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Case Number: T 0076/11 - 3.3.04

Application Number: 06076852.0

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Language of the proceedings: EN

Title of invention:
Albumin fusion proteins

Applicants:
Human Genome Sciences, Inc.
Novozymes Biopharma DK A/S

Headword:
Albumin fusion proteins/HGS

Relevant legal provisions:
EPC Art. 56

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Decisions cited:
T 0390/88

Catchword:

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Case Number: T 0076/11 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 24 November 2015

Appellants: (Joint applicants)

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Decision under appeal:

Decision of the Examining Division of the European Patent Office posted on 29 June 2010 refusing European patent application No. 06076852.0 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairwoman G. Alt
Members: A. Chakravarty
M. Blasi

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division to refuse European patent application No. 06 076 852, published as EP 1 832 599. The application is entitled "*Albumin Fusion Proteins*".

II. The examining division decided that the subject-matter of all claims lacked an inventive step (Article 56 EPC) in view of US 5 876 969 which disclosed fusions of serum albumin to therapeutic proteins in general.

III. With the statement of grounds of appeal, the appellants requested the grant of a patent based on the claim request considered by the examining division, i.e. that filed with the letter dated 12 December 2008. In response to the findings of the examining division on the matter of inventive step, the appellants submitted a document entitled "experimental annex", in which the expression of fused (to serum albumin) and unfused human butyryl-cholinesterase in Chinese hamster ovary cells was compared.

IV. Claim 1 of the sole claim request reads:

"1. An albumin fusion protein comprising a serum cholinesterase polypeptide fused to albumin, or albumin fragment or variant, wherein said albumin or albumin fragment or variant has the ability to prolong the serum half-life of the unfused serum cholinesterase polypeptide and wherein said albumin fusion protein has serum cholinesterase activity."

V. Oral proceedings before the board took place on 24 November 2015. At the end of the oral proceedings, the chairwoman announced the decision of the board.

VI. The following documents are relevant to the present decision:

D3: US 5 876 969

D8: Doctor et al. (1991), Neuroscience and Behavioural Reviews, 15, 123 to 128.

D11: US 6 001 625

D12: US 5 659 750

D16: Lockridge et al. (2005), J. Med. Chem. Biol. Radiol. Def., 3, 1 to 23.

Experimental annex: filed with the statement of grounds of appeal

VII. The arguments of the appellants may be summarised as follows:

Inventive step

Document D3 (column 2, line 22-57), cited by the examining division as the closest prior art for assessing inventive step, disclosed that proteins, including enzymes, may be fused to albumin to increase their stability. However, the document did not make any recommendations about which enzymes would be suitable for this. The skilled person would therefore have turned to the examples and would have recognised that suitable polypeptides were only those which, in their unfused state, had short half-lives, insufficient for their intended therapeutic use. Document D3 did not recommend fusing enzymes with sufficiently long half-lives to albumin and made no mention of serum cholinesterase.

Document D8, which was concerned with serum cholinesterases, related in particular to their use in the detoxification of organophosphates. It showed that serum cholinesterases were stable enzymes, having sufficiently long half-lives for use in the scavenging of toxic organophosphate and thus were a perfectly satisfactory solution to the problem of treating organophosphate poisoning. This adequate half-life was supported by the evidence provided in (post-published) document D16. Regardless of whether document D3 or document D8 was taken as a starting point, the person skilled in the art would have had no incentive to modify serum cholinesterase because the serum half-life of serum cholinesterase was considered acceptable for its therapeutic purpose by the skilled person at the effective date of the application. The situation was therefore analogous to that considered in decision T 390/88, Reasons 8, where the board concluded that a document disclosing a particular satisfactory film did not prompt the skilled person to find alternatives, but instead hesitate to depart from the solution it afforded.

The examining division had suggested that the application as filed contained no disclosure of a therapeutic indication for the claimed fusion proteins. This was incorrect however in view of the reference in the table on page 25 of the application to documents D11 and D12 which both related to the use of serum cholinesterases in the treatment of organo-phosphate poisoning.

Furthermore, the application as filed related to albumin fusion proteins comprising a therapeutic protein, and pharmaceutical formulations thereof for administration

to a patient (see paragraph [0009]). It was therefore implicit in the application that efficient production of the fusion proteins was desirable. The "experimental annex" filed with the statement of grounds of appeal included experimental evidence that showed that unfused human butyryl-cholinesterase was expressed at a relatively low level of from 1 to 5 mg per litre of culture medium in a mammalian cell culture. In contrast, an albumin fusion protein comprising human BChE was expressed much more efficiently. This improved expression in a mammalian cell culture system was not predicable from the cited prior art and warranted recognition of an inventive step.

VIII. The appellants requested that the decision under appeal be set aside and that the case be remitted to the examining division with the order to grant a patent on the basis of the set of claims filed with the letter dated 12 December 2008, and a description to be adapted thereto.

Reasons for the Decision

Claim 1

Inventive step

Closest prior art

1. To assess whether or not a claimed invention meets the requirements of Article 56 EPC, the boards of appeal apply the "problem and solution" approach, which requires as a first step, the identification of the closest prior art. In accordance with the established case law of the boards of appeal, the closest prior art is a teaching in a document conceived for the same

purpose or aiming at the same objective as the claimed invention. The commonality of structural features is a secondary criterion (see Case Law of the Boards of Appeal of the European Patent Office, 7th edition 2013, I.D.3.1).

2. The purpose of the claimed invention is to provide a protein having serum cholinesterase activity with a longer serum half-life than the unfused cholinesterase, which half-life is sufficient for the therapeutic purpose.

3. Document D3 discloses "*recombinant polypeptides composed of an active part derived from a natural or artificial polypeptide having a therapeutic activity and coupled to an albumin or to a variant of albumin*" (see column 1, lines 14 to 18). The therapeutic protein to be coupled to serum albumin may be an enzyme (see column 2, lines 24 and 25), although a serum cholinesterases as a therapeutic protein is not disclosed. Coupling is achieved by recombinant production of a fusion protein comprising the therapeutic protein and the albumin (see column 3, lines 36 to 42). The coupling to albumin was done to overcome disadvantages of (unfused) therapeutic polypeptides such as "*low stability in vivo, [...] complex or fragile structure, the difficulty of producing them on an industrially acceptable scale [...], [...] problems of administration, of packaging, of pharmacokinetics [...]*" (see column 1, lines 33 to 45). A particular benefit of coupling a therapeutic protein to serum albumin is a high plasma stability (see column 1, lines 55 and 56). Thus the purpose of the disclosure of document D3 is the provision of stabilised therapeutic proteins in general.

4. Document D8 discloses that exogenously administered acetyl- (isolated from fetal bovine serum) and butyryl-cholinesterase (isolated from human serum) will sequester organophosphates before they reach their physiological targets and are therefore potentially useful as pretreatment test drugs, based on the fact that both enzymes are globular in form, easily purified from serum, and are relatively stable (see page 124, paragraph bridging columns 1 and 2).

5. Documents D11 and D12 (see Section VII) also concern (unfused) acetyl- (documents D11 and D12) and butyryl- (documents D11) cholinesterases and their use in detoxifying organophosphates. In both documents D11 and D12 the serum cholinesterase is modified by substitution of certain amino acids and is a further development of the teachings of document D8. Document D11 for example, discloses a human butyryl-cholinesterase in which the glycine at the 117 position is substituted by histidine leading to increased enzymatic efficiency (see column 2, lines 17 to 34).

6. Thus the serum cholinesterases disclosed in documents D8, D11 and D12 share the purpose of the invention in as far as they have serum cholinesterase activity with serum half-life sufficient for the therapeutic purpose. They are all therefore equally good candidates for representing the closest prior art for the assessment of inventive step of the subject-matter of claim 1.

7. The board has selected the serum cholinesterases disclosed in document D11 from among the above documents, as representative of the closest prior art and as the starting point for the assessment of inventive step.

8. The difference between the serum cholinesterases representing the closest prior art and the claimed subject-matter is that the former are unfused while the latter are fused to an "albumin, or albumin fragment or variant".

9. The technical effect of this difference is that the enzymes are more stable which, *inter alia*, leads to a prolonged serum half-life in comparison to the unfused serum cholinesterases, this latter effect being a feature of the claim.

10. The appellants argued that an additional effect of the fusion with albumin was an improved expression of the claimed fusion proteins in a recombinant system, compared to the unfused proteins representing the closest prior art, as shown in the "experimental annex" filed with the statement of grounds. This effect was said to be surprising and not obvious from document D3 or any other of the cited documents. Furthermore, the improvement was foreshadowed in the application as filed which disclosed that a "*preferred embodiment [was] a polynucleotide encoding an albumin portion of an albumin fusion protein of the invention [...] optimized for expression in yeast or mammalian cells*" (paragraph [0055]) and in paragraph [0145] "*expression from certain promoters can be elevated in the presence of certain inducers*."

11. However, contrary to the view expressed by the appellants, the board cannot identify in or deduce from the application any disclosure of the technical effect of the suitability of the claimed fusion proteins to be produced in unexpectedly high yield in recombinant systems. Nor can the board identify any direct or indirect foreshadowing of it in the application as

filed. The passages of the application as filed cited by the appellants as reflecting the effect merely disclose the possibility of recombinant production of the claimed fusion proteins. They make no mention of any yield effect resulting from the fusion of therapeutic proteins, especially serum cholinesterase to serum albumin. Thus, the evidence provided in the "experimental annex" is not taken into account by the board its assessment of inventive step (see also Case Law of the Boards of Appeal of the European Patent Office, *supra*, I.D.4.4.1, 4.4.2 and 4.6).

Objective technical problem and solution

12. In view of the closest prior art, the difference thereto and the technical effect achieved of this difference and further considering the disclosure of the application, the problem to be solved by the claimed subject-matter is the provision of a more stable serum cholinesterase having a prolonged serum half-life in comparison to the unfused enzyme.

13. The appellants argued that the skilled person would not have formulated such a problem because the serum half-life of serum cholinesterase was known to be adequate for its intended purpose, this being as pretreatment drugs for organophosphate toxicity. Thus, the skilled person would have considered that no improvement of the serum half-life was necessary (see Section VII, paragraphs 1 and 2).

14. However, the first steps of the problem-solution approach, i.e. the determination of the closest prior art and of the difference between the claimed invention and this closest prior art and of the technical effect of this difference, serve to define the objective

technical problem which, once formulated, is then normally not put into doubt. The board does not see a reason to deviate from this long established approach. This application of the problem and solution approach is also the reason why the appellants' arguments based on decision T 390/88 (see Section VII) cannot succeed.

Obviousness

15. Document D3 discloses polypeptides containing an active part derived from a polypeptide having a therapeutic activity, coupled to an albumin or a variant of albumin (see column 1, lines 14 to 22). The purpose of the fusion of the therapeutically active part to the albumin was to overcome problems associated with *i.a.* "*low stability in vivo, their complex or fragile structure, the difficulty of producing them on an industrially acceptable scale*" also overcoming "*problems of administration, of packaging, of pharmacokinetics and the like*" (see column 1, lines 33 to 43).

15.1 In summary, document D3 discloses that therapeutic proteins in general, regardless of their therapeutic activity or particular sequence, may be stabilised by providing them in fusion with serum albumin. Stabilisation is disclosed as having diverse benefits including prolongation of the serum half-life (see column 1, lines 44 to 56). Document D3 relates to therapeutic proteins in general (cf. claim 1) including enzymes (cf. claim 4) but makes no mention of serum cholinesterases.

16. The board considers that the skilled person starting from the closest prior art represented by document D11 and seeking to solve the problem formulated above would, in the light of the disclosure of document D3, have

understood that serum cholinesterases could be stabilised by fusion to serum albumin and that the resulting fusion protein would retain serum cholinesterase activity. The skilled person would also have expected that such a fusion protein would exhibit the technical effects known from document D3 to be associated with stabilisation (see point 15, above). These technical effects include a prolonged serum half-life.

17. Thus, in view of the above considerations, the subject-matter of claim 1 is considered to be an obvious solution of the technical problem for the skilled person.

18. The appellants' claim request therefore fails to meet the requirements of Article 56 EPC and is not allowable.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

D. Hampe G. Alt

Decision electronically authenticated