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Datasheet for the decision of 4 March 2010

Case Number: T 0996/07 - 3.3.04

Application Number: 99904442.3

Publication Number: 1051519

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Language of the proceedings: EN

Title of invention:
Methods to identify polynucleotide and polypeptide sequences which may be associated with physiological and medical conditions

Applicant:
Evolutionary Genomics, LLC

Headword:
Polynucleotide sequences / EVOLUTIONARY GENOMICS

Relevant legal provisions:
EPC Art. 54

Keyword:
"Main request - novelty (no)"
"Auxiliary requests I and II - novelty (no)"

Decisions cited:
-

Catchword:
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Case Number: T 0996/07 **-** 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 4 March 2010

Appellant: (Applicant)
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Representative:
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Decision under appeal:
Decision of the Examining Division of the European Patent Office posted 18 December 2006 refusing European patent application No. 99904442.3 pursuant to Article 97(1) EPC 1973.

Composition of the Board:

Chairman: C. Rennie-Smith
Members: M. Wieser
R. Gramaglia

Summary of Facts and Submissions

I. The appeal was lodged by the Applicant (Appellant) against the decision of the Examining Division to refuse under Article 97(1) EPC 1973 the patent application EP 99 904 442.3 (published as WO 99/39 006), having the title: "Methods to identify polynucleotide and polypeptide sequences which may be associated with physiological and medical conditions".

II. The Examining Division decided that claim 1 of the main request and of auxiliary requests I and II before it did not meet the requirements of Article 54 EPC, as the subject-matter of these claims was anticipated by the disclosure in prior art document (5).

III. In the letter setting out the grounds for appeal, dated 27 April 2007, the Appellant requested to set aside the decision under appeal and to grant a patent on the basis of claims 1 to 21 filed with letter of 25 August 2006 or, alternatively on the basis of auxiliary request I or II, both filed with letter of 27 April 2007.

Oral proceedings were requested should the Board not allow these requests.

Claims 1 to 21 of Appellant's main request were identical to the claims of the main request before the Examining Division.

IV. The Board expressed its preliminary opinion in a communication dated 23 November 2009 which was annexed to the summons to oral proceedings.

By a letter dated 2 March 2010 the Appellant withdrew its request for oral proceedings.

Oral proceedings were held on 4 March 2010 in the absence of the Appellant.

V. Claim 1 of Appellant's main request read as follows:

"A method of identifying a non-human primate polynucleotide sequence encoding a polypeptide, which is a candidate sequence for association with a physiological condition that is present in the human or non-human primate, but absent in the non-human primate or human, respectively, or that is enhanced in the human or non-human primate, relative to the non-human primate or human, respectively, comprising the steps of:

a. comparing polypeptide-coding polynucleotide sequences of the human and non-human primate; and

b. selecting from the compared sequences a human or non-human primate polynucleotide sequence, that contains an evolutionarily significant nucleotide change as compared with the corresponding sequence of the non-human primate or human, respectively, whereby the candidate sequence is identified."

Dependent claims 2 to 21 referred to preferred embodiments of the method according to claim 1.

VI. Claim 1 of auxiliary request I differed from claim 1 of the main request in so far, as the "physiological condition" was defined as being the "resistance to a disease".

Claim 1 of auxiliary request II differed from claim 1 of the main request in so far, as the "physiological condition" was defined as being the "resistance to cancer or resistance to an infectious disease".

VII. The following documents are referred to in this decision:

(1) Nature, vol.385, 1997, pages 151 to 154; and

(5) Immunogenetics, vol.40, 1994, pages 184 to 191.

VIII. The submissions made by the Appellant in writing, as far as they are relevant to the present decision, may be summarised as follows:

While document (5) merely exemplified the commonly known use of K_A/K_S-type methods for evaluating whether certain differences in known genes were based on evolutionary factors, the invention according to claim 1 of the main request related to a method of screening for candidate sequences of human or non-human primate origin which were associated with desirable physiological conditions and traits. Thus, the method of claim 1 referred to a novel use of K_A/K_S-type methods.

Moreover, document (5), neither directly nor *"a contrario"*, as held by the Examining Division, disclosed a step wherein those sequences were selected

from the sequences compared between the human and non-human primate which contained an evolutionarily significant nucleotide change. Therefore, the final statement in document (5), that the data disclosed therein might be relevant for the investigation of infectious diseases such as HIV and SIV, does not allow the conclusion that the selection and identification of sequences containing an evolutionarily significant nucleotide change were considered relevant in the context of such diseases.

Document (1) was analysed in the Examining Division's communication dated 20 December 2002 (see point 2.1). The Appellant argued that this document, although it observed positive evolution in the lysozyme protein in different monkey species, did not correlate this with a change in a physiological trait. Document (1) did not, therefore, relate to a screening method whereby a candidate sequence relevant to a physiological condition was identified (see letter dated 24 September 2003, section 2.1).

Accordingly, the subject-matter of the claims of the main request and of auxiliary requests I and II were novel over the disclosure in the prior art documents on file.

Reasons for the Decision

The present decision is concerned exclusively with the issue of novelty (Article 54 EPC).

Main request

1. Claim 1 refers to a method for identifying a polynucleotide sequence which is a **candidate sequence** for association with a **physiological condition**. The method comprises a step wherein various polynucleotide sequences are compared and a further step, wherein a sequence containing an **evolutionarily significant change** is selected.

The description of the application as published does not contain an explicit definition of the term **"candidate sequence".** Therefore, the Board, when interpreting this term, will apply the commonly used meaning of the term "candidate", which according to the Oxford Dictionary defines a person or thing regarded as suitable for a particular fate, treatment, or position.

A **"physiological condition"** is defined on page 18, lines 3 to 4 of the application as published, as being "any condition or state that be measured and/or observed" (sic).

The term **"evolutionarily significant change"** is defined on page 19, lines 3 to 5 of the application as published, as being a change between two species that may be attributed to a positive selective pressure. A method for determining the presence of such change is to apply a K_A/K_S-type analytical method (page 19,

lines 5 to 7). The principle of this method, which is acknowledged to be known in the art, is described on page 3 of the application as published.

2. Document (5) investigates structure, diversity and evolution of the T-cell receptor VB gene (TCRBV) repertoire in primates by using a K_A/K_S-type analytical method (see the abstract, page 185, right column, first paragraph, and page 188, table 1; "d_n" and "d_s" in table 1 are equivalent to K_A and K_S). It is found that diversity in the TCRBV sequences from rhesus monkeys, chimpanzees and humans has not been driven by "positive Darwinian selection", which, in the language of the application in suit, means that the sequences do not contain evolutionarily significant changes. As a consequence of this result document (5), of course, does not disclose the selection of a sequence containing such evolutionarily significant change.

3. The Examining Division, in point 2.3 of the appealed decision, took the view that document (5) disclosed all steps of the method of claim 1, including the step wherein a decision was taken as to whether or not a change in a nucleic acid was evolutionarily significant. As this decision could result in two possible conclusions only, the actual outcome of the individual experiment disclosed in document (5) represented an ***a contrario*** disclosure of step b. specified in claim 1. The document was therefore considered to anticipate the subject-matter of claim 1 contrary to the requirements of Article 54 EPC.

4. The Board agrees in so far as document (5), when applying a K_A/K_S-type analytical method, includes a step wherein the K_A/K_S ratio is calculated on the basis of which it is determined whether or not a change in a nucleic acid was evolutionarily significant. K_A/K_S ratios significantly greater than 1.0 are considered to be strong evidence of positive Darwinian selection ("evolutionarily significant change"), K_A/K_S ratios less than 1.0 are generally taken as evidence that the sequences have evolved under negative or purifying selection (see application as published, page 19, lines 7 to 10 and document (1) page 151, right column).

5. However, even if the calculation of the K_A/K_S ratio has two possible consequences only, i.e. a sequence change may either be evolutionarily significant or not, this does not mean that the specific example of document (5), showing that TCRBV sequences of different primates do not contain evolutionarily significant changes, is an ***a contrario*** disclosure of a method comprising the selection of a sequence containing such evolutionarily significant change.

6. The disclosure in document (5) is therefore not considered as anticipating the subject-matter of claim 1.

7. Document (1), co-authored by one of the present inventors, investigates the episodic adaptive evolution of primate lysozymes, a family of hydrolytic enzymes.

K_A and K_S calculations were made for all possible pairwise comparisons of various primate lysozyme DNA sequences (page 151, right column, last paragraph). The

results, comprising K_A/K_S values of hominoids, including humans, are presented in figure 1 on page 152 and discussed on pages 152 to 153.

All comparisons between the colobine and hominoid lysozymes gave K_A/K_S ratios greater than 1.0 (range 1.33 - 3.49) and the average was statistically significant (K_A/K_S = 3.0; $P > 0.05$) (page 152, left column, lines 14 to 17). The conclusion is drawn that the analyses carried out strongly suggest that there have been major episodes of positive Darwinian selection during the evolution of lysozymes (page 153, left column, lines 8 to 10).

8. On page 151, left column, last paragraph, it is stated that colobine monkeys have a complex foregut in which bacteria ferment leafy plant materials, followed by a true stomach that expresses high levels of the bacteriolytic enzyme lysozyme. Other primates have simple stomachs with lysozyme expressed only in the pyloric region.

In the light of this disclosure and in consideration of the definitions given in point (1) above, a polynucleotide sequence encoding a lysozyme is considered as being a sequence "which is a candidate sequence for association with a physiological condition that is present in the human or non-human primate, but absent in the non-human primate or human, respectively".

9. According to the method disclosed in document (1) polynucleotide sequences of human (hominoid) and non-human primates are compared and a sequence is

identified, namely the sequence coding for a lysozyme, which contains an evolutionarily significant nucleotide change as compared with the corresponding sequence of the non-human primate or human, respectively.

10. With regard to the Appellant's argument that the prior art merely exemplified the known use of K_A/K_S-type methods for evaluating whether differences in known genes were based on evolutionary factors while the invention related to a method of screening for sequences of human or non-human primate origin which were associated with desirable physiological conditions and traits, the Board notes that this is not reflected by the wording of the claims.

11. Also the examples of the present application do not disclose screening of a variety of human or non-human primate sequences, but refer to K_A/K_S calculations obtained by pairwise comparisons of different primate sequences coding for well known disease associated polypeptides (ICAM-1, ICAM-2, ICAM-3, MIP-1 alpha, 17-beta-hydroxysteroid dehydrogenase, tyrosine kinase).

12. Accordingly, document (1) discloses all features of the method of claim 1. The subject-matter of claim 1 is therefore not novel contrary to the requirements of Article 54 EPC.

Auxiliary requests I and II

13. Lysozyme is known to be a bacteriolytic enzyme (document (1), page 151, left column, last paragraph),

and thus provides some protection against bacterial infection.

The enzyme (designated as 3.2.1.17 in the Enzyme Nomenclature of the International Union of Biochemistry and Molecular Biology (IUBMB)) damages bacterial cell walls by catalyzing hydrolysis of 1,4-β-linkages between *N*-acetylmuramic acid and *N*-acetyl-D-glucosamine residues in a peptidoglycan and between *N*-acetyl-D-glucosamine residues in chitodextrins (Enzyme Nomenclature 1992, IUBMB, Academic press, Inc., page 348).

14. Accordingly, the subject-matter of claim 1 of auxiliary requests I and II, wherein the "physiological condition" is defined as being the "resistance to a disease" or the "resistance to cancer or resistance to an infectious disease", respectively, is not novel in the light of the disclosure in document (1).

Therefore, also these requests do not meet the requirements of Article 54 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

Registrar: Chairman:

P. Cremona C. Rennie-Smith