Commissioner’s Decision #1381

Décision du Commissaire #1381

TOPIC: O00

SUJET: O00

Application No.: 2,513,249

Demande n°.: 2,513,249

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,513,249, 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 Board and the decision are as follows:

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INTRODUCTION

[1] This decision deals with the review of the rejection of patent application number 2,513,249, entitled "Method for *In Vivo* Regulation of Cardiac Muscle Contractility", filed on January 12, 2004 by the Applicant, The Regents of the University of California. The application was rejected on the grounds that the claimed invention is obvious, contrary to section 28.3 of the *Patent Act*.

BACKGROUND

[2] The present application relates to a method for treatment of congestive heart failure (CHF), a chronic and progressive disease in humans. Over time, the heart muscle in patients suffering from CHF loses its ability to contract and pump blood at a rate sufficient to meet the body's requirements. The claimed invention treats CHF by restoring levels of a molecule associated with the disease through genetic alteration of heart muscle cells, the result being improved muscle contractility and cardiac performance.

[3] Prior to the filing of the present application, adrenaline-like drugs had been used to treat CHF by stimulating heart muscle activity, but no long-lasting therapy had been developed that addressed the underlying condition.

[4] The present application discloses a long-lasting gene therapy method that restores depleted *in vivo* levels of an enzyme known as "sarco/endoplasmic reticulum Ca2+ ATPase" (SERCA2) that is associated with CHF. The therapy uses a man-made viral vector, an "adeno-associated virus" (AAV), to carry a new copy of a polynucleotide that encodes the SERCA2 enzyme into damaged heart muscle cells. The viral vector can infect damaged heart muscle cells and is able to insert the new SERCA2-encoding polynucleotide into the DNA of the damaged cells, but is not able to replicate inside it. When a sufficient number of damaged heart muscle cells are "transduced" in this manner, SERCA2 enzyme levels are restored and the diseased heart as a whole is again able to contract with adequate force.

CASE HISTORY

[5] A chronology of key events is set out below:

Date	Event
January 12, 2004	Application filed
February 8, 2013	Final Action issued
July 11, 2013	Response to Final Action received
December 20, 2013	Application transferred to Patent Appeal Board (PAB)
June 27, 2014	Panel's Initial Review letter
September 24, 2014	Applicant's response to Initial Review letter
October 8, 2014	Hearing
October 15, 2014	Applicant's first post-hearing submission
December 15, 2014	Panel's post-hearing letter
January 9, 2015	Applicant's second post-hearing submission

[6] As indicated above, the application was rejected in a Final Action on February 8, 2013 because the four claims on file were considered obvious in view of a prior art publication. In response to the Final Action, the Applicant amended the claims and submitted that the invention was non-obvious. A Summary of Reasons (SOR) was prepared and forwarded to the Board along with the rejected application because the Examiner maintained that the invention was obvious.

[7] This Panel was established and, during the course of our initial review of the rejected application, certain issues requiring clarification were identified. The Panel noted that the Final Action provided a limited characterization of the common general knowledge of the skilled person and that the obviousness analysis did not fully account for relevant factors (the so-called "obvious to try" factors as set out in the case law). The Applicant was notified of these issues in a letter dated June 27, 2014 and was also informed that the

claims would be construed in accordance with the latest Office guidance on claim construction (*Examination Practice Respecting Purposive Construction*; PN2013-02). A hearing was scheduled and the Applicant was offered the opportunity to provide, in advance of the hearing, a written response addressing the issues identified during the initial review.

[8] On September 24, 2014 the Applicant responded to the Initial Review letter and provided written submissions consisting of arguments supported by a declaration. The Applicant also submitted a proposed claim set to address the obviousness defect by further clarifying the scope of the claims.

[9] The hearing was held on October 8, 2014, after which time the Applicant further augmented its position as follows. A first post-hearing submission was received from the Applicant on October 15, 2014 and included a declaration from one of the inventors as well as scientific articles. The Panel considered that this submission raised new issues, including whether a new prior art reference was relevant to the obviousness assessment. Accordingly, the Panel sent a letter on December 15, 2014. The Applicant's second post-hearing submission was received on January 9, 2015. The Applicant maintained that the invention was non-obvious and provided a new set of proposed claim amendments to further clarify the scope of the claims.

LEGAL PRINCIPLES

Claim Construction

[10] A purposive construction of the claims precedes patentability considerations. It determines the meaning and scope of the claims from the perspective of the notional skilled person who possesses the common general knowledge in the pertinent art field: *Free World Trust v Électro Santé Inc*, 2000 SCC 66, at paras 44-55 [*Free World Trust*]. During purposive construction, the elements of the claimed invention are identified as essential or non-essential: *Free World Trust* at para 31. According to the *Examination Practice Respecting Purposive Construction* (PN2013-02), the essential elements of a claim are those elements that contribute to the proposed solution to the problem identified in the application.

Obviousness

[11] Section 28.3 of the *Patent Act* sets out the information that may be considered in assessing whether a claim is obvious:

> 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.

[12] A four-step approach for assessing obviousness was set out by the Supreme Court of Canada in *Apotex Inc v Sanofi-Synthelabo Inc*, 2008 SCC 61 [*Sanofi*]:

> (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?

[13] At the fourth step the Court indicated that an "obvious to try" enquiry might be appropriate in areas of endeavour where advances are often won by experimentation, such as the pharmaceutical industry. A non-exhaustive list of factors to be taken into consideration is proposed at paragraphs 69 and 70 of *Sanofi*:

> (1) Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified 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?

(4) What is the course of conduct which was followed which culminated in the making of the invention?

[14] In *Apotex Inc v Pfizer Canada Inc*, 2009 FCA 8 at para 29 [*Pfizer*], the Federal Court of Appeal rejected a "worth a try" standard and clarified that the correct approach under the *Sanofi* enquiry is "obvious to try", where the word obvious means "very plain". The court in *Pfizer* stated that "an invention is not made obvious because the prior art would have alerted the person skilled in the art to the possibility that something might be worth trying. The invention must be more or less self-evident." In *Pfizer Canada Inc v Novopharm Inc*, 2009 FC 638 at para. 56 the Federal Court indicated that an invention is "only obvious if the skilled person has good reason to pursue 'predictable' solutions that provide a 'fair expectation of success'".

[15] The question of obviousness is not to be approached with the benefit of hindsight because "it is far too easy to see how the alleged invention could have been arrived at, even easily, once it has been done": *Janssen-Ortho Inc v Novopharm Ltd*, 2006 FC 1234 at para 113, aff'd 2007 FCA 217 [*Janssen-Ortho*] (see also *The King v Uhlemann Optical Co* (1951), [1952] 1 SCR 143 at 152 on the same point).

[16] It bears repeating that the obviousness inquiry is to be taken from the perspective of the ordinary skilled person: *Beloit Canada Ltée/Ltd. v. Valmet Oy* (1986), 8 CPR (3d) 289 (FCA) [*Beloit*].

THE ISSUE

[17] The issue is whether claims 1-4 are obvious.

ANALYSIS

Claim construction

The person skilled in the art

[18] In the Final Action, the person skilled in the art was identified as "a clinical research cardiologist having knowledge of mouse models of human cardiac diseases as well as knowledge of human clinical trials based on said mouse models."

[19] In the Applicant's Written Submissions dated September 24, 2014 it was submitted that this identification was incomplete and that "the POSITA [person of skill in the art] would also have knowledge of gene therapy protocols (including the various vectors utilized in such protocols) and have an understanding of the challenges associated with such protocols". We agree and therefore further characterize the skilled person in such terms.

The relevant common general knowledge (CGK) of the person skilled in the art

[20] The common general knowledge (CGK) takes into account the prosecution history, statements in the description, the Applicant's submissions and supplied declarations. It is also assessed based on information disclosed in certain relevant scientific publications that appear to have been widely read at the relevant date, including:

- W.H. Dillmann, *Changing the cardiac calcium transient: SERCA2 overexpression versus phospholamban inhibition*, in *Molecular Approaches to Heart Failure Therapy*, pp. 69-75, G. Hasenfuss et al. (eds.), Springer-Verlag Berlin Heidelberg, 2000 [*Dillman* review article].

- D.C. White and W.J. Koch, *Myocardial Gene Transfer*, Current Cardiology Reports, 3: 37-42, 2001 [*White*].

- J.M. Isner, *Myocardial Gene Therapy*, Nature, 415:234-239, 2002 [*Isner*].

- Svensson et al., *Efficient and Stable Transduction of Cardiomyocytes After Intramyocardial Injection or Intracoronary Perfusion With Recombinant Adeno-Associated Virus Vectors*, Circulation 99: 201-205, 1999 [*Svensson*].

[21] There are three aspects of the CGK that warrant consideration: 1) the nature of CHF; 2) what was commonly known about gene therapy; and 3) the ability of adeno-associated virus (AAV) vectors to insert, or "transduce", genes into heart muscle cells.

The nature of CHF

[22] With respect to the nature of CHF, the CGK includes the following:

- CHF is a chronic, progressive disease for which no long-term solution was known (para 6 and 18 of the description).
- There were at least three strategies for long-term treatment of CHF, one of which involved using SERCA2-encoding polynucleotides delivered using a viral vector (para 13 of the description; *Isner* p. 236; *White* p. 40; *Dillmann* review article p. 69).
- The known association between CHF and SERCA2 led to the widely postulated theory that abnormalities in cardiac muscle contractility are directly linked to impaired SERCA2 activity (paras 5-13 of the description; *Dillmann* review article).
- Studies in neonatal heart cells indicated that a compensatory effect could be identified when a SERCA2-encoding polynucleotide was introduced into the cells *in vitro* (*Dillmann* review article p. 72).
- No clinical trials based on any of the strategies had been conducted on humans; all work was pre-clinical experimentation involving rodent models (para 13 of the description; *Isner* p. 236; *White* p. 40; *Dillmann* review article).
- There were various known reproducible experimental rodent models that were considered acceptably predictive of human CHF conditions (para 71 of the description).

Gene therapy

[23] With respect to gene therapy, the CGK includes the following:

- Gene therapy involves delivering a therapeutic polynucleotide to cells using various means, one of which is infection of cells using a virus carrying the polynucleotide. This is called "transduction" (*White* p. 37).

- Gene therapy is an unpredictable art (para 8 of the *Jaski* declaration, *infra*).

- Non-invasive means (i.e., infusion) for introduction of gene therapy vectors into target tissue is preferred over direct injection into the target tissue for long-term therapy in order to avoid loss of gene expression and inflammation at the site of injection (paras 11, 18 and 69 of the description).

- Genes encoding proteins or enzymes that must remain inside a cell (such as SERCA2) to achieve a biological effect must be delivered to a relatively large target population of cells to correct the underlying pathogenetic defect (*Isner* p. 234).

- Various gene therapy viral vectors were known, including adenoviral vectors (AdV) and adeno-associated viral vectors (AAV). Each has advantages and disadvantages (paras 45-50 of the description; *White* p. 37, *Isner* p. 236-237).

- AdV vectors are able to efficiently transduce mature heart muscle cells and can be produced in highly concentrated form. However, they are of limited therapeutic value because patients develop an immune response to the virus and the duration of gene expression is limited (*Isner* p. 236; *White* p. 37).

- AAV vectors are able to stably transfect heart muscle cells but are less likely to cause patients to develop an immune reaction (*White* p. 37).

- AAV cannot replicate on its own; it requires certain "replication-helper" functions to be provided inside the cell in order for it to package therapeutic polynucleotides into infectious viral particles. AAV replication-helper function can be provided through various means, including through the use of adenoviral helper virus, certain specialized genetic constructs, and using adenoviral helper virus-free systems; the

latter avoids contamination of AAV vector preparations with adenovirus (paras 48, 49 and 51 of the description).

The ability of AAV vectors to transduce genes into heart muscle cells

[24] In relation to the ability of AAV vectors to transduce genes into heart muscle cells, the CGK includes the following:

- Efficient transduction (50%) of heart muscle cells *in vitro* can be achieved with the addition of a small amount of adenovirus to boost efficiency (*Svensson* p. 202).
- *In vivo* transduction efficiency of AAV in mice hearts can be 25% relative to that obtainable with adenovirus (*Svensson* p. 204).
- Mice hearts can be transduced at 50% efficiency with a reporter transgene when they have been removed from the body (i.e., *ex vivo*, rather than *in vivo*) and held at low temperature (*Svensson* p. 204).
- The review article by *White* (p. 37) states that "the efficiency of transfection [with AAV] appears to be significantly lower than that of adenovirus" and "the peak efficiency was approximately 25% of that of a similar dose of adenovirus." The *Isner* review article indicates (p. 237) that AAV has been shown to be able generate widespread transduction of cells.
- The expression efficiency of the AAV with target transgenes is consistent and well known in the art. This leads to the expression of the transgene in about 50% of heart muscle cells (para 122 of the description).

The problem and solution that the invention addresses

[25] Our Initial Review letter indicated that the problem appears to relate to improved methods for regulating cardiac muscle contractility for the treatment and control of the progression of CHF. However, the Applicant submitted that the problem proposed by the Panel was too broad because it fails to exclude prophylaxis. On this point there was also disagreement between the Examiner and the Applicant in relation to the claim language.

[26] During prosecution the Applicant submitted that the expression "for treating human heart failure associated with a decline in endogenous SERCA2 activity" excludes any prophylactic use of an AAV vector encoding SERCA2. In contrast, the SOR maintained that the invention encompasses both prophylactic and restorative treatments.

[27] Although a broad dictionary-based interpretation of the term "treating" can encompass prophylaxis, having reviewed the record in this case, we agree with the Applicant that the skilled person would not view a solution to a prophylaxis problem as necessarily being one that restores function lost due to established disease. Here the solution proposed and the invention claimed is to "replace normal endogenous SERCA2 activity" such that there is an "improvement of cardiac performance" (emphasis added) as compared to pre-transduction over the long-term, i.e., "detectable at 4 weeks or more post administration." Prophylactic treatment of a non-diseased heart is thus not within the scope of the invention because it would neither replace lost SERCA2 activity nor improve cardiac performance.

[28] The solution proposed by the Applicant relates to the use of an AAV vector encoding SERCA2 to *restore* cardiac function and thereby treat human heart failure associated with a decline in endogenous SERCA2 activity in a subject with *pre-existing* disease. Prophylactic treatment does not form part of the solution.

Representative claim

[29] Claim 1 is representative of claims 1-4 under review:

> 1. Use of a SERCA2 encoding polynucleotide in the preparation of a medicament for treating human heart failure associated with a decline in endogenous SERCA2 activity, wherein the medicament is adapted for infusion into the subject's heart and transduction into failing cells thereof via an adenoviral helper virus-free adeno-associated viral (AAV) vector encoding the SERCA2 polynucleotide for expression of a therapeutically effective amount of SERCA2 wherein about 50% of affected cardiac cells express SERCA2 to replace normal endogenous SERCA2 activity as demonstrated by an increase from pre-transduction levels in the speed of systolic contraction or diastolic relaxation in the subject's heart detectable at 4 weeks or more

post administration, wherein an increase in either speed, or both, is indicative of an improvement of cardiac performance.

The claims are directed to medical uses

[30] The language of claim 1 is consistent with the phrasing of a "Swiss-type" medical use claim. In this instance claim 1 defines the use of a SERCA2 encoding polynucleotide, in the preparation of a medicament, wherein the medicament is intended for treating human heart failure associated with a decline in endogenous SERCA2 activity. A literal interpretation may suggest that the use in claim 1 of a SERCA2 encoding polynucleotide is simply for the manufacture of a medicament.

[31] In *Novartis Pharmaceuticals Canada Inc v Cobalt Pharmaceuticals Company*, 2013 FC 985, para. 101 the Federal Court indicated that in that case the "artificial nature" of Swiss-type claims should be disregarded and that the "real subject matter of the claim" should instead be considered.

[32] In this case, the skilled person would similarly understand that the real subject matter of claim 1 relates to the medical use of a polynucleotide, and this is how we construe claim 1.

The essential elements of claim 1

[33] For the reasons set out below, a purposive construction of claim 1 indicates that the following elements are essential:

(i) use of a SERCA2-encoding polynucleotide;

(ii) for treating a human subject;

(iii) with existing heart failure associated with a decline in endogenous SERCA2 activity;

(iv) by infusion;

(v) via an adeno-associated viral (AAV) vector;

(vi) the AAV vector is adenoviral helper virus-free;

(vii) about 50% of affected cardiac cells express SERCA2 to replace normal endogenous SERCA2 activity as demonstrated by an increase from pre-transduction levels in the speed of systolic contraction or diastolic relaxation in the subject's heart;

(viii) that is detectable at 4 weeks or more post administration;

(ix) wherein an increase in either speed, or both, is indicative of an improvement of cardiac performance.

[34] The use of a SERCA2-encoding polynucleotide is essential because the proposed solution is based on the use of such a polynucleotide in order to provide long-lasting restoration (i.e., at 4 weeks or more post-administration) of the SERCA2 enzyme. Ultimately, humans are the targets of the proposed therapy.

[35] As indicated above at paras 25-28, the proposed solution does not include prophylaxis. It relates to treating subjects with pre-existing CHF.

[36] Delivery of the SERCA2-encoding polynucleotide by infusion is an essential element of the claim because the CGK and the description indicate that delivery by that means avoids triggering inflammation at the site of delivery and is required in the context of long-term therapy (i.e., four weeks or more) in order to efficiently transduce a sufficient number of heart cells through a limited number of administrations (paras 11 and 18 of the description).

[37] The description gives considerable attention to AAV vectors and an adenoviral helper virus-free AAV vector system in particular, indicating that these elements are essential. The examples further indicate that such a vector system was in fact successfully used to restore SERCA2 activity on a long-term basis in a mouse model of CHF: very significant increases in all the contractile parameters were obtained in hearts of the mouse model used; contractile functions were all returned towards the normal range (para 123).

[38] In order to ameliorate contraction of the whole of the diseased organ, a relatively large number of affected heart muscle cells, i.e., about 50%, must be transduced to express SERCA2 and thus restore normal enzyme activity.

Claim 2

[39] The only other independent claim, claim 2, is a claim that does not adopt the Swiss-type medical use format but instead directly claims the use of a SERCA2 polynucleotide. Apart from having a different format, the claimed use is otherwise the same as that of claim 1 and is construed to have the same essential elements.

Dependent claims 3-4

[40] Claims 3 and 4 depend, respectively, on claim 1 and 2. Each is drawn to one of the two alternative indicators of improved cardiac performance that are mentioned in element (vii) of claim 1, i.e., increased speed of systolic contraction or increased speed of diastolic relaxation of the subject's heart muscle.

The *Sanofi* four-step approach to obviousness

Step 1: Identify the notional "person skilled in the art" and the common general knowledge of that person

[41] The skilled person and their common general knowledge have been identified at paras 18-24.

Step 2: Identify the inventive concept of the claim in question or if that cannot readily be done, construe it

[42] The Final Action states that "[t]he inventive concept of the claims is the use of an adeno-associated viral vector encoding the SERCA2 polynucleotide in a medicament adapted for infusion into a human heart to improve cardiac performance of a heart suffering from heart failure wherein 50% of the affected cardiac cells express SERCA2."

[43] In its submissions, the Applicant similarly indicated that "the inventive concept relates to use of an AAV vector encoding SERCA2 to restore cardiac function and thereby treat human heart failure associated with a decline in endogenous SERCA2 activity in a subject previously diagnosed with decreased contractility, wherein the medicament is for infusion into the subject's heart and transduction into failing cells thereof for expression of a

therapeutically effective amount of SERCA2 wherein about 50% of affected cardiac cells express SERCA2."

[44] In our view, it is apparent from a reading of the specification as a whole that, in this case, the inventive concept of claim 1 and claim 2 is the combination of essential elements identified above at para 33.

[45] No further inventive concept(s) for the claims were identified in the Final Action, nor do the submissions from the Applicant provide an indication of any additional distinguishing features in the claims. This inventive concept applies to claims 1 and 2. As noted previously, dependent claims 3 and 4 are narrower in scope, as they are limited to each of the two alternative measures of improvement in cardiac performance set forth in claims 1 and 2.

Step 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

[46] There are two prior art publications on record. The first is the *Fraley et al.* reference (*Fraley*) that was identified in the Final Action:

> Fraley, *et al., Sustained Sarcoplasmic Reticulum Ca2+-ATPase 2A Transgene Expression Mediated by AAV Results in Improved Contractility in a Mouse Model of Decreased Cardiac Function*, *Circulation*, vol. 106, November 5, 2002, Page II-31.

[47] The second prior art publication on record came to our attention as the result of the Applicant's first post-hearing submission dated October 15, 2014. The Panel considered that this submission raised new issues, including whether a new prior art reference was relevant to the obviousness assessment. The new prior art reference is the *Miyamoto* reference and was put on record in the Panel's post-hearing letter dated December 15, 2014:

> Miyamoto *et al., Adenoviral gene transfer of SERCA2a improves left-ventricular function in aortic-banded rats in transition to heart failure*, *Proc Natl Acad Sci*, vol. 97: 793-798, 2000.

Fraley

[48] *Fraley* is an abstract taken from the proceedings of a scientific conference. It is co-authored by Dr. Dillmann, one of the inventors of the present invention. In general, it discloses that favourable prophylactic results were obtained when a mouse model for CHF was administered an AAV-SERCA2 vector and then later tested for protection against development of decreased heart contractility.

[49] One difference between *Fraley* and the inventive concept of claims 1 and 2 lies in the timing of administration of an AAV vector encoding SERCA2. In *Fraley* the treatment is prophylactic in nature because AAV-SERCA2 is administered before CHF has been established in the mouse model. Effects are evaluated after disease symptoms are induced. In contrast, the inventive concept relates to treatment of established disease and requires administration of AAV-SERCA2 after disease has set in. Since *Fraley* discloses neither transduction of "affected" cardiac cells (and not at the level of 50%), nor restoration of SERCA2 activity to normal endogenous levels, *Fraley* does not teach improved cardiac function.

[50] *Fraley* also does not disclose treatment in humans, administration by infusion, or the use of an adenoviral helper virus-free AAV vector.

[51] In sum, the teachings of *Fraley* differ from the inventive concept in the following respects:

(i) there is no disclosure of treatment of humans;

(ii) there is no disclosure of treatment of existing CHF;

(iii) there is no disclosure of transduction of "affected" cardiac cells at the level of 50% and restoration of SERCA2 activity to normal endogenous levels;

(iv) the vector was administered by injection not infusion; and,

(v) there is no disclosure that the AAV vector system is adenoviral helper virus-free.

Miyamoto

[52] *Miyamoto* discloses studies performed using a rat model of CHF in which a SERCA2-encoding polynucleotide was delivered with an adenoviral vector to cells of a heart in

transition to CHF. The authors conclude that "in an animal model of heart failure where SERCA2a protein levels and activity are decreased and severe contractile dysfunction is present, overexpression of SERCA2a *in vivo* restores both systolic and diastolic function to normal levels" (see abstract).

[53] Limitations of the study are noted and the authors acknowledge that "the results obtained in this rat model of heart failure may not be applicable to human failing cardiac cells" and that the "intervention we performed was acute because SERCA2a expression was transient" (p. 797).

[54] The article ends by noting that their results indicate it is possible to rescue a failing heart by expressing SERCA2, but notes that for sustained improvement, a number of molecular abnormalities other than SERCA2 will probably need to be targeted.

[55] We note that a commentary on the *Miyamoto* paper is found in the *White* review article, which indicates that "these studies are encouraging" but are limited because of the lack of data past the acute window after delivery of the SERCA2-encoding polynucleotide (p. 40). Further, "the long-term (or even more meaningful short-term) effects of this approach remain to be documented. The question remains as to whether this strategy is targeting a fundamental defect in cardiac dysfunction and thus potentially preventing or reversing heart failure, or simply improving contractility transiently".

[56] *Miyamoto* suggests on page 798 that other vectors, including AAV vectors, may be used in the future to address the shortcomings of the adenoviral vectors they used. As regards the potential use of AAV vectors, we note that *Miyamoto* directs the reader to the *Svensson* article, discussed above at para 24. We note also that the *Svensson* article does not mention the use of adenoviral helper virus-free AAV vectors.

[57] The disclosures in *Miyamoto* differ from the inventive concept in the following respects:

a) the treatments were performed using a rat model, not humans;

b) *Miyamoto* uses an adenoviral vector rather than an AAV vector;

c) there is no disclosure of transduction of about 50% of affected cardiac cells with an AAV vector;

d) the vector was administered by injection, not infusion;

e) there is no disclosure that the AAV vector system is adenoviral helper virus-free; and

f) there is no disclosure that the observed effects were detectable more than 4 weeks post administration.

[58] One other difference between *Miyamoto* and the inventive concept lies in the difference between a heart in "transition" to heart failure, as disclosed by *Miyamoto*, versus a heart with established heart failure, as found in the inventive concept.

[59] Having reviewed *Miyamoto* and the Applicant's second post-hearing submissions on this point, we believe the skilled person would acknowledge a difference between a heart in transition to heart failure versus one with existing disease; the former being "in transition from compensated hypertrophy to heart failure" (see abstract of *Miyamoto*) as opposed to a heart with established disease. However, we do not believe, as the Applicant also submitted, that the skilled person would understand the work done by *Miyamoto* to be prophylactic in nature. There are indications that disease had begun in the animal model used (see table 1 for instance).

Summary of the differences that exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim

[60] There are a number of differences that exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim. They can be summarized as follows:

(1) The experimentation of *Fraley* and *Miyamoto* was pre-clinical involving rodent models of CHF, not humans.

(2) *Miyamoto* used a model in which the hearts were in transition to heart failure, delivered a SERCA2-encoding polynucleotide using a different vector (an

adenoviral vector; not an AAV vector), and did not achieve a long-lasting restorative effect that was detectable at 4 weeks or more post administration.

(3) *Fraley* delivered a SERCA2-encoding polynucleotide to healthy hearts and observed only a prophylatic effect, not a restorative effect.

(4) Neither *Fraley* nor *Miyamoto* disclose the use of an AAV vector system that is adenoviral helper virus-free.

(5) Neither *Fraley* nor *Miyamoto* disclosed the combination of elements found in the inventive concept that requires "about 50% of affected cardiac cells express SERCA2 to replace normal endogenous SERCA2 activity . . . that was detectable at 4 weeks or more post administration".

(6) Neither *Fraley* nor *Miyamoto* disclose delivery of a SERCA2-encoding polynucleotide by infusion; each discloses delivery by injection.

Step 4: 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?

Submissions and declarations

[61] There are submissions and declarations that were put on record during prosecution and this review that are helpful to the obviousness analysis. These include:

- A declaration from Dr. Brian Jaski. The *Jaski* declaration was submitted to this Office during prosecution in support of the Applicant's claim, and we agree with the Examiner and the Applicant that it provides information that is relevant to the degree of unpredictability in the art.

- The first Dillmann declaration. Dr. Wolfgang Dillmann is an inventor of the present invention as well as other issued patents. The first *Dillmann* declaration was submitted to this Office as part of the Applicant's pre-hearing written submissions dated September 24, 2014. In general, the first declaration outlines the actual course of conduct followed by the inventors in developing the present invention.

- The second Dillmann declaration. The second *Dillmann* declaration accompanied the Applicant's first post-hearing submissions dated October 15, 2014. It provides information relevant to the degree of unpredictability in transfecting damaged heart muscle cells in numbers sufficient to restore levels of SERCA2.

- A scientific article by Suarez et al., referred to in the second *Dillmann* declaration, was co-authored by Dr. Dillmann and was published July 15, 2004. It provides information relevant to the degree of unpredictability in the art after the claim date.

Obvious to try factors

[62] The question is whether the differences between the inventive concept and the state of the art constitute steps that require any degree of invention. The assessment of the differences cannot be on the basis of hindsight analysis (*Janssen-Ortho*).

[63] It is at this step of the obviousness enquiry that the Supreme Court in *Sanofi* has set forth several "obvious to try" considerations, noted above at para 13. The Applicant was informed in our Initial Review letter that the obvious to try enquiry was considered appropriate in this case.

(1) Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons skilled in the art?

[64] The common general knowledge suggests that one approach to treating CHF involves increasing SERCA2 activity in heart muscle cells (*Dillmann* review article p. 69). There were also rodent animal models of CHF available that were considered acceptably predictive of human CHF conditions. *Fraley* reported lasting expression of SERCA2 and prophylactic results in a mouse model using an AAV vector system. *Miyamoto* reported transient restoration of cardiac function using an adenoviral vector system in a rat model.

[65] However, the consideration here is whether the invention, more or less self-evidently, ought to work for lasting treatment of established CHF, not for prophylaxis as disclosed in *Fraley* and as was argued in the Final Action and Summary of Reasons. Further, the

question is whether it will work in humans on a lasting long-term basis, not on a transient basis as disclosed in *Miyamoto.* Having considered the record as a whole, we are of the view that it was not self-evident that the invention ought to work.

[66] Against the encouraging results indicated in the state of the art stands, firstly, the reality that human cardiac gene therapy, in general, was still an unpredictable field (*Jaski* declaration, para 8). In the particular field of CHF research, molecular targets other than SERCA2 had been identified. *Miyamoto* had worked with SERCA2 but believed that additional molecular abnormalities would likely need to be targeted.

[67] In our view, the warnings in the documents of record further indicate that the state of the art was not so advanced that a finite number of identified predictable solutions were known to persons skilled in the art. *Miyamoto* acknowledged that their rat model results may not be applicable to human failing cardiac cells and that their strategy would not be satisfactory for long-term treatment of established CHF; the results were transient. The *White* review article questioned whether *Miyamoto*'s strategy was "targeting a fundamental defect in cardiac dysfunction and thus potentially preventing or reversing heart failure, or simply improving contractility transiently."

[68] Notwithstanding the knowledge of favourable results for prophylaxis, and the knowledge from *Miyamoto* that transient restoration of cardiac function seemed possible, the *Suarez* article confirms that the art field was unpredictable (see abstract). That article indicates that it was still unclear to researchers whether lasting treatment of established disease could be achieved, even after the filing date of the present application.

[69] The documents of record also indicate that it was uncertain whether it was possible to achieve adequate levels of transduction of *damaged*, heart muscle cells with an AAV vector. This was a point of dispute during prosecution. Although paragraph 122 of the present description indicates that the commonly known transduction efficiency of AAV was about 50% of heart muscle cells, having reviewed all of the documents and submissions of record, we are not convinced that it had been established that *damaged*

heart muscle cells could predictably be transduced at the level required to effect a restorative treatment of the whole of a diseased heart.

[70] In that regard, the second *Dillmann* declaration (para 5) informs us that it was not clear to him whether a sufficient number of cells could be altered to affect contractility of the organ as a whole (e.g., at least about half the cells of the heart) and that favourable results at the time that heart failure begins does not make it predictable that the same would be true well after damage occurred.

[71] Further, *Miyamoto* and the review articles by *White* and *Isner* all refer to the *Svensson* article when discussing AAV transduction. *Svensson* makes no mention of efficient transduction of *damaged* heart muscle cells. Nor does it deal with restoration of lost enzymatic function. Considering all of the information of record it is our view that the skilled person would not regard as self-evident that transduction using an AAV system at the requisite 50% level of efficiency in damaged heart cells ought to work.

[72] This factor weighs in favour of the non-obviousness of claims 1 and 2.

(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?*

[73] Bearing in mind that the second factor is taken from the perspective of the skilled person at the relevant time without the benefit of hindsight, we are of the view that the information on record does not establish that only routine experimentation was required.

[74] Neither *Fraley* nor *Miyamoto* give clear direction to use an adenoviral helper virus-free AAV system as required in the inventive concept. This difference, as discussed below, represents a solution to a stumbling block encountered during the actual course of conduct taken by the inventors: they were unable to obtain incorporation of sufficient levels of

SERCA2 into heart muscle cells due to contamination of AAV vector compositions with adenovirus (the first *Dillmann* declaration, paras 9-10).

[75] *Fraley* is silent on this aspect. There were other types of AAV systems known and it does not follow that the AAV system of *Fraley* must have inherently been adenoviral helper virus-free. Although adenoviral helper virus-free AAV systems were known *per se*, the information of record does not establish that it was routine to use an adenoviral helper virus-free AAV system in the specific context of the present invention; i.e., remediation of CHF.

[76] On the contrary, in the context of remediation of CHF *Miyamoto* directs the skilled person to an AAV vector system as described in the *Svensson* article. However, the *Svensson* article neither discloses an adenoviral helper virus-free AAV system nor does it direct the skilled person to use such a system.

[77] As regards the amount of effort required to achieve the invention, the difference between the publication date of *Fraley* and the priority date of the present application is about two months, which could suggest that the effort that would have been required to achieve the invention was not prolonged and arduous. However, that would be to presume that the skilled person and the inventors were on equal footing. We recall from *Beloit* that it is incorrect to ask what "competent inventors did or would have done to solve the problem" because "inventors are by definition inventive".

[78] In our view, the skilled person and the inventors would not have been on equal footing at the time the invention was made. Dr. Dillmann, being a co-author of the *Fraley* abstract, had the benefit of the *Fraley* research for a longer period of time and was familiar with it. Dr. Dillmann is an experienced researcher with issued patents to his credit. It was he and his co-inventors, seemingly possessed with the inventive faculty, who had an inside track on the invention. It was they who proceeded for the first time to successfully treat established disease in an animal model on a long-term basis on the basis of their

knowledge and insights. We would not characterize this work as routine to the skilled person.

[79] *Miyamoto* does suggest the potential use of AAV vectors, amongst others, to address problems in their studies. However, the fact that *Miyamoto* was available three years before the priority date of the present application suggests that other researchers did not directly arrive at the invention even though it is arguable that extending *Miyamoto*'s work might have been a logical thing to do.

[80] This factor weighs in favour of the non-obviousness of claims 1 and 2.

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

[81] The prior art and the common general knowledge might disclose some motivation to find the solution the application addresses since *Fraley* and *Miyamoto* tested hypotheses, based on SERCA2 transduction, that are not inconsistent with the solution the application addresses. *Fraley* is concerned with prophylaxis while *Miyamoto* is concerned with examining the feasibility of rescuing disturbed calcium cycling and improving cardiac function through restoration of SERCA2. However, as suggested above, any motivation would be tempered by uncertainty in the state of the art.

[82] On the record before us, we therefore consider that this factor weighs neither for nor against a finding of obviousness of claims 1 and 2.

(4) *What was the actual course of conduct which culminated in the making of the invention?*

[83] Unlike the other three, the fourth factor is necessarily taken into account from the perspective of the inventors.

[84] In the first declaration by Dr. Dillmann (paras 9 and 10) he declares that he and his co-inventors were unable to obtain incorporation of sufficient levels of SERCA2 into heart muscle cells due to contamination of their initial AAV vector compositions with adenovirus helper that was required for AAV production. Once addressed through the

identification of an adenoviral helper virus-free AAV system, the inventors proceeded to *in vivo* testing on animals with established disease, as outlined in example 1 of the present specification. The results were favourable, for the first time indicating long-term restoration of contractility in an animal model (para 12).

[85] This factor weighs in favour of a finding of non-obviousness because we are persuaded there was inventive effort actually undertaken in solving problems encountered during the course of making the invention.

Conclusions

[86] Having considered the obvious to try factors, we find that, on balance, they support a finding of non-obviousness.

[87] With the benefit of impermissible hindsight it could be argued that the invention was "worth a try"; but that is not the correct approach. The invention must be obvious to try, "where the word 'obvious' means 'very plain'" (*Pfizer*). Having carefully reviewed the record, which includes documents that were not before the Examiner, we find that the differences between the inventive concept of the claims and the state of the art constitute steps that would require a degree of inventive ingenuity.

[88] In summary, claims 1 and 2 would not have been obvious on the claim date to the skilled person. It follows that dependent claims 3 and 4 would also not have been obvious.

[89] Having found that claims 1-4 on file are non-obvious and compliant with section 28.3 of the *Patent Act*, it is not necessary to consider any proposed claim amendments.

RECOMMENDATION OF THE BOARD

[90] We recommend that the rejection be withdrawn and the application proceed to allowance in accordance with subsection 30(6.2) of the *Patent Rules*.

Ed MacLaurin	Paul Fitzner	Christine Teixeira
Member	Member	Member

DECISION

[91] I concur with the findings and the recommendation of the Board. In accordance with subsection 30(6.2) of the *Patent Rules*, the rejection of the application is withdrawn and the application is to proceed to allowance.

Agnès Lajoie

Assistant Commissioner of Patents

Dated at Gatineau, Quebec,

this 25th day of June, 2015