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# D E C I S I O N
# of 26 July 2005

**Case Number:** W 0006/05 - 3.3.8

**Application Number:** PCT/CA 2003/01523

**Publication Number:** 1554587

**IPC:** G01N 33/68

**Language of the proceedings:** EN

**Title of invention:**
Isolated post-translationally modified proteins for monitoring and diagnosing muscle damage

**Applicant:**
Queen's University at Kingston

**Opponent:**
-

**Headword:**
Modified proteins/KINGSTON

**Relevant legal provisions:**
PCT Art. 17(3)(a), 19
PCT R. 13.1, 13.2, 40.1, 40.2(c), 40.3

**Keyword:**
"Refund of three additional search fees (yes) - invitation to pay additional fees not based on invention first mentioned in the claims"

**Decisions cited:**
W 0004/87, W 0007/90, W 0031/90, W 0003/93, W 0004/94

**Catchword:**
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number:** W 0006/05 - 3.3.8

**International Application No. PCT/**CA 2003/01523

# D E C I S I O N
## of the Technical Board of Appeal 3.3.8
## of 26 July 2005

**Applicant:** Queen's University at Kingston

**Representative:** Scribner, Stephen J.
Parteq Innovations
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Kingston, Ontario K7L 3N6 (CA)

**Decision under appeal:** **Protest according to Rule 68.3(c) of the Patent Cooperation Treaty made by the applicants against the invitation of the European Patent Office (International Preliminary Examining Authority) to restrict the claims or pay additional fees dated 3 June 2004.**

**Composition of the Board:**

**Chairman:** L. Galligani
**Members:** T. J. H. Mennessier
M. B. Günzel

## Summary of Facts and Submissions

I. International patent application PCT/CA 2003/001523 (published as WO-A-2004/034060) was filed on 10 October 2003 with 26 claims:

**Claims 1** read as follows:

"1. An isolated post-translationally modified myofilament protein comprising a troponin I protein phosphorylated at its C terminus **or** adjacent to its minimal inhibitory region." (emphasis added by the Board)

**Claims 2 to 10** which were dependent on claim 1 read as follows:

"2. The isolated post-translationally modified myofilament protein of claim 1 wherein the troponin I is phosphorylated at its C terminus **and** adjacent to its minimal inhibitory region." (emphasis added by the Board)

"3. The isolated post-translationally modified myofilament protein of claim 1 wherein the troponin I is **fast skeletal troponin I** phosphorylated at **serine 117 or serine 168**." (emphasis added by the Board)

"4. The isolated post-translationally modified myofilament protein of claim 1 wherein the troponin I is **fast skeletal troponin I** phosphorylated at **serine 117 and serine 168**." (emphasis added by the Board)

"5. The isolated post-translationally modified myofilament protein of claim 1 wherein the troponin I is **human cardiac troponin I** phosphorylated at **serine 198**." (emphasis added by the Board)

"6. The isolated post-translationally modified myofilament protein of claim 1 wherein the troponin I is **human cardiac troponin I** phosphorylated at **serine 149 and serine 198**." (emphasis added by the Board)

"7. The isolated post-translationally modified myofilament protein of claim 1 wherein the troponin I is **rat cardiac troponin I** phosphorylated at **serine 150 or serine 199**." (emphasis added by the Board)

"8. The isolated post-translationally modified myofilament protein of claim 1 wherein the troponin I is **rat cardiac troponin I** phosphorylated at **serine 150 and serine 199**." (emphasis added by the Board)

"9. The isolated post-translationally modified myofilament protein of claim 1 wherein the troponin I is **slow skeletal troponin I** phosphorylated at **serine 118 or serine 168**." (emphasis added by the Board)

"10. The isolated post-translationally modified myofilament protein of claim 1 wherein the troponin I is **slow skeletal troponin I** phosphorylated at **serine 118 and serine 168**." (emphasis added by the Board)

**Claims 11 to 26** were directed to inventions which were defined with a back-reference to the protein of claim 1.

Namely:

- **claim 11** related to a method of detecting native troponin I and phosphorylated troponin I involving the use of a compound that bound to both native troponin I and a protein of claim 1 (**claim 12** was dependent on claim 11 and covered a specific embodiment thereof);

- **claim 13** was directed to a method for distinguishing native troponin I from a phosphorylated troponin I involving the use of a compound that bound to native troponin I but not to a protein of claim 1 (**claim 14** was dependent on claim 13 and covered a specific embodiment thereof);

- **claim 15** related to a kit for distinguishing native troponin I from a phosphorylated troponin I comprising a compound that bound to both native troponin I and a protein of claim 1 (**claims 16 and 17** were dependent on claim 15 and covered a specific embodiment thereof);

- **claims 18 and 19** were directed to a compound (an antibody or an aptamer, respectively) which selectively bound to a protein of claim 1.

- **claim 20** related to a method of diagnosing or monitoring injury of skeletal and cardiac muscle in a subject comprising determining the presence of a protein of claim 1 in a biological sample from said subject;

- **claim 21** was directed to a method for assessing efficacy of a therapy for muscle damage in a subject comprising a step of determining the presence of a

protein of claim 1 in a biological sample from said subject;

- **claim 22** was directed to a method for assessing appropriateness of a level of training and/or enhancement performing drug in a subject comprising monitoring of the protein of claim 1 in said subject; and

- **claim 23** related to a composition comprising an agent which altered a phosphorylation state of a protein of claim 1 (**claims 24 and 25** were dependent on claim 23 and covered specific embodiments thereof while **claim 26** was directed to a method for modulating a phosphorylation state of troponin I in a subject comprising administering to the subject a composition of claim 23).

II. On 3 June 2004, the European Patent Office, acting as an International Searching Authority (ISA) invited the applicants to pay within a time limit of forty five days six additional search fees pursuant to Article 17(3)(a), Rule 40.1 and 40.3 PCT and issued, as an annex to the invitation, a communication relating to the results of the partial international search carried out on the group of inventions first mentioned therein.

III. The invitation to pay additional search fees stated the seven groups of inventions to which the application was found to relate, namely:

"1. Claims: 1-4, 11-26 (all in part)

An isolated post-translationally modified myofilament protein comprising a "fast skeletal troponin I" protein phosphorylated at "serine 117", methods and reagents (antibodies) to distinguish said phosphorylated "fast skeletal troponin I" from the native troponin I and methods of diagnosis of injury to cardiac and skeletal muscle comprising determining the phosphorylation state of "fast skeletal troponin I"."

"2. Claims: 1-4, 11-26 (all in part)

An isolated post-translationally modified myofilament protein comprising a "fast skeletal troponin I" protein phosphorylated at "serine 168", methods and reagents (antibodies) to distinguish said phosphorylated "fast skeletal troponin I" from the native troponin I and methods of diagnosis of injury to cardiac and skeletal muscle comprising determining the phosphorylation state of "fast skeletal troponin I"."

"3. Claims: 5, 6 (completely) and claims 1, 2, 11-26 (all in part)

An isolated post-translationally modified myofilament protein comprising a "human cardiac troponin I" protein phosphorylated at "serine 198", methods and reagents (antibodies) to distinguish said phosphorylated "human cardiac troponin I" from the native troponin I and methods of diagnosis of injury to cardiac and skeletal muscle comprising determining the phosphorylation state of "human cardiac skeletal troponin I"."

"4. Claims: 1, 2, 7, 8 and 11-26 (all in part)

An isolated post-translationally modified myofilament protein comprising a "rat cardiac troponin I" protein phosphorylated at "serine 150", methods and reagents (antibodies) to distinguish said phosphorylated "rat cardiac troponin I" from the native troponin I and methods of diagnosis of injury to cardiac and skeletal muscle comprising determining the phosphorylation state of "rat cardiac troponin I."

"5. Claims: 1, 2, 7, 8 and 11-26 (all in part)

An isolated post-translationally modified myofilament protein comprising a "rat cardiac troponin I" protein phosphorylated at "serine 199", methods and reagents (antibodies) to distinguish said phosphorylated "rat cardiac troponin I" from the native troponin I and methods of diagnosis of injury to cardiac and skeletal muscle comprising determining the phosphorylation state of "rat cardiac troponin I."

"6. Claims: 1, 2, 9, 10 and 11-26 (all in part)

An isolated post-translationally modified myofilament protein comprising a "slow skeletal troponin I" protein phosphorylated at "serine 118", methods and reagents (antibodies) to distinguish said phosphorylated "slow skeletal troponin I" from the native troponin I and methods of diagnosis of injury to cardiac and skeletal muscle

comprising determining the phosphorylation state of "slow skeletal troponin I"."

"7. Claims: 1, 2, 9, 10 and 11-26 (all in part)

An isolated post-translationally modified myofilament protein comprising a "slow skeletal troponin I" protein phosphorylated at "serine 168", methods and reagents (antibodies) to distinguish said phosphorylated "slow skeletal troponin I" from the native troponin I and methods of diagnosis of injury to cardiac and skeletal muscle comprising determining the phosphorylation state of "slow skeletal troponin I"."

IV. The following documents are referred to in the present decision:

D1: J. M. Wilkinson and R. J. A. Grans, Biochem. J., Vol. 149, 1975, Pages 493 to 496

D2: A. J. G. Moir et al., FEBS Letters, Vol. 42, No. 3, June 1974, Pages 253 to 256

D3: T. S. Huang et al., FEBS Letters, Vol. 42, No. 3, June 1974, Pages 249 to 252

D4: Database EMBL online, "TRIF Rabit Standard", Accession Number P02643

D5: Nina Buscemi et al., Circ. Res., Vol. 91, No. 6, 20 September 2002, Pages 509 to 516

D6: Monica X Li et al., Biophysical Journal, Vol. 82, No. 1, Part 2, January 2002, Page 389a, Abstract No. 1894

D7: Samuel V. Perry and Heather A. Cole, Biochem. J., Vol. 141, 1974, Pages 733 to 743

V. The reasons for the finding of non-unity were indicated as being associated with an *a posteriori* objection raised in view of the relevant state of the art.

The reasoning was as follows:

The modification of troponin I proteins by phosphorylation on serine residues had been well documented in the prior art. In particular, documents D1 to D4 disclosed phosphorylation of serine 117 of rabbit fast skeletal troponin I while documents D5 and D6 disclosed phosphorylation of serine 149 of cardiac troponin I.

In view of that prior art, the problem underlying the invention could be defined as the provision of a further troponin I protein phosphorylated on a serine residue. Seven solutions had been proposed each represented by an isolated post-translationally modified myofilament protein as referred to in claims 3 to 10 as originally filed.

Due to the fact that troponin proteins phosphorylated on serine and their possible involvement in disruption of normal mechanisms in the regulation of muscle contraction was known in the art, due to the essential difference in structure of the different groups of

inventions 1 to 7, and due to the fact that no other technical features could be distinguished which in the light of the prior art could be regarded as special technical features, the application lacked unity, contrary to the requirements of Rule 13.1 PCT.

VI. On 16 July 2004, the applicants filed a reply to the invitation to pay additional fees. The applicants maintained that the groups of inventions 1, 2, 6 and 7 - 2, 6 and 7 relating to isolated post-translationally modified protein comprising a fast skeletal troponin I proteins phosphorylated at ser 168, a slow skeletal troponin I protein phosphorylated at ser 118 and a slow skeletal troponin I protein phosphorylated at ser 168 - should be considered unitary. Together with their reply, the applicants filed an amended set of claims, in which ***in vivo*** phosphorylated troponin I was referred to and claim 1 recited that the protein was a skeletal troponin I. In a reasoned statement it was explained that, as it was derivable from the enclosed document D7, phosphorylation of troponin I *in vitro* was expected to be very different from that *in vivo*, the amended claims were new and inventive over the documents cited in the invitation to pay additional search fees. The applicants requested that the search be extended to inventions 2, 6 and 7 as defined in the amended claims 1 to 4 and 9 to 26. They requested that, should the ISA not consider groups of inventions 1, 2, 6 and 7 as a unitary group, three additional fees be deducted from their deposit account and inventions 2, 6 and 7 as identified by the ISA be searched.

VII. On 12 January 2005, the ISA transmitted the International Search Report, which had been established for the inventions 1, 2, 6 and 7 it had identified in the invitation to pay additional search fees.

VIII. On the same date, the ISA communicated to the applicants the results of its review under Rule 40.2(e) PCT. It was confirmed that for exactly the same reasons as explained in the invitation to pay additional search fees, the application lacked unity within the meaning of Rule 13.1 PCT. It was also noted that there was no provision in the PCT for providing amendments in the application before the ISA and that the arguments put forward by the applicants which were centered on the amended claims did not justify a finding of unity among groups of inventions 1, 2, 6 and 7.

The applicants were invited to pay within one month the protest fee.

IX. The protest fee was paid by the applicants on 11 February 2005. In their letter with the same date they stated that the three additional searches which had been carried out by the ISA had resulted in the citation of only a single additional document, which moreover was of category "A". They concluded that this was an indication that the group of inventions 1, 2, 6 and 7 as identified by the ISA in the invitation to pay additional search fees was unitary.

## Reasons for the Decision

*Admissibility of the protest*

1. In reply to the invitation to pay additional search fees, the applicants filed an amended set of claims and, in support of their view that the four groups of inventions 1, 2, 6 and 7 as identified by the ISA formed a unitary group of inventions, gave grounds relying on that set of claims.

2. There is no provision for amendments during proceedings before the ISA. According to Article 19 PCT, only after having received the international search report is an applicant entitled to one opportunity to amend the claims of the international application. Therefore, the set of claims filed with the reply to the invitation to pay additional search fees cannot be taken into consideration.

3. Rule 40.2(c) PCT provides that applicants "may pay the additional fee under protest, that is, accompanied by a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive".

4. A request that additional search fees be refunded constitutes a protest.

5. It follows from Rule 40.2(c) PCT however that applicants paying the additional fees under protest, in support of that protest, must give grounds showing why

the applicants take the view that the claims objected to by the ISA do not lack unity.

6. Under consistent Board of Appeal case law (cf. W 4/87, OJ EPO 1988, 425), this substantive reasoned statement must also be filed within the prescribed time limit under Article 17(3)(a) and Rule 40.3 PCT for paying the fees.

7. In the present case, the protest was filed within the prescribed time limit, but its reasoning was defective in that the grounds given by the applicants in support of their protest, although sufficiently extensive in themselves, relied not on the claims as filed, but on a non-permissible amended set of claims.

8. Nevertheless, the Board is prepared to accept in the present case that the incomplete and wrong reasoning made by the ISA (see infra) has confused the applicants to such an extent that they have not reacted in an appropriate manner.

9. For that reason, the protest is considered to be admissible.

*Merits of the protest*

10. Pursuant to Article 154(3) EPC the Boards of Appeal of the EPO are responsible for deciding on a protest made by an applicant against the payment of an additional fee charged by the EPO under the provisions of Article 17(3)(a) PCT.

11. Pursuant to Rule 40.2(c) PCT the Boards of Appeal are empowered to examine protests against the payment of additional search fees and shall, to the extent that they find the protest justified, order the total or partial reimbursement of the additional fee.

12. According to Article 17(3)(a), first sentence, PCT if the ISA considers that the international application does not comply with the requirement of unity of invention as set out in the Regulations it shall invite the applicant to pay additional fees. Article 17(3)(a), second sentence, PCT further stipulates that **the ISA shall establish the international search report on those parts of the international application which relate to the invention first mentioned in the claims ("main invention")** and, provided the required fees have been paid within the prescribed time limit, on those parts of the international application which relate to inventions in respect of which additional fees were paid.

13. It follows therefrom that, when deciding for which of the inventions contained in an application the search fee already paid is to be used and for which invention(s) additional search fees are to be requested, **the ISA is not free to choose at its discretion**. It has the legal obligation to search for the one search fee paid for the first invention (or unitary group of inventions), i.e. the invention (or unitary group of inventions) **first mentioned in the claims**, and it can ask for the payment of additional fees only for searching further inventions (or groups of inventions) contained in the application (see e.g. decisions W 7/90 dated 19 October 1990, point 4 et seq. of the reasons

and W 31/90 dated 30 November 1990, point 7 of the reasons).

14. It also follows therefrom that the justification for asking for the payment of additional fees has to be based on the finding that there are further inventions (or groups of inventions) which are non-unitary *a priori* or *a posteriori* in comparison with the invention (or unitary group of inventions) first mentioned in the claims ("main invention").

15. This requirement is not a formality but an important procedural requirement which is intended to prevent the ISA from choosing arbitrarily which invention (or unitary group of inventions) to search. It is up to the applicants to determine by the way and the order in which they draft the claims which invention (or unitary group of inventions) is in the context of the search to be regarded as the core of their application and shall therefore form the starting point for any search to be made.

16. In the present case, the ISA, when issuing its invitation to pay additional fees, has not correctly identified those parts of the application which related to the invention first mentioned in the claims and thus has not prepared an international search report on it. The invention first mentioned in the claims was, in fact, in relation to an "isolated post-translationally modified myofilament protein wherein the troponin I protein is phosphorylated at its C-terminus" (emphasis added). Instead, the ISA identified as the first group of inventions an isolated post-translationally modified myofilament protein comprising a "fast skeletal

troponin I" protein phosphorylated at "serine 117" (a serine located adjacent to the minimal inhibitory region), this being referred to for the first time in claim 3. This group was searched, was compared with the inventions to which are directed claims 4 to 10 and led to the ISA's finding that the application contained 7 groups of inventions.

17. The reasons given by the ISA for this way of acting are legally defective and do not justify that an invention other than that contained in claim 1 be defined as the first invention ("main invention") and be made the basis for the ISA's finding of non-unity in the present case.

18. The ISA's reasoning ignored the "main invention" and failed to identify the special technical features on the basis of which one or more relationships may exist among the inventions covered by claim 1. This failure prevented the ISA from recognising that the proteins encompassed by claim 1, which as first invention comprise troponin I protein phosphorylated at its C-terminal, constitute the core of a unitary group of inventions that are linked by a special technical feature within the meaning of Rule 13.2 PCT, ie. the presence of **troponin I phosphorylated at its C-terminal**. This technical feature is special as myofilament proteins comprising such a troponin are not disclosed in the documents cited by the ISA in its communication accompanying the invitation to pay additional search fees. This unitary group of inventions (see claims 1 (in part), 2 (as a whole), 3 (in part), 4 to 6 (each as a whole), 7 (in part), 8 (as a whole), 9 (in part), 10 (as a whole) and 11 to 26 (all in part) is the "first

invention" mentioned in the claims. Therefore, the search fee initially paid should have been used for searching it and any finding of further non unitary claimed inventions should have been based on a comparison with this invention.

19. According to Rule 40.1 PCT the ISA's invitation to pay additional fees provided for in Article 17(3)(a) PCT shall specify the reasons for which the international application is not considered as complying with the requirement of unity invention.

20. The purpose of the protest procedure under Rule 40.2 PCT is to enable the justification for the invitation to pay additional fees to be submitted to substantive review. The only issue to be examined by the Board therefore is whether, considering the reasons given by the ISA and the submissions made by the applicant in support of the protest, retaining additional search fees was justified. The Board cannot investigate *ex-officio* whether an objection of lack of unity would have been justified for reasons other than those given (W 3/93, OJ EPO 1994, 931, Headnote III and point 4 of the reasons; W 4/94, OJ EPO 1996, 73, point 5.5 of the reasons). To the extent that the reasons given by the ISA for charging additional fees are insufficient or wrong, the protest is justified and the fees have to be reimbursed, irrespective of whether or not, as a result, the finding of non-unity could be regarded as justified as to substance.

21. It follows therefrom that in the present case the additional fees paid under protest are to be reimbursed without considering the question of unity in substance. Moreover, the protest fee must also be refunded.

**Order**

**For these reasons it is decided that:**

1. Three additional search fees are reimbursed.

2. The protest fee is reimbursed.

The Registrar: The Chairman:

G. Rauh L. Galligani