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Application No. / Patent No.	Ref.	Date
01 104 586.1 - 1212 / 1129717 /	T35074PCEPT2	30.06.2008
Proprietor TERMAN, David S., et al		

Interlocutory decision in Opposition proceedings (Art. 101(3)(a) and 106(2) EPC)

The Opposition Division - at the oral proceedings dated 15.04.2008 - has decided:

Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the Convention.

The reasons for the decision are enclosed.

Documents for the maintenance of the patent as amended:

Description, Pages

1, 2, 5-7, 10, 12-21	of the patent specification
3, 4, 8, 9, 11, 22	filed during Oral proceedings on 15.04.2008

Claims, Numbers

1	filed during Oral proceedings on 15.04.2008

Drawings, Figures

1, 2	filed during Oral proceedings on 15.04.2008

Possibility of appeal
This decision is open to appeal according to Article 106(2) EPC. Attention is drawn to the attached text of Articles 106 to 108 and Rules 97 to 98 EPC.

Opposition Division:

Chairman:	Fotaki, Maria
2nd Examiner:	Smalt, Rolf
1st Examiner:	Moonen, Peter

Weinachter, Robert
Formalities Officer
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Enclosure(s): 10 page(s) reasons for the decision (Form 2916)
Wording of Art. 106 - 108 and R. 97 - 98 EPC (Form 2019)
Documents relating to the amended text
Minutes of oral proceedings

to EPO postal service: 18.06.08

Registered letter with advice of delivery
EPO Form 2327 12.07CSX

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Application No.: 01 104 586.1

Patent No.: EP-B- 1129717

A copy of the communication (communication, decision, minutes) was printed for and notified to each of the following representatives/parties:

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INTERLOCUTORY DECISION

According to Article 101(3) EPC

Facts and Submissions

I.

European Patent number 1 129 717 was granted in response to European Patent Application number: 01 104 586.1, which was derived from the earlier application 91 903 963, published as WO 91/10680. Date of filing 17.01.1991.
Claimed priority: 17.01.1990 (US 466,577).

The mention of the grant of the patent was published in European Patent Bulletin 2005/37 of 14.09.2005.

The Proprietors of the patent are Terman & Stone (represented by Dr.H. Wichmann of Isenbruck et al.).

Notice of Opposition has been filed by the Opponent Active Biotech AB on 13.06.2006 (represented by Ms.S. Roques of J.A. Kemp & Co.).

The single claim of the main and only maintained request under consideration has been filed during Oral Proceedings held on 15.04.2008. Also newly filed were amended description pages 3,4,8, 9, 11, 22 of the patent, and Figures 1 and 2. Said single claim reads as follows:

Use of an agent which is a homologue of a *Staphylococcal aureus* enterotoxin A (SEA) or B (SEB) that has a z value exceeding 10 in Monte Carlo analysis using an algorithm described by Lipman and Pearson, said homologue being mitogenic to T lymphocytes, in the manufacture of a medicament for administration to a patient to treat carcinoma.

A list of the documents was cited and numbered as follows:

I. D1-D19 and P10: in the Notice of Opposition;

ii. D20-D50 and P9: in the reply letter of the Proprietor of 04.12.2006;

iii. D51-D52: in the reply letter of the Opponent of 04.03.2008;
iv. D53-D65: in the reply letter of the Proprietor of 31.03.2008.

The most relevant documents to the interlocutory decision have been:

D1 WO 91/10680, filing date 17.01.1991: the originally filed parent application
P1 US 466,577, filing date 17.01.1990; the priority document of D1
D2 US application serial No. 07/416530, filing date 03.10.1989 (the "grandparent")
D9 WO 91/04053, filing date 14.09.1990: interfering patent application
D10 WO 92/01470, filing date 16.07.1991: interfering patent application
P10 SE 9002479-5, filing date 20.07.1990: the priorty document of D10
D11 Shcheglovitova et al., EKSP ONKOL 11 (1989) 73-74- English translation
D13 Hedlund et al., Cellular Immunology **129** (September 1990) 426-434; intermediate publication
D14 Dohlstein et al., Immunology **71** (September 1990) 96-100; intermediate publication
D15 Lipman & Pearson, Science **227** (1985) 1435-41
D19 Declaration of Dr. Pearson, filing date 08-11-2000
D21 Declaration of Prof.H. Grey, August 2002
D22 Declaration of Prof.H. Grey, September 2003
D31 Terman & Stone Proc Int Workshop on Superantigens, N.Y.; p13, post-published
D52 Terman, Methods Enzymol **137** (1988) 496-515
D54 Das & Langone, J Immunology **142** (1989) 2943-8
D62 Bertram et al., Cancer Res **45** (1985) 4486-94
D65 Brodin et al., Adv Drug Del Rev **31** (1998) 131-142 (post-published)

Annex 1: Results of present day FASTA alignments, filed with the Notice of Opposition

II.

I. The Opponent requested the contested patent to be revoked in its entirety in accordance with Articles 99 and 100(a), (b) and (c) EPC.

Essentially, the Opponent put forward the following facts and arguments, still relevant to the subject-matter of the main request:

(a) The subject-matter of the European patent is not patentable in view of a lack of

novelty under Article 54(3) EPC and of an inventive step under Article 56 EPC. With respect to the lack of novelty the Opponent cites D9 and D10; relevant to the novelty objection is, that it is argued that the main claim is not entitled to the priority date of P1. With respect to the lack of an inventive step, it is essentially submitted by the Opponent that the subject-matter of the claim is obvious to the skilled person on the basis of the closest prior art document D52.

(b) The European patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. Three different lines of reasoning were followed to demonstrate an insufficiency, insofar that the skilled person was not sufficiently enabled to carry out the invention, in particular with respect to the technical requirements of the techniques.

(c) The subject-matter of the European patent extends beyond the content of the earlier application as originally filed (reference being made to Article 76(1) EPC).

III.

Conversely, the Patentee requests rejection of the Opposition and maintenance of the patent with the claim and other documents as filed during the Oral Proceedings of 15.04.2008.

In support of the request, the Patentee has submitted the following arguments: None of the available documents is prejudicial to the novelty, even if the priority claim is not recognised, as the documents do not refer to the use of SEA and SEB homologues in the treatment of patients having carcinoma. In the light of the closest prior art document D11 the invention is not made obvious to the skilled person. This person would also not be hindered to carry out the invention as claimed, eg as the technique options made no essential difference. Finally, the claimed invention has a clear basis in the originally filed parent application D1.

IV.

All Parties have requested Oral Proceedings; these were held on 15.04.2008. The minutes of the Proceedings are on file. Essentially, the arguments delivered by the Parties in the Proceedings expanded on the earlier raised arguments, except that

the opponent now identified D52 as the closest prior art document. Some of the objections raised in the Notice of Opposition have become moot due to the limitation of the subject-matter claimed in the new main request filed during the Oral Proceedings.

An Official Communication concerning substantive examination resulting in a brief preliminary opinion was issued on 03.01.2008, setting out the points to be discussed, and annexed to the summons to Oral Proceedings.

The Oral Proceedings were concluded with the interlocutatory decision to maintain the patent according to the main request.

Reasons for the Decision

1. Admissibility

The Opposition is admissible, because it meets the requirements of Articles 99(1) and 100 EPC and of Rules 3(1) and 76 EPC.

2. Amendments

The amended description pages of the patent, the Figures and the claim of the main request are admissible in respect of Article 76(1) and 123(2) and (3) EPC, since their subject-matter neither extends beyond the content of the earlier (parent) application as filed, nor extends the protection conferred by the European patent.

Article 76(1) EPC: Extension beyond the content of the earlier application **D1.**
The Opponent has in particular argued that the manufacture of a medicament for administration to a patient to treat carcinoma has no basis in D1. O submitted that D1 refers only in the examples of this application to carcinomas and on page 52 mentioned only that "the data given herein for rabbits with carcinoma is expected to be predictive of success when the compositions are applied to humans with spontaneous tumours as well". In addition, the Opponent missed for the claimed homologues of SEA or SEB the link with the examples: the examples do not

mention homologues.

The Opposition Division (OD) can follow the Proprietor with respect to the claimed subject now limited to homologues of the enterotoxins SEA or SEB applied in the examples, and considered to overcome in this way the first objection of the Opponent. With respect to the link of the examples to the use of homologues, the OD considers that the specification of D1 as a whole provides sufficient basis: at numerous positions in the application reference is made not only to SEA and SEB, but also to polypeptides having structural and reactive similarities (see eg page 25 lines 9-16), which would lead to similar results in animal studies.

3. Priority right: Article 87 EPC

The claimed subject-matter is not entitled to the claimed priority date of **P1** (17.01.1990). The OD has followed the position of the Opponent in this respect, in view of the overlapping "grandparent" application **D2**, filed October 3, 1989. A statement in this respect has also been made on the top of page 1 of D1, referring to P1 as a continuation in part of D2.

It is agreed that D2 does not mention the homologues as defined in the claim of the main request. However, the OD cannot follow the position of the Proprietor, that therefore D2 is directly not anymore of relevance.

The OD considers that D2 discloses not only the use of the enterotoxins themselves (in the treatment of carcinoma) but also of an homologue of SEB following in the structural and functional definition of the claimed subject-matter (see eg example 12 of D2). A same part of the invention was according to the OD disclosed in D2 and in P1, leading to a loss of the entitlement of the subject-matter of the claim of the main request, encompassing this same part of the invention already disclosed in D2.

4. Novelty

The Opponent has cited documents **D9** and **D10** under Article 54(3) EPC against the claimed subject-matter. D9 has a filing date in the priority interval of the

opposed patent and is, taking account of the denied entitlement to priority for the opposed patent, fully citable under Article 54(3) EPC. D10 is considered to be entitled to the claimed priority date (see also priority document **P10**, on file); the filing date of P10 is in the priority interval of the opposed patent. The subject-matter of P10/D10 is therefore, taking account of the denied entitlement to priority for the opposed patent, fully citable under Article 54(3) EPC.

The OD can however not follow the position of the opponent that D9 and D10 are prejudicial to the novelty of the claimed subject-matter. Both D9 and D10 are not considered to have all technical features in common with the subject-matter of the claim of the main request.

D9 discloses pharmaceutical compositions for treating malignancies/cancers comprising eg staphylococcal enterotoxines and related proteins like bacterial exoproteins. This document however does not refer to the treatment of carcinomas, and is therefore not considered to be prejudicial.

D10: subject-matter already disclosed in P10 is relevant. P10 discloses antibody conjugates useful in a method for treating cancer; the conjugates are made up of eg enterotoxins attached to antibodies directed against unwanted cells in the body (to achieve the desired tumour targeting). The enterotoxins may include SEA, SEB and related proteins having essentially the same mode of action. The conjugation may be by chemical cross-linking or in the form of a fusion protein (page 2 of P10). It is the opinion of the OD that novelty of the presently claimed subject-matter may be acknowledged over the disclosure of D10 as an overlap in subject-matter is absent. P10/D10 is not referring to the use of a homologue of SEA or SEB in the manufacture of a medicament for administration to a patient to treat carcinoma. The examples of P10 (page 6 and further) refer to the use of an antibody raised against human colon carcinoma cell line and chemically cross-linked to SEA by itself (example 4); this conjugate was tested for binding to colon carcinoma cell lines. The claims of P10 (eg claim 7) do not relate to a specific (targeted) treatment of carcinoma, let alone with conjugated homologues of SEA or SEB.

5. Inventive step

The subject-matter of the claim is founded on an inventive step (Article 56 EPC), in particular as it is considered that at the filing date the skilled person would not expect to be successful in the medical treatment as claimed.

I. In the Oral Proceedings the Opponent identified **D52** as the closest prior document and stated as the technical problem the putting into effect the use of toxins as suggested in D52.
The OD cannot however follow the opponent that D52 is the closest state of the art. D52 is an article authored by one of the inventors of the opposed patent, and considers the preparation of Protein A for the treatment of cancer. It is agreed that D52 concerns not only the preparation of Protein A and also mentions the presence of a number of contaminants including staphylococcal enterotoxins. D52 does not however specify in isolation the use of purified enterotoxins in the treatment of patients having a carcinoma; it is mentioned that the contaminants (various staphylococcal products working alone or together) may contribute to the observed antitumour effects of protein A. The Proprietor referred in this respect also to **D54**, published after D52, mentioning the dissociation between mitogenic activity of enterotoxin contaminants and the anti-tumour activity of Protein A (in particular the last paragraph on page 2947). Taking the technical problem as put forward by the Opponent the OD cannot follow that the proposed solution was obvious to the skilled person.

ii. The OD agrees with the choice of the closest state of the art of D11 as stated by the Proprietor; D11 was in the written phase also taken by the Opponent as the closest prior art document. The definition of the technical problem then given was: the provision of a new way to treat carcinoma in humans; the solution being the the use of S. aureus enterotoxins/homologues to treat carcinoma.

The several statements on page 3 of D11 would not lead the skilled person to pursue further to find a solution as presently claimed.
Thus, the OD considers that it was not obvious for the person skilled in the art to arrive at the proposed solution; he could do it, but would not do it in view of the negative results given in D11, and in the absence of other direct hints to positive results with carcinoma.

iii. Other documents referred to as alternative closest prior art documents by the

Opponent are **D13** and **D14** (both citable in view of the denied entitlement of claim 1 to the priority date of P1). The OD can however follow the Proprietor that these documents do not differ in their teaching with respect to the expectation of success of solving the technical problem, formulated as the provision of a new way to treat carcinoma in humans. Both documents relate to SE dependent cell-mediated cytotoxicity (SDCC) for killing MHC class II-expressing target cells and possible therapeutical use thereof, however without any indication that the skilled person would be succesfull in vivo eg in the treatment of patients having carcinoma.

6. Disclosure of the invention

The Opponent has argued along three different lines that the disclosure of the invention is insufficient:

i. Although the patent has disclosed positive results for a rabbit model of carcinoma using only SEA, it is not disclosed how the negative results of eg D11 are explainable.
ii. The functional feature in the claim, ie the need for the homologue to be mitogenic to T-lymphocytes, is not sufficiently defined, as it lacks relevant information to carry out the invention.
iii. The structural feature of the homologues in the claim ("*a z value exceeding 10 in* ...") poses a problem to the skilled person, as apparently different algorthms with different results are possible; moreover, the results are dependent on the size of the available databases, which size increase with time, and in the FASTA search a number of parameters have to be set. The z value specified by the claim encompasses a wide array of proteins which are in no way related to SEs, are not SE homologues and which cannot be used in the invention.

With respect the first line of reasoning the Proprietor mentioned that indeed D11 is unsuccessful, but that this is common to the treatment of for example patients having cancer (reference was made to a well known monoclonal antibody in breast cancer and uracil treatment) having many negative outcomes but nevertheless are considered to be succesfull drugs in the treatment of cancers. The OD can follow this line of reasoning. The declarations of Dr. Grey (D21/D22), provided by the Proprietor, make clear that the criteria for testing a compound for the treatment of

cancer do not present an undue burden; the physician will not be hindered by varying succes rates to try a drug if it is succesull. D31 is a post published document providing proof that a homologue can be succesfull. D65 is another post-published document (page 133, right column) providing proof that native SEA alone does not work for an undefined cancer. A varying success however does not make a therapeutical method useless.

With respect to the second line of reasoning, the OD can follow the reasoning of the Proprietor: tests for mitogenicity to T lymphocytes are in the art, and a particular level of activity is not considered to be a necessary feature for the homologues.

With respect to the third line of reasoning the Proprietor has for example in the reply letter of 04.03.2008 referred to the declaration of Dr. Pearson concerning the two algorithms and parameters used:
"If a z value exceeding 10 is obtained, then that protein has statistically significant homology to the native SE or SpE protein irrespective of which precise combination of FASTA parameters was used. This "sequence homology" would satisfy one of the two tests required by the present claims, the other, independent test requiring the demonstration of superantigen biological activity".
See page 7 of P´s letter.
The line of arguing of the Opponent has been that the present day FASTA program cannot be used to identify whether a protein would, or would not, have a z value over 10 using the methodology referred to in the opposed patent. In view of the statement of Dr. Pearson the OD is satisfied that the skilled person can put the invention into practice across the breadth of the claims without undue burden: the claim specifies only homologues of SEA and SEB which should have the functional biological activity to be encompassed by the claim.

5. Decision

The Patent Proprietor approved the text of the new request forming the basis of the present interlocutory decision. The Opponent had also the opportunity to comment during the Oral Proceedings.

The grounds of opposition under Article 100(a), (b) and (c) EPC do not prejudice maintenance of the patent in amended form.

The Opposition Division therefore is of the opinion that, taking into consideration the amendments made, the patent and the invention to which it relates meet all the requirements of the EPC.

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Application No. / Patent No.	Ref.	Date
01 104 586.1 - 1212 / 1129717 /	T35074PCEPT2	30.06.2008
Proprietor TERMAN, David S., et al		

Provision of a copy of the minutes in accordance with Rule 124(4) EPC

The attached copy of the minutes of the oral proceedings is sent to you in accordance with Rule 124(4) EPC.

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Enclosure(s): Copy of the minutes (Form 2309)

Registered Letter
EPO Form 2042 12.07CSX

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Application No.: 01 104 586.1

Patent No.: EP-B- 1129717

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Application No.: 01 104 586.1

Patent No.: EP-B-1129717

Minutes of the oral proceedings before the OPPOSITION DIVISION

The proceedings were public.

Proceedings opened on 15.04.2008 at 9:00 hours

Present as members of the opposition division:

Chairman:	Fotaki, Maria
1st member:	Moonen, Peter
2nd member:	Smalt, Rolf
Minute writer:	Smalt, Rolf

Present as or for the party or parties:

- For the Proprietor(s): TERMAN, David S., et al

  Representative: Hendrik Wichmann, EPA
  Accompanied by: Dr. David S. Terman, inventor / proprietor

- For the Opponent 1: Active Biotech AB

  Represenative: Sarah Roques, EPA
  Accompanied by: Dr. Goran Forsberg, Head of Scientific Affairs at Active Biotech AB

The identity of the person/s (as well as, if applicable, that of the witness or witnesses) and, where necessary, the authorisation to represent/authority to act were checked.

Essentials of the discussion and possible relevant statements of the parties:

Abbreviations used: Ch = chairperson; O = opponent; OD = opposition division; P = proprietor.

Ch, after opening formally, requested the representatives to introduce their respective accompanying persons. P requested that Mr. Terman may speak on technical issues only, referring to the guidelines E-III 6 and G4/95. O objected, as legal submissions by Mr. Terman were not allowed, and any technical submissions were not pre-announced. P cited T621/98 in an argument that parties are not accompanying persons. O considers this to apply only to nationals of contracting states, which Dr. Terman is not. Ch allowed submissions by Dr. Terman on existing technical arguments. The same applies to Dr. Forsberg, accompanying O.

Ch confirmed the current and pending requests for P as a main request with three claims and an auxiliary with two claims, both of 31.3.2008. Amended pages of the description are not presently part of any of the requests, but could be submitted later, depending on the outcome of the discussion in light of Art.123(2) EPC. O requests revocation in its entirety, based on objections under Art.76(1), 123(2), 100(a) (Art.54 and 56) and 100(b) EPC.

Ch accepted D1-D65 into the proceedings, but noted that D51 and D52 were missing in the file, although it was not disputed that they had been filed. O submitted further copies.

A discussion of the term carcinoma in light of Art.76(1) EPC ensued, in which O submitted that treatment of carcinoma in conjunction with enterotoxin homologue had no basis in the parent application as filed (D1). Page 52 of D1 describes carcinoma from rabbit, and human spontaneous tumours. On page 35 in line 17 onwards, the VX-2 papilloma-derived carcinoma model in rabbit is described. Reference was also made to the mitogenicity to cells in claim 23 of D1, and page 18, lines 9-13 and 18-19, where the term highly mitogenic is used, whereas the present claims are much more moderate in their requirements. Objection is also made to the use of a fusion protein as a medicament; page 43 line 43 of D1 talks only of fusion proteins for production purposes of homologous (i.e. endogenous) protein, which is then processed to yield the native protein. The newly filed figure 1 is considered to contravene Art.123(2) EPC.
P objected that the fusion protein as medicament issue was raised for the first time at oral proceedings. With regards to carcinomas, the test animal is based thereon, so it is inconceivable that the skilled person would not consider it. Reference is made to D1, page

15, in relation to the Lipman-Pearson method, and furthermore to page 25, lines 9-16, page 35, page 48 last line to page 49. line 5 with regard to related proteins, and page 52. D5, and expert declaration submitted during examination, clearly indicates that the product is intended for human treatment; nobody is seriously or primarily interested in treating tumours in test animal species.
O considered that D1 is limited to homologues active in the VX-2 model, which is more limiting that a mere structural limitation on the basis of a Z-value. The highly mitogenic argument is repeated.
P considers that the Z-value obtained from the Lipman-Pearson algorithm is a purely structural definition.
After a suspension of the proceedings from 10:10 to 10:35 hrs, Ch announced that:
1) the OD is of the view that the application as a whole provides basis for the use of homologues of the protein for treating carcinoma's, page 52 provides basis for application to humans. Basis under Art.76(1) EPC is therefore acknowledged, but only for the agents as provided in the examples and homologues thereof; not any homologues.
2) the new figure 1 contravenes Art.123(2) EPC.
3) opinion is reserved on the term highly mitogenic, as P has not been heard on this point.
4) basis is not acknowledged for fusion proteins in conjunction with treatment, also in view of point 1) above.
The main request is therefore considered not allowable, the auxiliary request is.

P filed an amended claim as replacement auxiliary request 1 (AR1).
O submitted in light of Art.76(1) EPC that page 52 of D1 relates to compositions used in the examples, not to homologues.
P considered there to be basis for homologues of SPE (not SE) on page 14, line 11 onwards of D1, and further made reference to page 25, line 9 in connection with generic and specific language, page 14, line 31 and page 52. Dr. Terman added that he considers the statements on page 25 to form the bridging paragraph.
O considered page 25 to be in the context of tumours, not carcinomas; they only appear in the examples. Dr. Terman made reference to D5, which describes VX-2 as a reliable model for carcinoma, that carcinoma is implicit in the application, and that the standard for testing the homologues is the VX-2 model.

After suspension from 11:25 to 11:45 hrs, Ch announced that the OD considers claim 1 of AR 1 referring to SEA, SEB, and their homologues to meet the requirements of Art.76(1)

EPC, and invited P to make a submission on the term highly mitogenic.

P referred to page 17, line 32, where no mention is made of highly, and to D21, item 6, and D22: declarations by Dr. Grey of the National Cancer Institute. Further reference was made to page 18, lines 4-5 of D1.
O referred to page 18 of D1, in which a distinction is made of SE's with e.g. phytohemaglutinin on the basis of the former being highly mitogenic.

After suspension from 11:55 to 12:02 hrs, Ch announced the OD's opinion that claim 1 that uses the term mitogenic on its own is considered to meet the requirements of Art.76(1) EPC. Discussion on allowability of figure 1 and amended pages is postponed until P has had an opportunity to file adapted drawings and/or description pages.

The next substantive issue discussed was that of novelty, combined with the issue of the priority document D2 and the continuation in part in the US.
O submitted that all features of the application are disclosed in D2, in particular reference to carcinoma is made on page 36 of D2. The Z-value of in excess of 10 obtained with the Lipman & Pearson algorithm is not critical; it is the same invention. Reference is made to page 3 of D19 and page 1439 of D15, which indicate that Z values in access of 6 are probably significant, and those in excess of 10 are considered to be significant. This value is hence the standard to be regarded as significant.
P argued that in view of G2/98, under point 6.6, the subject-matter submitted by O to be already present in D2 does not meet the standard of directly and unambiguously derivable.

After suspension form 12:25 to 12:32 hrs, Ch announced that claim 1 of auxiliary request 1 is not considered to enjoy priority right of 17.01.90 (filing of D2), and that D9 and D10 therefore are regarded as prior art under Art.54(3) EPC.
O submitted that D10 discloses treatment of carcinomas on page 3, line 27 and page 5, line 27. The claims of D9 do not exclude class II-expressing CTR's.
P held that D9 does not relate to carcinomas, but that it only mentions lymphomas and melanomas. The same argument applies to D10. Reference was made also to D27, page 237.
O referred to D10, page 5, line 23, describing an antibody directed to a tumour antigen. Further reference was made to page 10 and page 6, paragraph 3.

After a break between 12:44 to 13:28, Ch announced that the OD considers novelty of claim 1 of AR 1 to be acknowledged over D10 and D9. O was invited to address inventive step in view of D11.
O referred to D52, page 496, the last paragraph of page 497 describing Staphylococcus enterotoxins as strong T cell mitogens, and page 499 mentioning them to be useful in tumour therapy based on work performed on carcinomas. Reference was also made to D51, page 1117, right-hand column.

P considered D11 to represent the closest prior art, and noted that the results obtained therein where characterised as statistically unreliable; see page 3, paragraphs 1 and 2. In D62, SE's are excluded as the source of the mitogenic activity in extracts: page 4490, right-hand column, paragraph 3. In D54, it is shown to make no difference for mitogenicity whether SE's are added or not.
O submitted that D13 and D14 have become relevant for inventive step in view of the priority situation. It was furthermore considered that D53 to D65 merely represent different routes of investigation, but that no consistent technical prejudice could be derived there from. Reference was also made to the principle of the awarding protection commensurate with the extent to which the invention could be regarded as sufficiently disclosed.
Dr. Terman pointed out that in D66, SE was added to protein A, with no effect, as was the case in D54, previously referred to. In D34, the guidelines from the National Cancer Institute, a minimum ratio of tumour vs. control of 140% is indicated for these tests to be considered as moderately effective, and 150% to be designated as extremely effective. The study showed a ratio of 130%, which must therefore be discarded as not effective.
O regarded D52 as the closest prior art, which describes studies on tumours, but work leading up to it was based on carcinomas. It suggests to purify the effective factor, which is hence non-inventive.
Dr. Terman referred in response to D62, page 4490, right-hand column, middle paragraph, which states that the mitogenicity is inactivated by mild heating to 56°C, where enterotoxins are notoriously heat resistant.
Dr. Forsberg replied that such mild heating is known to cause precipitation of e.g. proteinaceous factors, which could clearly cause coprecipitation of the SE's, which are present in the picomolar range.

After suspension between 14:15 and 14:30, Ch announced that the OD regards D11 as the closest prior art, the objective problem therefore being the provision of new ways for

the treatment of carcinomas. The claimed subject-matter of the present auxiliary request is considered inventive.

Submissions are invited in light of objections under Art.100(b) EPC.
O argued that the Z value changes over time, as it is amongst others dependent on the database size. It is furthermore submitted that from D10, figure 2 (legend on page 37) it follows that antibody-SEA fusions are effective, but SEA alone is not. D65, on page 133 (cited by P on page 5 of the submissions of 31.3.'08) states that a conjugate is required for effectiveness. D31, D32, D34 and D38 all state that a conjugate is needed to achieve the desired effect. Furthermore, the effect was only shown in the VX-2 model, and is not repeatable in other models, including that used in D11. Only highly mitogenic homologues (may) work, but the claims are not so limited.

P relied on D65, page 133 and D21 and D22 to show that SE's alone do work, tested in the VX-2 model, considered to be suitable by Dr. Thompson (of D5). Dr. Terman added that D31 shows remission in the VX-2 model with SE's alone.
Ch enquired what the difference was between the teaching of the patent and that of D10 and D11, which showed doubtful success. Dr. Terman explained that there are multiple models showing significant effect with unconjugated SE's, but the effect may be tumour-specific, and some may be resistant to a particular treatment.
O argued that D65, page 133 shows a lack of therapeutic effect of unconjugated SE's. D13 relates to MHC class II, which implies a lymphoma setting, not a carcinoma.

After suspension from 15:05 to 15:35 hrs, Ch announced that the subject-matter claimed in the auxiliary request is considered to be sufficiently disclosed, that there are large variations in the sensitivity of the sets of data discussed, and that there is no data to compare like with like in respect of the data obtained in the patent, i.e. O has not provided arguments substantiated by verifiable facts that the present data cannot be obtained with the information provided. Ch asked P for further submissions in respect of the figure and the description in light of the outstanding issues under Art.123(2) EPC. P replaced the main request with the single amended claim of AR 1, submitted replacement pages 3,4,8,9,11,22, and requested deletion of previous figure 1, with renumbering of old figures 2 and 3 to new figures 1 and 2.

On the basis of these application documents, Ch pronounced the decision of the OD to

maintain the patent in amended form in accordance with Art.101(3)(a) EPC.

After deliberation of the opposition division,

- the chairman announced the following **decision**:

"Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the European Patent Convention. The currently valid documents are those according to the Main request. "

Regarding the reasons for the decision, the chairman referred to:

Article 101(3)(a)EPC: Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the European Patent Convention.Patent is maintained as amended.

The chairman **closed the oral proceedings** on 15.04.2008 at 16:00 hours.

signed:

Fotaki, Maria
. . . . . .
Chairman

signed:

Smalt, Rolf
. . . . . .
Minute Writer

Enclosure(s):
New main request and amended pages 3,4,8,9,11,22, and figures 1 & 2 as filed during oral proceedings
Form 2339.4

Documents for the maintenance of the patent as amended

Description, Pages

1, 2, 5-7, 10, 12-21	of the patent specification
3, 4, 8, 9, 11, 22	filed during Oral proceedings on 15.04.2008

Claims, Numbers

1	filed during Oral proceedings on 15.04.2008

Drawings, Sheets

1/2, 2/2	filed during Oral proceedings on 15.04.2008

After deliberation of the opposition division,

- the chairman announced the following **decision**:

"Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the European Patent Convention. The currently valid documents are those according to the Main request.
"

Regarding the reasons for the decision, the chairman referred to:

Article 101(3)(a)EPC: Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the European Patent Convention.

The chairman **closed the oral proceedings** on 15.04.2008 at 16:00 hours.

Fotaki, Maria
Chairman

Smalt, Rolf
Minute Writer

Annex(es):
New main request and amended pages 3,4,8,9,11,22, and figures 1 & 2 as filed during oral proceedings

Form 2339.4