the *Patent Act*. Finally, we invited the Applicant to provide further written submissions in response to the Panel's preliminary review. The Panel Letter indicated that if the Applicant did not inform the Panel by October 6, 2017 of its intention to provide further submissions, the Panel would complete the review and provide its recommendation to the Commissioner without further communication.

[10] Since the Applicant did not reply to the Panel Letter, the Applicant's representative was contacted by phone. On November 10, 2017, the representative confirmed that the Panel Letter had been received and that no reply would be forthcoming.

ISSUES

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

i) whether the subject-matter of claims 1-14 on file lack utility, contrary to section 2 of the *Patent Act*;

ii) whether the subject-matter of claims 1-14 on file would have been obvious, contrary to section 28.3 of the *Patent Act*; and

iii) whether claims 1-14 on file encompass a method of medical treatment, a subject-matter that lies outside the definition of an invention as defined in section 2 of the *Patent Act.*

LEGAL PRINCIPLES AND PATENT OFFICE PRACTICES

Purposive construction

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

Utility

[13] Utility is part of the definition of "invention" in section 2 of the *Patent Act* which states that the claimed subject-matter must be "useful":

> ***invention*** means any new and useful art, process, machine, manufacture or composition of matter, or any new and useful improvement in any art, process, machine, manufacture or composition of matter.

[14] The utility requirement was described by the Supreme Court of Canada in *Consolboard Inc. v. MacMillan Bloedel (Saskatchewan) Ltd.*, [1981] SCR 504 (*Consolboard*), at p. 525:

> There is a helpful discussion in Halsbury's Laws of England, (3rd ed.), vol. 29, at p. 59, on the meaning of 'not useful' in patent law. It means "that the invention will not work, either in the sense that it will not operate at all or, more broadly, that it will not do what the specification promises that it will do". [emphasis added]

[15] The utility of the claimed subject-matter must be ascertained at its outset because being useful is a "condition precedent to an invention" (see *Consolboard* at p. 527). In *AstraZeneca Canada Inc. v. Apotex Inc.*, 2017 SCC 36 at para 53, the Supreme Court of Canada stated that the "[u]tility will differ based on the subject-matter of the invention as identified by claims construction" and outlined at paras 54 and 55 the approach that should be undertaken to determine whether a patent discloses an invention with sufficient utility under section 2 of the *Patent Act*:

> [54] To determine whether a patent discloses an invention with sufficient utility under s. 2, courts should undertake the following analysis. First, courts must identify the subject-matter of the invention as claimed in the patent. Second, courts must ask whether that subject-matter is useful — is it capable of a practical purpose (i.e. an actual result)?
>
> [55] The Act does not prescribe the degree or quantum of usefulness required, or that every potential use be realized — a scintilla of utility will do. A single use related to the nature of the subject-matter is sufficient, and the utility must be established by either demonstration or sound prediction as of the filing date (*AZT*, at para. 56).

[16] Therefore, utility must be established either by demonstration or sound prediction as of the Canadian filing date. Utility cannot be supported by evidence and knowledge that only became available after the filing date (see also *Apotex Inc. v. Wellcome Foundation Ltd.*, 2002 SCC 77 at para 56 (*AZT*), cited in the passage above).

[17] The doctrine of sound prediction allows establishing asserted utility even where that utility had not been fully verified as of the filing date. However, a patent application

must provide a "solid teaching" of the claimed invention as opposed to "mere speculation" (*AZT*, at para 69).

[18] The soundness of a prediction is a question of fact (*AZT*, at para 71). A sound prediction analysis should consider three elements (*AZT*, at para 70):

1) there must be a factual basis for the prediction;

2) the inventor must have at the date of the patent application an articulable and "sound" line of reasoning from which the desired result can be inferred from the factual basis; and

3) there must be proper disclosure of the factual basis and line of reasoning.

[19] These elements are assessed from the perspective of the POSITA to whom the patent application is directed, taking into account the CGK of the POSITA. Further, with the exception of CGK, the factual basis and the line of reasoning must be included in the patent application (see *Bell Helicopter Textron Canada Limitée v. Eurocopter, société par actions simplifiée*, 2013 FCA 219, at paras 152 and 153).

[20] Although a prediction does not need to amount to a certainty to be sound, there must be a *prima facie* reasonable inference of utility (*Mylan Pharmaceuticals ULC v. Eli Lilly Canada Inc.*, 2016 FCA 119, at para 55, *Gilead Sciences, Inc. v. Idenix Pharmaceuticals Inc.*, 2015 FC 1156, at para 251).

Obviousness

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

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

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

[22] In *Apotex Inc v. Sanofi-Synthelabo Canada Inc.*, 2008 SCC 61 at para 67 (*Sanofi*), the Supreme Court of Canada stated that it is useful in an obviousness inquiry to follow the following four-step approach:

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

[23] In the context of the fourth step, the Court in *Sanofi* accepted that it may be appropriate in some cases to consider an "obvious to try" analysis. For a finding that an alleged invention is "obvious to try", it must be more or less self-evident to try to obtain the alleged invention in advance of routine testing. The mere possibility that something might work is not sufficient.

[24] The Court in *Sanofi* listed the following non-exhaustive factors to be considered in an "obvious to try" analysis:

> (1) 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?

(2) 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?

(3) Is there a motive provided in the prior art to find the solution the patent addresses?

Statutory subject-matter and methods of medical treatment

[25] The definition of invention is set out in section 2 of the *Patent Act* which is cited above in the "Utility" section.

[26] Methods of medical treatment and surgery are not statutory subject-matter and are excluded from the definition of invention (see *Tennessee Eastman Co. v. Commissioner of* Patents (1970), 62 C.P.R. 117 (Ex. Ct.), aff'd [1974] S.C.R. 111).

[27] The Office's current practice with regard to the patentability of medical use claims is explained in Practice Notice 2015-01, entitled *Revised Examination Practice Respecting Medical Uses* (*PN 2015-01*). The Office's practice was revised during the course of prosecution of the present application between the sending of the FA and the SOR, in response to the decision in *AbbVie Biotechnology Ltd. v. Canada (Attorney General)*, 2014 FC 1251.

[28] According to *PN 2015-01*, medical use claims are generally permitted as long as they do not amount to a method of medical treatment. The determination of whether the subject-matter of a claim is statutory is based on the essential elements of the claim as determined by a purposive construction as outlined in *MOPOP*, §13.05.

[29] Further, where an essential element only serves to instruct a medical professional "how" to treat a patient rather than "what" to use to treat the patient, it must be determined whether the essential element prevents, interferes with or requires the professional skill of a physician. If the answer is "yes", the claimed use will be

considered to encompass a method of medical treatment that falls outside the definition of an invention as set out in section 2 of the *Patent Act*.

[30] However, *PN 2015-01* also recognizes that there may be instances where essential elements serve to instruct a medical professional "how" to treat a patient but are not considered to prevent, interfere with or require the professional skill of a physician. For example, essential elements that narrow treatment to a fixed dosage, a fixed dosage regimen or to a patient sub-population are not considered to point to a limitation of a physician's professional skill or judgment.

ANALYSIS

Purposive construction

The POSITA and the relevant CGK

[31] In the Panel Letter, we identified the POSITA as a composite person made up of individuals with different areas of expertise that includes a clinician and a scientist both specializing in neurodegenerative disorders related to defective, diseased or damaged neurons and experimental models thereof as well as a physician experienced in stereotaxic surgery of the brain.

[32] With respect to the CGK possessed by the POSITA, we considered that such a person would know:

- The pathophysiology of the common neurological diseases and disorders such as Alzheimer's disease and Parkinson's disease, including the type of neurons and regions of the brain commonly affected by neurodegeneration, and the different rat and non-human primate models of neurodegenerative disorders;

- The different neurotrophins, their positive role in the development and regulation of neurons in mammals and their promising potential to

manipulate the natural course of neuronal dysfunction after injury or to treat neurodegenerative conditions associated with nervous system diseases;

- Experimental methods for the local delivery of therapeutic agents to the central nervous system ("CNS") and their respective challenges, including *ex vivo* gene therapy using grafted transfected cells expressing the therapeutic agent of interest and direct *in vivo* gene therapy using different vector systems and genes expressing the therapeutic agent of interest, including the adeno-associated viral vector system as one of the most promising long-term transduction means for the CNS; and

- The processes related to stereotaxic surgery of the brain, including the generation of stereotaxic coordinates of target regions from magnetic resonance imaging ("MRI") scans and including the intracranial delivery of therapeutic compositions.

The problem to be solved and the proposed solution

[33] In the Panel Letter at page 9, we identified that the problem to be solved is "to provide a method for the successful chronic delivery of neurotrophins to target damaged CNS tissues with minimal side effects."

[34] With respect to the solution, we expressed the view in the Panel Letter at page 9 that the proposed solution is "to deliver a neurotrophin within 500μm of a targeted damaged neuron and no more than 10mm from another delivery site by *in vivo* direct gene transfer of the neurotrophin encoding transgene into cells neighboring the target neuron with a recombinant expression vector for expression of the desired neurotrophin *in situ*."

The essential elements that solve the identified problem

[35] Independent claims 1 and 12 read as follows:

> 1. Use of an adeno-associated virus (AAV) expression vector comprising a neurotrophin encoding transgene to ameliorate defective, diseased or damaged cholinergic neurons in the brain of a mammal, wherein said AAV expression vector is for *in vivo* direct delivery into one or more delivery sites within a region of the brain containing targeted cholinergic neurons, wherein each of said one or more delivery sites is within 500μm from a targeted neuron and no more than 10mm from another delivery site.
>
> 12. Use of an adeno-associated virus (AAV) expression vector comprising a neurotrophin encoding transgene to ameliorate defective, diseased or damaged dopaminergic neurons in the brain of a mammal, wherein said AAV expression vector is for *in vivo* direct delivery into one or more delivery sites within a region of the brain containing targeted dopaminergic neurons, wherein each of said one or more delivery sites is within 500μm from a targeted neuron and no more than 10mm from another delivery site.

[36] In the Panel Letter, although we noted that claim 1 specifically relates to cholinergic neurons and claim 12 specifically relates to dopaminergic neurons, we identified the following common essential elements in independent claims 1 and 12:

i) Use of an AAV expression vector comprising a neurotrophin encoding transgene to ameliorate defective, diseased or damaged neurons in the brain of a mammal;

ii) The *in vivo* direct delivery into one or more delivery sites within a region of the brain containing targeted neurons; and

iii) Each of the one or more delivery sites is within 500μm from a targeted neuron and no more than 10mm from another delivery site.

[37] We note that independent claims 2 and 13 are "Swiss" style medical use claims. The form of this type of claims is typically *the use of compound X in the manufacture of a medicament for the treatment of Y*. A literal interpretation may suggest that the

contemplated use is simply for the manufacture of a medicament but the format also permits an interpretation of the claim as relating to a medical use for the compound, the latter interpretation being in line with the jurisprudence (for example, see *GD Searle & Co v Canada (Minister of Health)*, 2008 FC 437, aff'd 2009 FCA 35; *Eli Lilly Canada Inc v Apotex Inc*, 2008 FC 142; and *Pfizer Canada Inc v Apotex Inc*, 2007 FC 971, aff'd 2009 FCA 8). Although the use recited in claims 2 and 13 is focused on the manufacture of a medicament, the claims specify the contemplated therapeutic use, the mode of delivery and the delivery location. In our view, the claimed uses go beyond utilizing an AAV expression vector comprising a neurotrophin encoding transgene to make a medicament; they further require the actual delivery of that medicament to ameliorate defective, diseased or damaged neurons in the brain of a mammal, according to the defined delivery location. Accordingly, we consider that although claims 2 and 13 are worded in the "Swiss" format, they essentially claim the same subject-matter as claims 1 and 12, respectively.

[38] Dependent claims 3-11 and 14 provide further limitations to the concentration of viral particles (claim 3), the unit dosage (claim 4), the delivery period of time (claim 5), the type of mammal and origin of the neurotrophin (claim 6), the nature of the neurotrophin (claims 7 and 8), the tissue location of the delivery sites (claims 9 and 10) and the neurodegenerative disorder to be treated by ameliorating the defective, diseased or damaged neurons (claims 11 and 14).

[39] As there has been no response from the Applicant, we therefore adopt for the purpose of this review the above identifications of the POSITA and the relevant CGK as well as the characterization of the problem to be solved, the solution and the essential elements.

Utility

[40] The following passage of the FA found on pages 2 and 3 relates to the lack of factual basis in the instant description supporting the utility of the claimed uses. It encapsulates well the utility issue before us with respect to claims 1 to 11 but also to claims 12 to 14, as the only significant difference between the claim sets is with respect to the specific type of targeted neurons (i.e., cholinergic vs. dopaminergic):

> [W]ith regard to the *in vivo* disclosure of the instant application, Example II teaches that the vector NGF-AAV was injected into the cholinergic basal forebrain. Following injection of NGF-AAV, gene expression was primarily manifested in neurons. Thus, the *in vivo* data disclosed in the instant application only demonstrates that gene expression was observed in the region of injection. It does not teach that expression of the NGF ameliorates defective, diseased or damaged cholinergic neurons. Thus, the application lacks a proper disclosure and factual basis for this subject matter.
>
> Finally, the applicant previously argued in their letter dated January 4, 2013 that success in the *ex vivo* milieu is not instructive for, or predictive of, success in the *in vivo* milieu. As previously stated in the office action dated July 22, 2013, although example II discloses *in vivo* injection of NGF into a single defined location in the rat brain, a specific protocol for *in vivo* delivery to sites containing targeted neurons for expression in or within 500 μm of a targeted neuron and no more than 10 mm from another delivery site was not disclosed beyond a literal reference. Thus, the utility of an *in vivo* use to deliver a neurotrophin to one or more delivery sites within a region of the brain containing targeted cholinergic neurons, wherein each of said one or more delivery sites is within 500 μm from a targeted neuron and no more than 10 mm from another delivery site is questionable. The instant application is considered to lack a factual basis for the subject matter of claims 1-11. The defect is maintained.

[41] In the Panel Letter, we stated that we understood that the Applicant submitted in the R-FA that the utility of the claims on file is established by demonstration or, alternatively, by sound prediction. We summarized Applicant's arguments in that regard as follows:

- Example II demonstrates that the delivery of an AAV expression vector comprising a neuron growth factor ("NGF") encoding transgene treats defective, diseased or damaged neuronal cells;

- The specification discloses the factual basis supporting the prediction that the *in vivo* delivery of a gene encoding a neurotrophin can be useful to ameliorate defective, diseased or damaged cholinergic neurons and is found in the disclosed examples, notably Example II and Example VI; and

- With respect to the line of reasoning, the POSITA will appreciate that the therapeutic response observed with the delivery of cells expressing NGF to the targeted damaged neurons should also be observed with *in vivo* gene delivery.

Demonstration of utility

[42] Having reviewed Example II and the application as whole, we stated in the Panel Letter at page 13 that "the biological effect of *in vivo* gene delivery of NGF in close proximity to neurons was not evaluated, let alone any and all neurotrophins encompassed by the scope of the claims" and expressed the view that that POSITA would not interpret the results presented in Example II as supporting a demonstration of the utility for the claimed subject-matter. The Applicant must therefore rely on a sound prediction to satisfy the utility requirement of section 2 of the *Patent Act*.

Sound prediction of utility

[43] We expressed the view in the Panel Letter that the factual basis disclosed in the application at least comprises that persistent expression of NGF by targeted neurons was achieved following *in vivo* gene transfer with an AAV vector comprising the coding sequence of NGF and that intraparenchymal delivery of fibroblasts genetically modified to produce NGF prevented a loss of expression that is associated with basal forebrain cholinergic neuron dysfunction.

[44] With regard to the line of reasoning, we expressed the view in the Panel Letter at page 14 that the line of reasoning submitted by the Applicant is a sound one:

> We consider that the POSITA would also understand that a neurotrophin is the key active molecule as any predicted amelioration of defective, diseased or damaged neurons would be the result of a neurotrophin's activity on the neurons, independent of how the neurotrophin ended up in close proximity to the targeted neurons. Given that the specification reveals that expression of NGF at the target site produces a relevant therapeutic response (i.e., prevention of spontaneous loss of expression of the p75 receptor) and given that expression of NGF at the target site was successfully achieved by *ex vivo* and *in vivo* gene delivery, we are of the view that the POSITA would consider the line of reasoning to be sound as there is a *prima facie* reasonable inference of utility derivable from the factual basis.
>
> With respect to dependent claims 11 and 14 that recite the treatment of specific neurodegenerative disorders (i.e., Alzheimer's disease and Parkinson's disease), we are of the view that the POSITA would consider that the line of reasoning remains sound as there is also a reasonable inference of utility to be drawn: ameliorating neurodegeneration within the population of neurons and regions of the brain commonly affected by the recited neurodegenerative disorders would be useful in the treatment of such disorders.

[45] We further expressed the view that both the necessary factual basis and the line of reasoning are adequately disclosed in the application and considered that the POSITA would have soundly predicted that an AAV expression vector comprising a neurotrophin encoding transgene would ameliorate defective, diseased or damaged cholinergic or dopaminergic neurons in the brain of a mammal when delivered to a region of the brain of a mammal containing the targeted neurons and would be useful in the treatment of neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease.

Conclusion on utility

[46] In view of the above, we are of the view that the subject-matter of claims 1-14 is useful and complies with section 2 of the *Patent Act*.

Obviousness

Identify the POSITA and the relevant CGK

[47] The POSITA and the relevant CGK have been set out above as part of the purposive construction of the claims.

Identify the inventive concept

[48] In the Panel Letter at page 15, we agreed with the FA that the inventive concept of claims 1-11 on file is "the use of an AAV expression vector comprising a neurotrophin encoding transgene to ameliorate defective, diseased or damaged cholinergic neurons in the brain of a mammal, wherein said AAV expression vector is for *in vivo* direct delivery into one or more delivery sites within a region of the brain containing targeted cholinergic neurons, wherein each of said one or more delivery sites is within 500 μm of a targeted neuron and no more than 10 mm from another delivery site". We noted as well that the Applicant did not indicate disagreement with this assessment in the R-FA. Other than the type of neuron involved (i.e. dopaminergic neurons instead cholinergic neurons), we also expressed the view that the inventive concept of claims 12-14 on file is essentially the same. Accordingly, we apply this inventive concept in the analysis below.

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

[49] The following three prior art references are cited in the opening section of the FA and referred to in the R-FA:

- Tuszynski et al., *Gene Therapy,* 3, Pages 305-314, 1996 (referenced as D1 in the FA);

- WIPO international patent application WO 97/39629 A1, published October 1997; inventors: Bohn et al. (referenced as D2 in the FA); and

- Bankiewicz et al., *Experimental Neurology,* 144, Pages 147-156, 1997 (referenced as D6 in the FA).

[50] Having reviewed their disclosure, we expressed the view in the Panel Letter that D1 is the most pertinent and closest cited prior art document. We summarized that D1 discloses or teaches:

- that neurotrophic factors in general and NGF in particular showed beneficial effects on basal forebrain cholinergic neuronal degeneration;

- that the delivery of NGF-secreting fibroblasts within 250µm of the targeted cholinergic neurons successfully prevent cholinergic neuronal degeneration; and

- that delivering the NGF-secreting fibroblasts at the proximity of the targeted neurons with accuracy is an important factor because NGF-secreting grafts that were placed at distances greater than 3mm from host target neurons did not prevent neuronal degeneration and NGF diffusion through brain parenchyma appears to be limited to no more than 10mm from a delivery site. Accordingly, the number of required graft sites would vary depending of the size of the affected regions.

[51] In light of the above teachings, we considered that D1 discloses the "proof of concept" that the delivery of a neurotrophin within the close vicinity of targeted neurons (i.e., as close as possible from the targeted neurons, including within 250µm) produces a beneficial biological response that is therapeutically relevant to neurodegenerative disorders and that D1 also teaches how to circumvent an observed low diffusion of a neurotrophin in the brain parenchyma with multiple contiguous delivery sites (no more than 3mm in the case of NGF) in order to cover large targeted regions of the brain if needed.

[52] We also considered that the disclosure of D6 was relevant as well with respect to the obviousness analysis. We understood that D6 identifies the AAV viral vector system as one of the promising vehicles for *in vivo* transfer of genes to the CNS in the

context of a gene therapy for a neurodegenerative condition (i.e., Parkinson's disease) and teaches that an initial experiment using injections of AAV vectors results in a limited and highly concentrated infection of the brain in close proximity to the injection site.

[53] With respect to the disclosure of the D1 and D6, the Applicant submitted in the R-FA that the teachings of D1 do not relate to *in vivo* gene therapy and *in vivo* delivery sites and that there is nothing in D6 to suggest that one or more delivery sites is within 500μm from a targeted neuron and no more than 10mm from another delivery site and that, to the contrary, D6 requires delivery to sites far removed from the targeted cell populations.

[54] For the reasons detailed in the Panel Letter, we expressed the view that although the teachings of D1 relate to the *ex vivo* gene delivery of neurotrophins and that an *ex vivo* gene delivery technique is different from an *in vivo* delivery gene delivery technique, we considered that the POSITA would have been aware that the local delivery of a genetically encoded therapeutic agent into a targeted region of the CNS is the underlying principle common to both delivery techniques. The POSITA would consider that the teachings of D1 with respect to the importance of accurately delivering the neurotrophin to the targeted neurons are also applicable to the *in vivo* gene delivery technique and would consider that it is otherwise common sense to deliver a therapeutic agent in the closest possible vicinity of a targeted cell population.

[55] With regard to the teachings of D6, we expressed the view that D6 does not teach away from delivering the AAV expression vector within the close vicinity of a targeted region of the brain. To the contrary, we considered that D6 teaches that the proximity of the delivery sites to the targeted cell population is an important factor in the context of *in vivo* gene delivery techniques.

[56] In light of the above, we are of the view that the differences between the "state of the art" and the inventive concept of claims 1-14 on file are that D1 does not teach delivery of a neurotrophin using *in vivo* direct gene delivery with an AAV expression vector and that D6, although its disclosure relates to the delivery of therapeutic agents into the CNS in general, does not specifically disclose or teach the delivery of a neurotrophin into the CNS.

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?

[57] In the Panel Letter, we acknowledged the Applicant's submissions that we understood to relate to the "obvious to try" analysis described in *Sanofi* and accepted that it is appropriate in the instant case to examine whether the differences between the "state of the art" and the inventive concept constitute steps which would have been "obvious to try" to the POSITA.

[58] In the context of one claimed embodiment, we framed the relevant question as whether it would have been more or less self-evident to the POSITA, based on the teachings of D1 and D6 and taking into account the CGK, that delivering a neurotrophin with an AAV expression vector into a region of the brain containing targeted cholinergic (claims 1-11) or dopaminergic (claims 12-14) neurons with accuracy (i.e., within 500µm from a targeted neuron) ought to work to ameliorate defective, diseased or damaged cholinergic or dopaminergic neurons and be useful for the treatment of Alzheimer's disease (claims 1-11) or Parkinson's disease (claims 12-14).

[59] Given that D1 discloses that the delivery of a neurotrophin within the close vicinity of targeted neurons (i.e. as close as possible from the targeted neurons, including within 250µm) produces a beneficial biological response that is therapeutically relevant to neurodegenerative disorders, we expressed the view in the Panel Letter that it would have been more or less self-evident to the POSITA that using an

alternate commonly known experimental gene therapy delivery technique or targeting a different population of neurons in a different region of the brain both ought to work. Although we considered that this assessment is largely determinative of the "obvious to try" inquiry in this case, we made the following observations with regard to the other non-exhaustive factors to be considered in an "obvious to try" analysis:

- it appeared to us that there are a finite number of identifiable predictable solutions known to the POSITA for the chronic local delivery of therapeutic agents to the CNS and we considered that among the known vector systems for *in vivo* gene transfer, the AAV vector system was one of the most promising long-term transduction means for the CNS; and

- With respect to the extent, nature and amount of effort required to achieve the invention , we considered that the POSITA is familiar with the techniques used to construct AAV vectors and the use thereof in the context of *in vivo* gene transfers and noted that the instant description does not appear to disclose any teachings regarding the production of suitable AAV vectors for *in vivo* gene transfers or regarding the stereotaxic delivery of such vectors over and above that which is CGK or taught by cited prior art documents.

[60] With regard to another embodiment of the subject-matter defined in independent claims 1 and 12 which encompasses multiples delivery sites, we expressed the view in the Panel Letter that it would have been more or less self-evident to the POSITA that this embodiment ought to also work because both D1 and D6 teach how to circumvent an observed low diffusion of a neurotrophin in the brain parenchyma with multiple contiguous delivery sites in order to cover large targeted brain regions if needed.

[61] As for the dependent claims 3-10 on file, we did not consider that an inventive step would have been required from the POSITA in respect of their further limitations to

a specific concentration of neurotrophin encoding viral particles (claim 3), a specific dosage volume (claim 4), a specific period time for the delivery (claim 6), the specific species (claim 6), a specific neurotrophin (claims 7 and 8), or the specific targeted region of the brain (claims 9 and 10).

Conclusion on obviousness

[62] In view of the above and in absence of response from the Applicant, we are of the opinion that the subject-matter of claims 1-14 on file would have been obvious at the claim date to the POSITA in view of the teachings of D1, D6 and the relevant CGK, contrary to section 28.3 of the *Patent Act*.

Subject-matter

[63] In the Panel Letter we noted that the analysis in the FA as to whether the subject-matter of claims 12-14 amounted to a method of medical treatment was conducted as per an outdated Practice Notice (*Examination Practice Respecting Medical Uses*, PN 2013-04). The Panel Letter also stated that under the current practice outlined in *PN 2015-01*, the inclusion of an essential element that serves to instruct a medical professional "how" to treat a patient is not necessarily determinative of the question of whether a claimed use encompasses a method of medical treatment; it must be determined whether an essential element prevents, interferes with or requires the professional skill of a physician. In other words, the relevant inquiry in the instant case is not whether one of the essential elements is statutory but rather whether any one of the identified essential elements prevents, interferes with or requires the professional skill of a physician.

[64] The Panel Letter acknowledged the Applicant's submission that the use of an AAV expression vector comprising a neurotrophin encoding transgene is an essential element. For the reasons detailed in the Panel Letter, we considered that the claimed essential elements of intracranially delivering the contemplated AAV expression vector comprising a neurotrophin encoding transgene within 500μm from a targeted neuron and no more than about 10mm from another delivery site entails a level of precision that requires stereotaxic surgery of the brain and hence, a surgical step and the professional skills of a physician.

Conclusion on subject-matter

[65] In view of the above, we are of the opinion that the claims on file are directed to subject-matter that falls outside the definition of an invention as set out in section 2 of the *Patent Act*.

RECOMMENDATION OF THE BOARD

[66] We recommend that the application be refused on the basis that the subject-matter of claims 1-14 on file would have been obvious, contrary to section 28.3 of the *Patent Act*, and claims 1-14 on file encompass a method of medical treatment, subject-matter that lies outside the definition of an invention as defined in section 2 of the *Patent Act*.

Marcel Brisebois Member	Ed MacLaurin Member	Lewis Robart Member

DECISION

[67] I concur with the findings of the Patent Appeal Board and its recommendation that the application should be refused because the claims on file would have been obvious contrary to section 28.3 of the *Patent Act* and the claims on file encompass a method of medical treatment a subject-matter that lies outside the definition of an invention as defined in section 2 of the *Patent Act*.

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

Johanne Bélisle
Commissioner of Patents
Dated at Gatineau, Quebec,
this 2nd day of March , 2018