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Datasheet for the decision of 28 July 2009

Case Number: T 0394/06 - 3.3.04

Application Number: 01929345.5

Publication Number: 1265915

IPC: C07K 14/00

Language of the proceedings: EN

Title of invention:
Novel compounds

Patentee:
GlaxoSmithKline Biologicals S.A.

Opponent:
-

Headword:
CASB7439 polypeptide/GLAXOSMITHKLINE BIOLOGICALS

Relevant legal provisions:
EPC Art. 54(1)(2)(4)(5), 56, 83, 123(2)

Relevant legal provisions (EPC 1973):
-

Keyword:
"Novelty, inventive step, sufficiency of disclosure (yes), added matter (no)"

Decisions cited:
G 0005/83, T 0019/90, T 1127/05, T 0406/06

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0394/06 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 28 July 2009

Appellant: GlaxoSmithKline Biologicals S.A.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 21 September 2005 refusing European patent application No. 01929345.5 pursuant to Article 97(1) EPC 1973.**

Composition of the Board:

Chair: U. Kinkeldey
Members: B. Claes
R. Moufang

Summary of Facts and Submissions

I. The appellant (applicant) lodged an appeal against the decision of the examining division to refuse European patent application 01929345.5 having the title "Novel compounds". The application is based on international application PCT/EP01/01779 and was published as WO 01/62778 (which will be referred to in the present decision as the "application" or the "application as published").

II. The examining division refused the application on the grounds that the subject-matter of the claims before them relating to the fusion protein with SEQ ID NO:10 lacked inventive step (Article 56 EPC) and the subject-matter of the claims relating to the vaccine was not sufficiently disclosed (Article 83 EPC), the latter because no therapeutic effect had been demonstrated.

III. With the statement of the grounds of appeal the appellant filed a new main, an auxiliary request as well as a declaration by Mr Tiest and arguments in favour of patentability.

IV. The board summoned to oral proceedings and sent out a communication.

V. With a letter dated 26 June 2009, the appellant filed a new main request, three auxiliary requests, four further documents and a declaration by Dr Pilorget.

VI. Oral proceedings before the board took place on 28 July 2009. During these oral proceedings the appellant filed a new main request with 10 claims.

Independent claims 1 to 6, 9 and 10 of this new main request read:

"1. An immunogenic composition comprising a CASB7439 polypeptide which comprises an amino acid sequence which has at least 70% identity to the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:10 over the entire length of SEQ ID NO:2 or SEQ ID NO:10, or an immunogenic fragment of CASB7439 wherein the fragment comprises an amino acid sequence of one or more of SEQ ID NO:16 to SEQ ID NO:33, and a pharmaceutically acceptable carrier, for use in medicine.

2. An immunogenic composition comprising a polynucleotide encoding a CASB7439 polypeptide or fragment thereof according to claim 1, wherein the polynucleotide is selected from the group comprising SEQ ID NO:8 and SEQ ID NO:9; and a pharmaceutically acceptable carrier, for use in medicine.

3. An immunogenic composition comprising an effective amount of antigen presenting cells, modified by in vitro loading with a CASB7439 polypeptide according to claim 1, or genetically modified in vitro to express a CASB7439 polypeptide according to claim 1, and a pharmaceutically effective carrier.

4. A pharmaceutical composition comprising a CASB7439 polypeptide which comprises an amino acid sequence which has at least 70% identity to the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:10 over the entire length of SEQ ID NO:2 or SEQ ID NO:10, or an immunogenic fragment of CASB7439 wherein the fragment

comprises an amino acid sequence of one or more of SEQ ID NO:16 to SEQ ID NO:33, and a pharmaceutically acceptable carrier, for use in medicine.

5. A pharmaceutical composition comprising a polynucleotide encoding a CASB7439 polypeptide or a fragment thereof according to claim 4, wherein the polynucleotide is selected from the group comprising SEQ ID NO:8 and SEQ ID NO:9; and a pharmaceutically acceptable carrier, for use in medicine.

6. A pharmaceutical composition comprising an effective amount of antigen presenting cells, modified by in vitro loading with a CASB7439 polypeptide according to claim 4, or genetically modified in vitro to express a CASB7439 polypeptide according to claim 4, and a pharmaceutically effective carrier.

9. Use of a pharmaceutical or immunogenic composition according to any of claims 1 to 8, in the manufacture of a vaccine for immunotherapeutically treating a patient suffering from or susceptible to carcinoma in which the carcinoma is colon cancer, or other colon-associated tumours, or other colon associated diseases.

10. A pharmaceutical or immunogenic composition according to any of claims 1 to 8, for use in immunotherapeutically treating a patient suffering from or susceptible to carcinoma in which the carcinoma is colon cancer, or other colon-associated tumours, or other colon associated diseases.

Dependent claims 7 and 8 were dependent on claims 1 and 4.

VII. The following documents are mentioned in the present decision:

(3) Alders *et al.* (1997), Human Molecular Genetics, Vol. 6, No. 6, pages 859-867

(10) Luo *et al.* (2003), PNAS, Vol. 100, No. 15, pages 8850-8855

(11) Spisek *et al.* (2007), J. Exp. Med., Vol. 204, No. 4, pages 831-840

(12) Dong *et al.* (2004), British Journal of Cancer, Vol. 91, pages 1566-1570

(13) Declaration of Dr Anthony Pilorget

(14) Hunt et al. (1987), J. Immunol., Vol. 138, p. 2481-2487

VIII. The arguments of the appellant can be summarised as follows:

Novelty

– Document (3) disclosed the sequence for the human Achaete-Scute homologue 2 gene (HASH2) which was identical to CASB7439 of the invention. The document furthermore disclosed, besides the gene's chromosome location, that gene HASH2 was expressed in extravillus trophoblast cells only and that the

gene order and similar expression patterns in extra-embryonic tissues of mouse and man suggested conservation of this imprinted region in mouse and man.

– Document (3) did not mention any possible or potential medical use or application for the disclosed gene and protein product of the gene. The claims were therefore novel.

Inventive step

– Document (3) was not directed to a similar purpose or effect as the invention, nor did it belong to the same or a closely related technical field. However, given the absence of any more relevant prior art the disclosure in the document served nevertheless as closest prior art.

– The technical problem addressed by the invention was the provision of new immunogenic compositions for use in medicine, particularly in the treatment of colon cancer. This problem was clear from the description of the application as filed from page 1, lines 10-12 and 19-23.

– Extravillus trophoblast cells, which arose during a transient early development stage of the embryo, were immune privileged and did not present MHC Class I complexes (see document (14)). This fact in principle ruled out the possibility that expression of CASB7439 by such cells could either cause an innate immune response or cause the cells to be a target for antigen-specific immunotherapy.

– Since there was no mention in document (3) and any other cited document of any potential medical use or application for CASB7439, the prior art did not give the skilled man any motivation to formulate an immunogenic composition to target CASB7439, with any expectation of providing an advantageous medical effect.

– The extent of data within the application was more than adequate to support the "make plausible" test described in decision T 1329/04. The post filed data was not the sole basis to establish that the patent application solved the problem it purported to solve but rather it supported and increased confidence in the initial finding.

Sufficiency of disclosure

– The amino acid and nucleotide sequences of CASB7439 and the additional information on the recombinant processes for their production sufficed to allow a skilled person to generate these sequences in the laboratory. The present application additionally described immunological/vaccine formulations and compositions comprising CASB7439, and their use in medicine.

– The key contribution to the art were data that CASB7439 was clearly over-expressed in colon cancer and other cancers and had a very low expression in normal tissues (Example 1). The average over-expression in the cancerous tissues

was about 100 fold, and more than 90% of patients strongly over-expressed the CASB7439 transcript in tumours, compared to the very low levels of expression in adjacent normal colon tissue. Once the skilled man was presented with these data the pharmaceutical utility of the compounds was clear and confirmed that a vaccine targeting CASB7439 will specifically target tumour cells but not normal adult tissues.

– Data submitted during the international phase of the patent application suggested that two specific fragments of CASB7439 were immunogenic and might serve as a vaccine to induce a strong specific antibody response. The data further showed that a fragment of CASB7439 was recognised by human CD4+ T-cells and that human CD4+ T-cells recognised an E.coli-derived NS1-CASB7439 fusion protein. These data were compelling evidence that CASB7439 was an excellent cancer vaccine candidate, generating a human T-cell response, despite the human origin of the protein.

– Intranuclear proteins were constantly turned over in the cell and mechanisms existed which allowed such proteins to be processed and presented in MHC Class I cell complexes on the surface of cells including tumour cells. Indeed, also another transcription factor, i.e. Fos-related antigen I, could be used as an immunotherapeutic antigen (in the form of a DNA vaccine, see document (10)). Furthermore, documents (11) and (12) showed that transcription factors expressed by tumours, i.e. SOX2 and ZNF165, naturally elicited immune

responses in humans. These data showed that the epitopes contained in these transcription factors must be presented to the immune system in an accessible way. Document (13) presented data showing that CASB7439 was indeed effective as an immunotherapeutic treatment in a mouse tumour cell challenge model.

– In view of the above the invention met the requirements of Article 83 EPC.

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the following documents:

– claims 1 to 10 of the main request filed at the oral proceedings
– description: pages 1 to 49 as filed at the oral proceedings
pages 50 to 77 as published
pages 1 to 11 of the sequence listing as published
– figures 1 to 6 as published.

Reasons for the Decision

1. The appeal is admissible.

Added matter (Article 123(2) EPC) and clarity (Article 84 EPC)

2. Claims 1 and 4 find a basis in claim 1, claim 7 and claim 12 combined with the first sentence at page 1, all of the application as published. Claims 2 and 5 find a basis in claim 2 as published. Claims 3 and 6

find a basis in claim 5 as published. Claims 9 and 10 find a basis in claims 24 and 25 as published.

3. Accordingly the claims of the main request comply with the requirements of Article 123(2) EPC.

4. The board is also satisfied that the claims comply with the requirements of Article 84 EPC.

Novelty (Article 54 EPC)

5. Document (3), the most pertinent prior art document for the purpose of assessing novelty, discloses the nucleic acid and amino acid sequence for the human Achaete-Scute homologue 2 gene (HASH2) being identical to CASB7439 of the invention, i.e. SEQ ID NOs:1 and 2. However, neither document (3), nor any other cited document, discloses the implementation of the CASB7439 polypeptide or polynucleotide in medicine, or the use of the polypeptide or polynucleotide in the *in vitro* production of CASB7439 antigen presenting cells.

6. Independent claims 1 and 2 are for immunogenic compositions for use in medicine whereas independent claims 4 and 5 are for pharmaceutical compositions for use in medicine based on CASB7439 polypeptide or nucleic acid sequences. Accordingly, these claims, drafted in the so-called "first-medical-use" format are novel pursuant to Article 54(1),(2),(4) EPC.

7. Independent claims 3 and 6 are for an immunogenic and a pharmaceutical composition comprising an effective amount of *in vitro* modified CASB7439 antigen presenting cells and a pharmaceutically effective carrier. Since

the prior art lacks disclosure of the use of the CASB7439 polypeptide or polynucleotide in the *in vitro* production of antigen presenting cells the subject-matter of these claims is novel pursuant to Article 54(1),(2) EPC.

8. Since dependent claims 7 and 8 are dependent on claims for novel subject-matter, the subject matter of these claims is likewise novel pursuant to Article 54(1),(2),(4) EPC.

9. Unlike the other independent claims, claims 9 and 10 are drafted in the "further medical use" format.

9.1 Under the EPC 1973 a patent for a further medical application could, pursuant to case law established by decision G 5/83 (OJ EPO 1985, 64), be granted for a claim directed to the use of a substance or composition for the manufacture of a medicament for a specified therapeutic application ("Swiss-type claim"). The novelty of the subject-matter of such a claim could be derived not only from the novelty of the substance or of the method of manufacture, but also from the new therapeutic application (decision G 5/83, *supra*, points 20 and 21 of the reasons). This "special approach to the derivation of novelty" (see decision G 5/83, *supra*, point 21 of the reasons) constituted a narrow exception to the general novelty requirement and was not to be applied in other fields of technology.

9.2 Article 54(5) EPC, i.e. the article under the EPC 2000 which entered into force in 2007, permits purpose-related product protection for any further new and inventive medical use of a substance already known as a

medicament.

According to Article 1, No. 3 of the Decision of the Administrative Council of 28 June 2001 under Article 7 of the Act revising the EPC of 29 November 2000, revised Article 54(5) EPC is applicable to European patent applications pending at the time of the EPC 2000's entry into force, insofar as a decision on the grant of the patent has not yet been taken, and hence also to the present application (see decision T 1127/05 of 15 January 2008, points 1 to 8 of the reasons).

9.3 Whereas claim 9 is drafted in the so-called "Swiss-type claim" format, claim 10 is drafted in the format foreseen by Article 54(5) EPC.

9.4 In the context of claim 9 and as already mentioned in decision T 406/06 of 16 January 2008 (points 2 to 5 of the reasons), the question could arise whether the exception to the general novelty requirement, which was accepted in decision G 5/83, *supra*, under the EPC 1973 is still justified under the new legal framework which enables the applicant to frame its claims in accordance with the provision of Article 54(5) EPC in order to obtain patent protection for a new therapeutic application of a known medicament. In fact, if this question had to be answered in the negative, the novelty of Swiss-type claims would have to be assessed merely on the basis of the substance itself or the manufacturing process. Claim 9 lacks any features characterising a manufacturing process. Therefore, its subject-matter could be regarded as lacking novelty in view of any document disclosing the known medicament.

10. In the circumstances of the present case however the above question needs not to be answered by the board for the purpose of deciding the case. In fact, as emphasised in point 5, *supra*, the implementation of CASB7439 polypeptide or polynucleotide in medicine and the use of the polypeptide or polynucleotide for producing CASB7439 antigen presenting cells had not been disclosed in the prior art. Accordingly, claims 9 and 10 derive their novelty from the provisions of Article 54(1),(2),(4) EPC.

Inventive step (Article 56 EPC)

11. For assessing 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 and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications to arrive at the claimed invention.

12. In view of the above principles, the board considers that the closest prior art for the purpose of the assessment of inventive step is represented not by the disclosure in document (3), which concerns the cloning of a human gene identical to CASB7439 of the present invention as well as its chromosomal mapping and expression, but by immunogenic compounds applicable in the field of cancer immunotherapy which belong to the

common general knowledge of the skilled person in this technical area.

13. The technical problem to be solved by the claimed invention is then to be regarded as the provision of further immunogenic compounds applicable in the field of cancer immunotherapy. The board is satisfied, based on the disclosure and examples of the application, that this problem is solved by the subject-matter of the claims.

14. It therefore needs to be investigated whether or not the application of nucleic or amino acid sequences in this technical field was rendered obvious to the skilled person.

15. Neither document (3), as already emphasised in point 4, *supra*, nor any of the other cited prior art documents, foreshadow any potential medical use of CASB7439 nucleic or amino acid sequences.

16. In fact, document (3) discloses that expression studies showed that HASH2 is expressed in extravillus trophoplast cells only (page 859, right-hand column lines 23 and 24). Such cells of the early embryo migrate actively and selectively into the maternal tissue during early pregnancy leading to selective adaptations of the maternal spiral arteries (page 863, right-hand column, lines 14 to 16).

17. The appellant has furthermore argued that extracellular trophoblast cells, which thus arise during a transient early development stage of the embryo, are immune privileged cells and do not present MHC Class I

complexes (see document (14)). This fact, in principle, rules out the possibility that expression of CASB7439 by such cells can either cause an innate immune response or cause the cells to be a target for antigen-specific immunotherapy.

18. In view of the above considerations, the board is satisfied that the disclosure in document (3), does not incite the relevant skilled person to imply the sequences of the present invention in cancer immunotherapy. The same applies to all other prior art documents cited in these appeal proceedings. The prior art can therefore not be considered as pointing to the invention as presently claimed.

19. For the above reasons the subject-matter of claims 1 to 10 involves an inventive step (Article 56 EPC).

Sufficiency of disclosure (Article 83 EPC)

20. It is established case law of the boards of appeal that if an application is objected to for lack of sufficient disclosure, these objections have to be based on serious doubts which are substantiated by verifiable facts (decision T 19/90, OJ EPO 1990, 476).

21. In its decision, the examining division has argued that the claimed subject-matter relating to vaccines based on the CASB7439 polypeptide was not sufficiently disclosed in accordance with Article 83 EPC. There was no evidence derivable from the application or provided by the applicant that the sequences of the application had a therapeutic effect if used to treat a patient suffering from or susceptible to carcinoma, whereby the

carcinoma is colon cancer or other colon-associated tumours or diseases. The board notes that this objection would also relate to claims 9 and 10 of the main request before the board.

22. The board notes that in its argumentation the examining division, rather than applying it, has inverted the principle developed in the case law of the boards of appeal whereby it would be required to raise serious doubts which are substantiated by verifiable facts. Already for this reason the argumentation of the examining division must fail to substantiate an objection under Article 83 EPC.

23. The board notes furthermore that even if the approach taken by the examining division were adequate the appellant's arguments as summarised under the heading "*Sufficiency of disclosure*" in section VIII convincingly show compliance of the application with Article 83 EPC in the relevant aspects.

24. In particular, the appellant has shown that there is no reason to doubt that CASB7439, considered to be an intranuclear transcription factor, would not be suitable for producing vaccines for treating carcinoma patients. The appellant persuasively argued that in fact intranuclear proteins were constantly turned over in the cell and mechanisms existed which allowed such proteins to be processed and presented in MHC Class I complexes on the surface of cells including tumour cells. This was also true for transcription factors. Also other transcription factors could be used as an immunotherapeutic antigen (document (10)) and could naturally elicited immune responses in humans

(documents (11) and (12)). These data therefore showed that the epitopes contained in these transcription factors were presented to the immune system in an accessible way. Furthermore, document (13) presented data showing that CASB7439 was indeed effective as an immunotherapeutic treatment in a mouse tumour cell challenge model.

25. All the submissions of the appellant therefore support the conclusion that the disclosure of the application is sufficient. On the basis of the facts of this case, there are no serious doubts substantiated by verifiable facts which could justify an objection that the inventions was not sufficiently disclosed.

26. In view of the above considerations the board is satisfied that the claimed invention complies with the requirements of Article 83 EPC.

Further substantive requirements

27. The board is satisfied that the application as amended during the appeal proceedings complies with the requirements of the EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to grant a patent in the following version:

   – claims 1 to 10 of the main request filed at the oral proceedings

   – description: pages 1 to 49 as filed at the oral proceedings
   pages 50 to 77 as published
   pages 1 to 11 of the sequence listing as published

   – figures 1 to 6 as published.

The Registrar The Chair

P. Cremona U. Kinkeldey