**BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS**

**BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE**

**CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS**

**Internal distribution code:**
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [ ] To Chairmen
(D) [X] No distribution

# Datasheet for the decision of 23 September 2008

**Case Number:** W 0013/08 - 3.3.08

**Application Number:** PCT/US 99/31207

**Publication Number:** WO 00/70040

**IPC:** C12Q 1/68

**Language of the proceedings:** EN

**Title of invention:**
Cell concentration and lysate clearance using paramagnetic particles

**Applicant:**
Promega Corporation

**Opponent:**
-

**Headword:**
Paramagnetic particles/PROMEGA

**Relevant legal provisions:**
PCT Art. 34.3(a)
PCT R. 13.1, 13.2

**Relevant legal provisions (EPC 1973):**
EPC Art. 154(3)

**Keyword:**
"Unity of invention for groups of inventions 1 to 3 (no)"
"Unity of invention for groups of inventions 2 and 3 (yes)"

**Decisions cited:**
G 0001/89, W 0006/90

**Catchword:**
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number:** W 0013/08 - 3.3.08

**International Application No. PCT/**US 99/31207

# D E C I S I O N
**of the Technical Board of Appeal 3.3.08**
**of 23 September 2008**

**Applicant:** Promega Corporation
2800 Woods Hollow Road
Madison
W1 53711-5399 (US)

**Representative:** Michael Best & Friedrich LLP
One South Pinckney Street
Suite 700
Madison
WI 53703 (US)

**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 2 April 2001.**

**Composition of the Board:**

**Chairman:** L. Galligani
**Members:** M. R. Vega Laso
T. Bokor

## Summary of Facts and Submissions

I. International patent application PCT/US99/31207 with the title "Cell concentration and lysate clearance using paramagnetic particles" was filed on 30 December 1999 with thirty-six claims. The application was published as WO 00/70040.

II. An International Search Report was established for the claims as filed and sent to the applicant on 29 September 2000. On 1 December 2000, the applicant filed under Article 19 PCT an amended set of claims (claims 1 to 28) which replaced the claims originally filed.

III. Independent claims 1, 8 and 21 of the amended set of claims read as follows:

"1. A method of using magnetic particles to concentrate or harvest cells, comprising the steps of:

(a) combining cells with magnetic particles, under conditions wherein the cells selectively adsorb directly to the particles thereby forming a complex, wherein said magnetic particles are selected from the group consisting of (1) pH dependent ion exchange particles and (2) silica magnetic particles consisting essentially of a magnetic core coated with a siliceous oxide having a hydrous siliceous oxide adsorptive surface; and

(b) isolating the complex from the solution by application of magnetic force.

8. A method of clearing a solution of disrupted biological material, according to steps comprising:

(a) providing a solution comprising a disrupted biological material;

(b) combining the solution with second magnetic particles under conditions wherein the disrupted biological material selectively adsorbs directly to the particles, thereby forming a complex, wherein said magnetic particles are selected from the group consisting of (1) pH dependent ion exchange particles and (2) silica magnetic particles consisting essentially of a magnitude core coated with a siliceous oxide having a hydrous siliceous oxide adsorptive surface; and

(c) separating the complex from the solution by application of magnetic force.

21. A method of isolating a target nucleic acid from a disrupted biological material, comprising the target nucleic acid, a first non-target material, and a second non-target material, comprising the steps of:

(a) combining a solution of the disrupted biological material with first magnetic particles under conditions wherein the first non-target material selectively adsorbs directly to the particles, thereby forming a first complex, wherein said magnetic particles are selected from the group consisting of (1) pH dependent ion exchange particles and (2) silica magnetic particles consisting essentially of a magnetic core

coated with a siliceous oxide having a hydrous siliceous oxide adsorptive surface;

(b) separating the first complex from the solution of disrupted biological material by application of magnetic force, forming a cleared solution comprising the target nucleic acid and the second non-target material;

(c) combining the cleared solution with second magnetic particles under conditions wherein the target nucleic acid adsorbs to the second magnetic particles, forming a second complex;

(d) isolating the second complex from the cleared solution;

(e) washing the second complex by combining the second complex with a wash solution and separating the second complex from the wash solution by magnetic force; and

(f) combining the washed second complex with an elution solution, under conditions wherein the target material is desorbed from the second magnetic particles."

Dependent claims 2 to 7 and 9 to 20 concerned various embodiments of the methods claimed in, respectively, claim 1 and claim 8, on which they depended, directly or indirectly. Dependent claims 22 to 28 concerned different embodiments of the method of claim 21.

IV. On 2 April 2001 the European Patent Office, acting in its capacity as International Preliminary Examination Authority (IPEA), informed the applicant that the

application was not considered to comply with the requirements of unity of invention (Rule 13.1, 13.2 and 13.3 PCT). Therefore, the IPEA held that there were three inventions claimed in the international application. In accordance with Article 34(3)(a) and Rule 68.2 PCT, the applicant was thus invited either to restrict the claims to one invention, or pay the examination fees for two additional inventions within a time limit of one month.

V. In the Invitation to Restrict or to Pay Additional Fees, the IPEA reasoned that "[t]*he only common technical features which can be distinguished between the subject matter of claims 1, 8 and 21, are that said method claims refer to the use* [of] *magnetic particles to separate biological material present in a solution (e.g. cell, nucleic acid, etc) comprising the steps of: combining a solution containing said material with magnetic particles to form a complex, wherein said magnetic particles were selected from the group consisting of (1) pH dependent ion exchange particles and (2) silica magnetic particles consisting essentially of a magnetic core coated with siliceous oxide having a hydrous siliceous oxide adsorptive surface; and separating the complex from the solution by applying magnetic force.*"

VI. In the IPEA's view, these common technical features were known from documents:

(1): WO 98/31840, published on 23 July 1998;

(2): DE 43 07 262, published on 8 September 1994; and

(3): P.R. Levison et al., 1998, Journal of Chromatography A, Vol. 827, pages 337 to 334.

VII. The IPEA thus considered that, taking into account the state of the art, the subject-matter of claims 1, 8 and 21 was not linked by a common (new and inventive) special technical feature within the meaning of Rule 13.2 PCT. The claimed subject-matter was divided into the following three groups of inventions:

(i) Claims 1 to 7 directed to a method of using magnetic particles to concentrate or to harvest cells;

(ii) Claims 8 to 20 directed to a method of clearing a solution of disrupted biological material; and

(iii) Claims 21 to 28 directed to a method of isolating a target nucleic acid from a disrupted biological material.

VIII. On 30 April 2001, the applicant paid under protest two additional examination fees for the additional inventions (Rule 68.3(c) PCT). In its response to the IPEA's Invitation, dated 27 April 2001, the applicant maintained that unity of invention existed between all the claims of the application. In support of this view, it was submitted that:

- In each of the three groups of inventions indicated by the IPEA in the Invitation, either cells or disrupted biological material were combined with the same type of magnetic particles

under conditions wherein the cells or the disrupted biological material adsorbed directly to the particles, thereby forming a complex. Thus, in accordance with Rule 13.2 PCT a link existed between the separate embodiments claimed in the independent and dependent claims of the application.

- In the method of using paramagnetic particles to concentrate or harvest cells according to claims 1 to 7 (first group of inventions), the cells to be concentrated or harvested selectively adsorbed directly to the particles thereby forming a complex.

- The method of claims 21 to 28 (third group of inventions) included an initial step of combining a solution of the disrupted biological material with first magnetic particles under conditions wherein the first non-target material selectively adsorbed to the particles, thereby forming a first complex.

- Claims 8 to 20 (second group of the inventions) included the same step, in which the disrupted biological material selectively adsorbed directly to the particles. In both groups of claims, the same types of magnetic particles were used to adsorb to the disrupted biological material.

- The method of isolating DNA described in document (1) did not include any step of adsorption of disrupted biological material other than the target DNA to silica magnetic particles.

Therefore, it was clear that document (1) did not disclose this particular common element of the claims of groups 2 and 3 defined by the IPEA.

- Document (3) described various techniques for isolating nucleic acids using a specific type of magnetic bead with an anion exchanger, to which the nucleic acid of interest was adsorbed. However, at no point did document (3) teach or suggest the use of a magnetic particle with any type of ion exchanger to clear a solution of disrupted biological material or to isolate or harvest cells, a common element of all of the claims of the application.

- Since the applicant did not have sufficient time to obtain an English translation of document (2), its content could not be determined. Nevertheless, at least two of the three references cited in the IPEA's Invitation failed to teach or suggest the use of the types of magnetic particles used in the methods of the invention to clear a solution of disrupted biological material or to isolate or harvest cells.

IX. On 24 July 2001, the IPEA sent an Invitation to Pay a Protest Fee under Rule 68.3(e) PCT for the referral of the protest to a Board of Appeal. The invitation included the results of a review by a Review Panel of the justification for the Invitation to Restrict or to Pay Additional Fees of 2 April 2001. In the view of the Review Panel, the applicant had acknowledged that the use of magnetic particles as specified in claims 1, 8 and 21 to separate biological material present in a

solution (eg. cell, nucleic acid, etc) was a technical feature common to the three groups of inventions defined in the Invitation of 2 April 2001. With regard to the applicant's arguments in respect of document (1), the Review Panel considered that the applicant had implicitly acknowledged that the target DNA isolated according to the method of document (1) did indeed represent biological material. This also applied to document (3), since the sole difference between the teachings of documents (1) and (3) was that in the latter pH dependent ion exchange particles were used. Document (2), which was acknowledged in the application as filed to be a particularly relevant prior art document, disclosed the separation of biological material as well. Thus, the link between the three groups of inventions was known from prior art documents D1 to D3 and, therefore, no common inventive concept linked the three groups of inventions.

X. On 20 August 2001, the protest fee was paid. The applicant did not submit any further arguments in response to the findings of the Review Panel.

## Reasons for the Decision

1. The international application under consideration has an international filing date of 30 December 1999. Pursuant to Article 1(6) of the Decision of the Administrative Council of 28 June 2001 on the transitional provisions under Article 7 of the Act revising the European Patent Convention of 29 November 2000, Articles 154(3) and 155(3) EPC 1973 shall continue to apply to PCT application pending at the

time of entry into force of the EPC 2000. Details of the procedure are guided by the Decision of the President of the EPO dated 24 June 2007, Article 3 (Special edition No. 3 OJ EPO, 140), and the Notice of the EPO dated June 2007, points 6 to 9 (Special edition No. 3 OJ EPO, 142). Accordingly, the Boards of Appeal shall continue to be responsible for deciding on protests made against the charging of an additional fee under Article 17, paragraph 3(a) or Article 34, paragraph 3(a) PCT, in their capacity as a review body specified in Rule 40.2(c) PCT, second sentence.

2. The payment was made in time, and the protest is thus considered to have been made (Rule 40.2(e) PCT, second sentence). The protest is reasoned, pursuant to the requirements of Rule 40.2(c) PCT, first sentence and is therefore admissible.

*Examination of the protest*

3. According to Rule 13.1 PCT, an international patent application shall relate to one invention only or to a group of inventions so linked as to form a single inventive concept. If the International Preliminary Examining Authority (IPEA) considers that the international application does not comply with the requirements of unity of invention, it may invite the applicant, at his option, to restrict the claims so as to comply with the requirements or to pay additional fees (see Article 34.3(a) PCT).

4. In the present case, the Invitation to Restrict or to Pay Additional Fees issued by the IPEA on 2 April 2001 (in the following "the Invitation") established that

the requirement of unity of claims was not fulfilled because the single concept linking the three groups of inventions claimed was neither novel nor inventive in view of documents D1, D2 or D3. The IPEA defined the linking concept as the use of magnetic particles selected from the group consisting of (1) pH dependent ion exchange particles and (2) silica magnetic particles consisting essentially of a magnetic core coated with siliceous oxide having a hydrous siliceous oxide adsorptive surface, in a method to separate **biological material** present in a solution, the method comprising the steps of: combining a solution containing said material with magnetic particles to form a complex; and separating the complex from the solution by application of magnetic force.

5. In the IPEA's formulation of the general concept shared by the claimed inventions, the feature "biological material" - which does not appear as such in the claims - defines broadly the material that binds to the magnetic particles to form the complex, ie. cells (see method of claims 1 to 7), disrupted biological material (see method of claims 8 to 20) or nucleic acid (see method of claims 21 to 28). "Biological material" has, thus, the same meaning as the term "solute" used in the passage of the application starting on page 9, line 3 and ending on page 11, line 8. In this passage, "solute" is defined as "... *the type of material to be isolated from or removed from a solution using magnetic particles, according to a method of the present invention.*" (see page 9, lines 11 and 12). According to the application, the "solute" can be intact cells (see page 9, lines 12 and 13; and page 10, lines 10 and 11), disrupted biological material (see page 9, lines 14

and 15; and page 10, lines 12 to 21) or a target nucleic acid (see page 15, lines 15 to 17; and paragraph bridging pages 10 and 11). Hence, the concept linking the three groups of inventions formulated by the IPEA in the Invitation is in full agreement with the teaching of the application.

6. This linking concept was, however, considered to be known in the state of the art, as represented in particular by documents (1) to (3).

7. Document (1) describes methods of isolating biological target materials using silica magnetic particles, by combining the silica magnetic particles and a solution including the biological target material to form a complex (see page 7, lines 12 to 21). The biological material to be isolated is preferably a nucleic acid or a protein; however, also other biological materials can be isolated (see page 12, lines 2 to 18; and page 15). It is stated on page 10, lines 3 to 9 of document (1) that the most preferred form of silica magnetic particle is a "siliceous-oxide coated magnetic particle" or "SOCM particle" which is comprised of siliceous oxide coating a core of at least one particle of superparamagnetic or paramagnetic material. The SOCM particle used in the methods described in document (1) also has an adsorptive surface of hydrous siliceous oxide, a surface characterized by having silanol groups thereon (see page 10, lines 7 to 9).

8. Thus, having regard to the content of document (1), the concept linking the three groups of inventions defined in the Invitation, in particular the use of silica magnetic particles consisting essentially of a magnetic

core coated with siliceous oxide having a hydrous siliceous oxide adsorptive surface in a method aimed at separating certain biological material from further material present in the solution, is not new.

9. Nor is the concept of using pH dependent ion exchange magnetic particles, as document (3) describes the use of DEAE-Magarose, an ion exchange agarose bead containing a paramagnetic component, in a method of separating plasmid DNA from further biological material present in a bacterial cell lysate, or genomic DNA from bacterial cells and blood (see page 338, left column, second full paragraph, lines 11ff.)

10. The board thus concludes that, since the general concept shared by the three groups of inventions to which the claims relate, as defined in the IPEA's Invitation (see point 4 above) lacks novelty, the claims are not linked by a "special technical feature" within the meaning of Rule 13.2 PCT. Thus, the finding of the IPEA that the application including claims 1 to 28 filed on 1 December 2000 does not fulfil the requirement of unity of invention was justified.

11. The board has considered the arguments in support of unity of invention put forward by the applicant in its response dated 27 April 2001. In particular, the applicant argued that neither document (1) nor document (3) teaches or suggests a common element of all the claims of the application, namely the use of magnetic particles to clear a solution of biologically disrupted material **or** to isolate or harvest cells.

12. This argument cannot be accepted. As stated above, both types of magnetic particles specified in the claims were part of the state of the art at the priority date (see documents (1) and (3)). Moreover, it was known that such magnetic particles could be used in a method of separating the biological target material from further material present in the solution, by selectively adsorbing the biological target material (eg. plasmid or genomic DNA) to the surface of the particles, to form a complex which is subsequently isolated by applying magnetic force (see documents (1) and (3)).

13. Having regard to the state of the art as apparent from documents (1) and (3), the problem to be solved by the method of claims 1 to 7 (first group of inventions) can be formulated as applying the method described in these documents to the isolation of a different biological target material, and the proposed solution consists in the use of magnetic particles as specified in claim 1 to concentrate or harvest **cells**.

14. As concerns claims 8 to 20, the technical problem to be solved may be formulated as providing a method of enriching the desired biological target material **in the solution**. The solution proposed in claims 8 to 20 consists in adsorbing further biological material present in the solution (so-called "disrupted biological material") to the surface of the magnetic particles, and separating the complex formed, so that the biological target material remains in the solution. This is apparent from the passage on page 10, lines 17 to 21 of the application.

15. It follows from the above that the methods corresponding to the first and second group of inventions as defined in the Invitation differ not only in the technical problem solved, but also in the relevant effect achieved. Thus, a single general concept within the meaning of Rule 13.1 PCT linking the first and the second group of inventions cannot be acknowledged (see W 6/90; OJ EPO 1991, 438).

16. In its response to the Invitation, the applicant argued further that the method claimed in claim 8 for clearing a solution of disrupted biological material represented the first step of the method of isolating a target nucleic acid from a disrupted biological material as claimed in claim 21. Thus, the second and the third group of inventions shared a common element which was described neither in document (1) nor in document (3).

17. This argument, which was apparently not considered by the Review Panel when reviewing the Invitation, merits closer examination. The Board notes that the method of isolating a target nucleic acid from a disrupted biological material of claim 21 comprises two steps in which magnetic particles are used, the first step (see step (a)) consisting essentially in clearing a solution of disrupted biological material by a method as defined in claim 8.

18. The use of the magnetic particles specified in claims 8 and 21 for clearing a solution of disrupted biological material may, thus, be considered to be the general concept linking the inventions claimed in claims 8 to 20 (second group of inventions) and claims 21 to 28 (third group of inventions). Hence, the sole remaining

question is whether or not this concept can be viewed as an inventive link between the two groups, in view of documents (1) to (3) cited in the Invitation.

19. None of the prior art documents (1) to (3) appears to describe or even suggest removing **undesired** biological material from a solution by first selectively adsorbing the material to the surface of magnetic particles to form a complex, and then separating the complex by applying magnetic force. Rather, documents (1) to (3) describe only methods in which the biological **target material** is adsorbed to the particles to form a complex which is subsequently isolated from the solution.

20. The use of the magnetic particles specified in the claims for clearing a solution of disrupted biological material may, thus, be considered as a special technical feature within the meaning of Rule 13.2 PCT, which defines the contribution made by the methods of claims 8 to 28 over the prior art. Hence, a single general **inventive** concept linking the second and the third group of inventions defined in the Invitation and, consequently, unity of invention within the meaning of Rule 13.1 PCT for the inventions in claims 8 to 28 is acknowledged.

21. The Board wishes to note that, as stated in decision G 1/89 of the Enlarged Board of Appeal (OJ EPO 1991, 155; see point 8.1 of the Reasons), the consideration of the prior art made in the framework of assessing unity of invention under Rule 13.1 PCT represents only a **provisional** opinion on novelty and inventive step which is in no way binding upon the national or

regional authorities subsequently responsible for the further examination of the application.

22. Summarizing the above, the Board concludes that, contrary to the view expressed by the IPEA in the Invitation and confirmed by the Review Panel, the application relates to only **two** groups of inventions which are not so linked as to form a single general inventive concept, the first group of inventions corresponding to claims 1 to 7 (first group as defined in the Invitation), and the second group to claims 8 to 28 (second and third group as defined in the Invitation). Thus, the Invitation to pay additional fees is justified only for one additional examination fee.

*Refund of the protest fee*

23. The protest, as explained above, is partially justified. Pursuant to Rule 40.2(e) PCT, last sentence, the applicant is not entitled to the reimbursement of the protest fee, as the protest was not **entirely** justified.

## Order

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

Refund of one examination fee paid by the applicant is ordered.

The Registrar: The Chairman:

A. Wolinski L. Galligani