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D E C I S I O N
of 22 May 1996

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Application Number: PCT/GB 95/00737

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Applicant:
ISIS INNOVATION LTD. et al.

Opponent:
-

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W 0003/94, W 0006/90, G 0001/89

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Case Number: W 0001/96 - 3.3.4
International Application No. PCT/GB 95/00737

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 22 May 1996

Applicant: ISIS INNOVATION LTD.
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Subject of the Decision: **Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicant against the invitation (payment of additional fee) of the European Patent Office (branch at The Hague) dated 15 September 1995.**

Composition of the Board:

Chairwoman: U. Kinkeldey
Members: L. Galligani
R. Teschemacher

Summary of Facts and Submissions

I. International patent application PCT/GB 95/00737 was filed on 30 March 1995 with eleven claims.

Claims 1, 5 to 8 and 11 read as follows:

"1. The peptides, being either epitopes or potential epitopes for the stated HLA (human leucocyte antigen) class I molecules, conservative variants thereof, and longer peptides containing these sequences which are sub-units of the indicated antigens:

[*Table with label, sequence and position*]

these peptides being selected from three *Plasmodium falciparum* antigens, circumsporozoite protein (cp), thrombospondin-related anonymous protein (tr) and liver-stage antigen-1 (ls).

5. A vaccine comprising at least one peptide according to any one of claims 1 to 4, for immunisation against malaria.

6. Use of *Plasmodium falciparum* gene or protein TRAP (thrombospondin-related anonymous protein) as a cytotoxic T lymphocyte-inducing gene or protein for immunization against malaria.

7. Oligonucleotides which code for the peptides claimed in any one of claims 1 to 4.

8. A vaccine comprising at least one oligonucleotide according to claim 7 for expression *in vivo* for immunization against malaria.

11. Use of any of the peptides:

[*Table with label, sequence and position*]

and conservative variants thereof and longer peptides containing the sequences which are sub-units of the stated antigens, and of oligonucleotides which code for said peptides, as a cytotoxic T lymphocyte-inducer for immunization against malaria of individuals possessing a HLA-B7 allele."

Claims 9 and 10 relate to a method for inducing primary cytotoxic T lymphocyte response to a chosen antigen or microorganism.

Claims 2 to 4 concern specific embodiments of the peptides of claim 1.

II. On 15 September 1995 the European Patent Office (EPO), acting as an International Search Authority (ISA), invited the Applicant to pay within a time limit of 30 days **five** additional search fees pursuant to Article 17(3)(a) and Rule 40.1 PCT and issued a partial search report on Claims 1 to 5, 7, 8 (all partially) relating to the invention first mentioned.

III. The invitation stated that the application related to six groups of inventions (see for details point 5 of the Reasons) which were not linked by a single inventive concept.

The ISA observed that cytotoxic T lymphocyte (CTL)-inducing peptides of the HLA class I and their use in antimalarial vaccine were known in the prior art, for example, from the following documents:

(1) WO-A-93/20103;

(2) Nature, Vol. 360, 1992, pages 434 to 439.

Furthermore, the TRAP gene and protein of Plasmodium falciparum were also known in the art from the following documents:

(3) WO-A-90/01496;

(4) Nature, Vol. 335, 1988, pages 79 to 82.

In view of this state of the art, the problem underlying the present application was the provision of further Plasmodium falciparum polypeptides to be used as vaccines. The above groups 1 to 5 of inventions related to a plurality of solutions of different nature (based on the different primary structures, antigenic origin of the peptides and the different HLA class I molecules they bind to) which were not linked to each other by a special technical feature so as to form a single inventive concept. Moreover, the problem of inducing primary CTL responses to an antigen or microorganism and its proposed solution (group 6: claims 9, 10) was not essential to the solution of the first underlying technical problem. Thus, a single inventive concept was also missing between group 6 and the remaining groups of inventions.

IV. On 16 October 1995, the Applicant paid **four** additional fees under protest pursuant to Rule 40.2(c) PCT in respect of groups 2 to 5. The further search fee for group 6 was not paid; the Applicant acknowledged that this group constituted a separate invention. In support of the protest, the Applicant submitted that groups 1 to 5 were linked by the common utility of providing protection against malaria via peptides from antigens of Plasmodium falciparum. The application provided in groups 1 to 4 means of protecting individuals of

certain HLA groups, namely A2, B8, B17 and B7, where it could not have been expected that immunisation would work. In contrast to the present application, document (1) related to peptides recognisable by CTL from individuals with HLA types associated with protection from severe malaria, e.g. HLA-B53. As part of the discovery of peptides capable of eliciting a CTL response in individuals of the HLA groups A2, B8, B17 and B7, TRAP was identified as containing some of these peptides. For these reasons, group 5 shared the same general inventive concept with groups 1 to 4. The Applicant further submitted that, when carrying out an International Search for document (1), the ISA had not raised a comparable lack of unity objection and that, at any rate, the number of additional search fees in the present case was excessive.

V. On 23 January 1996 the ISA issued the international search report for those parts of the application for which search fees had been paid and communicated to the Applicant the result of its review under Rule 40.2(e) PCT which had confirmed the reasons given in the communication of 15 September 1995. The ISA did not see in the common utility (protection against malaria) a link for the different inventions. As for the Applicant's argument that the HLA groups A2, B8, B17 and B7 had not been previously associated with the protection from malaria, the ISA observed that this did not result explicitly or implicitly from the application or from the general knowledge and, thus, could not be taken into account (cf. decision W 3/94 OJ EPO 1995, 775, point 3 of the Reasons). Therefore, the Applicant was invited to pay within one month the protest fee.

VI. The protest fee was paid by the Applicant on 7 February 1996.

Reasons for the Decision

1. The protest is admissible.

2. According to Rule 13.1 PCT, the 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 ISA considers that the claims lack this unity, it is empowered, under Article 17(3)(a) PCT, to invite the Applicant to pay additional fees.

3. Lack of unity may be directly evident **a priori**, i.e. before the examination of the merits of the claims in comparison with the state of the art revealed by the search (cf., for example, decision W 6/90, OJ EPO 1991, 438). Alternatively, having regard to decision G 1/89 of the Enlarged Board of Appeal (OJ EPO 1991, 155), the ISA is also empowered to raise an objection **a posteriori**, i.e. after having taken the prior art revealed by the search into closer consideration. This practice is laid down in the PCT Search Guidelines, Chapter VII,9 (PCT Gazette 30/1992, 14025) which are the basis for a uniform practice of all International Searching Authorities. The Enlarged Board of Appeal indicated that such consideration represents only a provisional opinion on novelty and inventive step which is in no way binding upon the authorities subsequently responsible for the substantive examination of the application (point 8.1. of the Reasons for the decision). In point 8.2 of the Reasons, the Enlarged Board mentioned that such invitation to pay additional fees should always be made "with a view to giving the Applicant fair treatment" and should only be made in clear cases.

4. According to Rule 13.3 PCT, the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

5. Since there is no protest in respect of Claims 9 and 10 (group 6), only the remaining claims will be taken into consideration. These claims have been grouped by the ISA in the following way:

1. Claims 1 to 5, 7, 8 (all partially), relating to peptides with sequence ID 1-11 (**HLA-A2 group**), oligonucleotides encoding them and antimalarial vaccines comprising these peptides or oligonucleotides;

2. Claims 1 to 5, 7, 8 (all partially), relating to peptides with sequence ID 12-17 (**HLA-B8 group**), oligonucleotides encoding them and antimalarial vaccines comprising these peptides or oligonucleotides;

3. Claims 1 to 5, 7, 8 (all partially), relating to peptides with sequence ID 29-52 (**HLA-B17 group**), oligonucleotides encoding them and antimalarial vaccines comprising these peptides or oligonucleotides;

4. Claim 11, relating to the use of any of the peptides with sequence ID 18-28 (**HLA-B7 group**) or oligonucleotides encoding them as CTL-inducer for immunization against malaria in individuals possessing a HLA-B7 allele;

5. Claim 6, relating to the use of TRAP or its encoding gene as a CTL-inducer for immunization against malaria.

6. Prior art document (1) discloses a method of identifying peptides of an antigen of interest, in particular the Plasmodium falciparum antigens circumsporozoite protein, TRAP, sporozoite hepatocyte-binding antigen (Pfs 16) and liver-stage antigen-1 (cf. Claims 1 and 4), which comprises the steps of: ascertaining a "motif" of peptides bound to a chosen HLA class I molecule; providing peptides having this "motif" which are present in the sequence of the antigen of interest; screening the peptides for recognition by or induction of CTL. The method is exemplified in respect of HLA-B53 and HLA-B35 peptides (see Table on page 18) which are proposed as vaccines against malaria. The method is presented as being of general applicability to facilitate the search for HLA class I restricted epitopes (see page 2, lines 7 to 15).

7. In the light of document (1), the problem underlying the present application is to be seen in the provision of CTL epitopes for a further HLA class I subtype to be used as vaccine against malaria.

8. As a solution to the above problem, the Applicant now proposes in Claim 1 CTL epitopes for the HLA class I subtypes A2, B8 and B17. As derivable from the description, these have been identified by use of the same method known from the prior art [cf. page 3, lines 13 to 31 where reference is made to document (2) which constitutes essentially the scientific publication of the contents of document (1)]. The same approach was used for the identification of the peptides the use of

which as vaccine is the subject-matter of Claim 11 (HLA-B7 subtype) and of the TRAP CTL epitopes the use of which as vaccine is the subject-matter of Claim 6.

9. The HLA class I subtypes A2, B7, B8, B17 as well as the TRAP antigen of Plasmodium falciparum were part of the state of the art. This is mentioned, for example, in present description (cf. page 3, lines 35 to 36), in document (1) (cf. page 3, line 14), in document (2) (cf. page 434, left-hand column, first paragraph) as well as in documents (3) and (4). In most cases, their peptide binding "motifs" had also been described as mentioned, for example, also in the present description (see page 3, lines 35 to 36) and in document (1) (see page 3, line 14).

10. Claims 1, 6 and 11 in the present case relate to different, alternative solutions for different - although analogous - technical problems. Claim 1 itself relates to three different alternative solutions (cf. point 4 supra). These different problems and their solutions are not necessarily interrelated from a technical point of view so as to form a single general inventive concept. As a matter of fact, the claimed peptides have different primary structures, different antigenic origins and they are bound to different HLA class I molecules. In fact, the problem of the identification of CTL epitopes for HLA class I subtype A2 is technically independent from the problem of the identification of CTL epitopes for HLA class I subtype B8 or B7 or B17. Further, the provision of TRAP CTL epitopes to be used as a vaccine is not necessarily linked with the provision of peptides for a stated HLA class I. Although all the proposed alternative solutions derive from the analogous application of the same known method of document (1) to different HLA class I subtypes, this per se cannot constitute a unitary link

among them. In fact, in the light of the disclosure of a generally applicable method in document (1) and its exemplification in respect of the HLA-B53 and HLA-B35 subtypes, each successive identification of peptides bound to a further chosen HLA class I molecule carried out in an analogous manner constitutes a separate solution to a separate technical problem. Also the common utility (use as a vaccine) cannot provide such a unitary link because this was the known purpose of the prior art method and means as well.

11. As for the Appellant's argument that the unitary link lies in that for certain HLA groups, namely A2, B8, B17 and B7, it could not have been expected that immunisation would work, the Board observes that nothing in the application as originally filed or in the prior art or general knowledge allows the conclusion that the cited HLA groups constituted a special group within the HLA class I for which the application of the known method disclosed in document (1) required the adoption of a particular approach or special measures within a single general inventive concept.

12. For the foregoing reasons, in the Board's judgement, there is no "special technical feature" in the sense of Rule 13.2 PCT to link the mentioned groups 1 to 5 of inventions. Thus, the international application does not comply with the requirement of Rule 13.1 PCT and the invitation to pay the additional fees was justified.

Order

For these reasons it is decided that:

The protest according to Rule 40.2(c) PCT is dismissed.

The Registrar: The Chairwoman:

L. McGarry U. Kinkeldey