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Datasheet for the decision of 10 March 2010

Case Number: T 1918/06 - 3.3.04

Application Number: 90913598.0

Publication Number: 0489837

IPC: C12P 21/08

Language of the proceedings: EN

Title of invention:
Inhibition of lymphocyte adherence to vascular endothelium utilizing a novel extracellular matrix receptor-ligand interaction

Patentee:
Fred Hutchinson Cancer Research Center

Opponent:
Merck Serono S.A.

Headword:
Lymphocyte adherence/FRED HUTCHINSON CANCER RESEARCH CENTER

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 123(2)(3)

Relevant legal provisions (EPC 1973):
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Keyword:
"Admissibility of late filed requests (yes)"
"Main request - added matter (no), sufficiency of disclosure, clarity, novelty, inventive step (yes)"

Decisions cited:
G 0002/08

Catchword:
-

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Case Number: T 1918/06 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 10 March 2010

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 26 October 2006 concerning maintenance of European patent No. 0489837 in amended form.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: B. Claes
G. Alt

Summary of Facts and Submissions

I. This decision is on the appeal of the appellant (opponent) against the interlocutory decision of the opposition division to maintain the European patent No. 0 489 837 with the title: *"Inhibition of lymphocyte adherence to vascular endothelium utilizing a novel extracellular matrix receptor-ligand interaction"* in amended form. The patent is based on European patent application 90913598.0 which was published as WO91/03252.

II. Independent claim 1, dependent claim 3 and independent claim 13 of the granted patent read:

"1. Use of an antibody, or fragment or derivative thereof which binds to the α4β1 receptor and inhibits the adherence of nucleated hematopoietic cells to vascular endothelial cells for the preparation of a pharmaceutical composition for use in a mammal to suppress an immune response.

3. The use according to claim 1 or 2 wherein the antibody binds to the α4 subunit of the α4β1 receptor.

13. Process for the preparation of a pharmaceutical composition for suppressing an immune response in a mammal characterized in that as an essential constituent of said pharmaceutical composition an antibody or fragment or derivative thereof as defined in any one of claims 1 to 12 is used."

Claims 2 and 4 to 12 depended either directly or indirectly in claim 1.

III. The grounds of opposition invoked by the sole opponent were those under Article 100(a) EPC (in particular those under Article 54 and 56 EPC), Article 100(b) EPC and Article 100(c) EPC.

IV. The opposition division maintained the patent with independent claims essentially as granted, whereby however the wording "mammal" was limited by amendment to "human". In the course of the decision, the opposition division held that document (D10) was not prior art under Article 54(3) EPC as it had not been established that its priority documents had been filed at the EPO.

V. After the board summoned the parties to oral proceedings, the appellant filed, with a letter of 8 January 2010, a copy of a PCT form to support its arguments regarding document (D10); and the respondent (patentee) filed on 4 February 2010 a new main request and 3 auxiliary requests.

VI. Oral proceedings took place on 10 March 2010. During these proceedings the respondent filed a new main request with 6 claims. This new main request differed from the main request filed on 10 February 2010 only by an amendment in claim 6. Independent claims 1 and 6 of the new main request read:

"1. Use of a monoclonal antibody or fragment thereof which binds to the α4β1 receptor and inhibits the adherence of lymphocytes to vascular endothelial cells thereby suppressing the immune response for the preparation of a pharmaceutical composition for use in

a human to suppress the immune response, wherein the antibody or fragment thereof binds to the α4 subunit of the α4β1 receptor.

6. Process for the preparation of a pharmaceutical composition for suppressing the immune response in a human characterized in that as an essential constituent of said pharmaceutical composition an antibody or fragment thereof as defined in any one of claims 1 to 5 is used."

Claims 2 to 5 depended either directly or indirectly on claim 1.

VII. The appellant (opponent) requested that the decision under appeal be set aside and that the patent be revoked. The appellant also requested reimbursement of the appeal fee. In addition the appellant requested not to admit into the proceedings the requests filed by the respondent on 10 February 2010.

The respondent (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request filed during the oral proceedings.

VIII. The following documents are mentioned in this decision:

D1: Holzmann *et al.* (1989), Cell, Vol. 56, pages 37-46.

D2: Takada *et al.* (1989), EMBO J., Vol. 8, No. 5, pages 1361-1368.

D4: Holzmann & Weissman (1989), EMBO J., Vol. 8, No. 6, pages 1735-1741.

D8: Stevens *et al.* (1982), J. Immunol., Vol. 128, No. 2, pages 844-851.

D9: Freemont *et al.* (1983), Arthritis and Rheumatism, Vol. 26, pages 1427-1433.

D10: WO90/07321

D25: Jalkanen *et al.* (1987), Ann Rev Med., Vol. 38, pages 467-76.

D27: Holzmann & Weissman (1989), Immunological Reviews, No. 108, pages 45-61.

D32: Pals *et al.* (1989), Immunological Reviews, No. 108, pages 111-133.

D36: Kamata *et al.* (1995), Biochem. J., Vol. 305, pages 945-951.

D39: Schrieber *et al.* (1987), J. Rheumatol., Vol. 14, No. 2, pages 194-196.

D41: Streeter *et al.* (1988), J. Cell. Biol., Vol. 107, pages 1853-1862.

IX. The arguments of the appellant (opponent) in the case can be summarised as follows:

Admissibility of the requests filed on 10 February 2010

– The appellant argued that these requests should not be admitted as they had only been produced four weeks before the oral proceedings. This was surprising and allowed the appellant too little time to react. The amended claims took features from the description but the respondent did not give full details about the support for the amendments, referring to "many other passages" thereby leaving it to the appellant to find those other passages. If amendments were filed late, they should be clear. In the case of these requests, the claims were not narrower but different. The respondent had submitted in writing that the new requests were a response to the appellant's submission of 8 January 2010 but that was not a new submission but only a copy of a PCT form regarding the status of document (D10). Therefore, the requests were not a real response. The late filing was an abuse of procedure.

Added matter - Article 123(2) EPC

– The wording "wherein the antibody or fragment thereof binds to the α4 subunit of the α4β1 receptor" in claim 1 found no basis in the application as filed, neither as regards "binding" nor as regards "the α4 subunit". The passages on page 52, lines 5 to 11, and on page 54, lines 4 to 19, relied on by the respondent, did not support this introduced amendment in its general form.

– There was no support in the application as filed, and in particular not in the passage on page 61, lines 20 to 21, for the combination in claim 1 of the notion "binding to the α4 subunit of the α4β1 receptor" and "inhibits the adherence".

Article 123(3) EPC

– Since the independent claims had been amended to refer to "the immune response" as compared to "an immune response" in the claims as granted, this consisted of an *aliud* and meant that the scope of protection of these claims had changed, contrary to the requirements of Article 123(3) EPC.

Clarity

– Claim 1 was unclear because it was worded in a "circular" format whereby both the antibody and the medical use were defined by reference to "suppressing the immune response".

– It was unclear what the amendment in the independent claims, which now referred to "the immune response" instead of to "an immune response", changed in technical terms.

– The wording "for use in a human to suppress the immune response" did not define a disease and lacked any instruction for a treatment. The findings in decision G 2/08 of the Enlarged Board of Appeal, point 5.10.5, did not support the respondent's case since that decision related to dosage regimen. In particular the diseases

mentioned in dependent claim 4 (allergy, asthma or a chronic inflammatory skin condition) were different from the conditions mentioned on page 27, lines 25 to 35, of the application as filed.

Novelty

– Document (D10), which was prior art pursuant to Article 54(3),(4) EPC, related to the identification of molecules involved in "homing" of re-circulating lymphocytes to particular lymphoid sites. Homing of migrating lymphocytes could be an aspect of the inflammatory response and might result in autoimmune diseases. The identified molecules could lead to means for modulating the homing response (page 2, lines 30 to 37 and page 3, line 1) which could have therapeutic benefits (page 2, lines 20 to 35). Homing involved the binding of lymphocytes to endothelial cells (page 4, lines 15 to 25).

– The molecules involved in homing and identified in document (D10) were α4β1/VLA-4 intergrins (page 6, lines 20 to 24). The inhibition of homing with antibodies to the α4β1/VLA-4 intergrins in order to suppress an immune response was described in document (D10) on page 10, line 29 to page 11, line 16, and claimed in claim 6. The document furthermore exemplified the inhibition of lymphocyte binding to endothelial cells to suppress an immune response using an antibody to the α4β1/VLA-4 intergrin (page 44, line 22 ff., page 54, lines 26 to 37, page 55, lines 1 to 9 and claim 22). Although the experiment described in

document (D10) was performed in the mouse system, antibodies to human α4β1/VLA-4 intergrin were readily available in the prior art and it was specifically stated that the teachings related particularly to human hosts (page 4, lines 19 and 20).

– The disclosure in document (D10) thus anticipated the subject-matter of claim 1 which accordingly lacked novelty pursuant to Article 54 EPC.

Inventive step

– Document (D27) disclosed integrin molecules involved in lymphocyte homing to Peyer's patches. Antibody R1-2 recognised a murine Peyer's patch-specific lymphocyte homing receptor specific for Peyer's patch high endothelial venules ("HEV"; see page 47, lines 22 to 24), i.e. the α_{4m} subunit of LPAM-1 (page 48, lines 17 to 18 and ff.). The α_{4m} was homologous to the α_4 chain of the human integrin receptor VLA-4 (page 50, lines 26 to 27 and ff.), i.e. α4β1. The document demonstrated that the lymphocyte receptor systems for the recognition of and adhesion to HEV in mucosal lymphoid organs were similar in mouse and human. Two out of three antibodies directed against the α subunit of human VLA-4 inhibited the adhesion of human KCA B-cell lymphoma cells to murine Peyer's patch HEV (e.g. Figure 2 on page 55). One of those antibodies, antibody P4C2, was also used in the patent in suit. Document (D27) reported therefore that an antibody to the human α4β1 receptor (P4C2) could inhibit the adhesion of lymphoma cells to

vascular endothelial cells (HEV) and thus suppress lymphocyte homing, being an important aspect of the immune response.

– Starting from document (D27), which represented the closest prior art, the objective technical problem to be solved was to provide means for suppressing the immune response. The solution to that technical problem was immediately obvious to the skilled person, i.e. antibodies against the human α4β1 receptor disclosed in document (D27).

– The use of the antibodies described in document (D27) for suppressing the immune response in a human was a concept which would have immediately occurred to the skilled person since the entire disclosure of document (D27) was concerned with lymphocyte homing and antibodies interfering with this mechanism. Furthermore, document (D27) mentioned on page 45 in the 2nd sentence at least three antigenically and functionally distinct lymphocyte homing systems which had been identified, i.e. to peripheral lymph nodes, to mucosal tissues and to inflamed synovium. It would thus be immediately apparent to the skilled person that the inhibition of homing to for instance inflamed synovium, would suppress the immune response in the synovium in the same way as the inhibition of homing to mucosal tissue. For the latter, the Peyer's patch was a model and suppression could be achieved with antibodies to the α4β1 receptor. It would thus suppress the immune response in such tissue, e.g. in inflammatory bowel disease. The claimed subject-

matter was therefore obvious over the disclosure in document (D27) taken on its own.

– Document (D25), a review on lymphocyte and lymphoma homing receptors, disclosed on page 469, last paragraph to page 470, first paragraph, that specific monoclonal antibodies or pharmacologic agents could be developed to inhibit selectively lymphocyte migration to inflamed synovium (or other specific tissues) which might provide a highly selective, organ-restricted immunosuppressive therapy for rheumatoid arthritis and other immune-mediated, tissue-specific disease processes. In view of this teaching in document (D25) the skilled person would have immediately recognised that these antibodies could be applied in humans to suppress the immune response.

– If document (D25) was taken as the closest prior art then the problem to be solved would be to provide for those antibodies that influence lymphocyte homing. Combination with document (D27) therefore immediately provided the claimed solution.

– At the relevant date the skilled person knew that HEVs were not only relevant for the extravasation of lymphocytes into Peyer's patches but also for the extravasation of lymphocytes into sites of chronic inflammation (document (D8)) such as rheumatoid synovial membrane (document (D9)). Interfering with or preventing homing thus directly affected the immune response. Therefore test systems such as those described in documents

(D1), (D4) or (D27) were concerned with the influence of test substances such as antibodies on the immune response. To derive from test results the function (namely suppression of an immune response) for which those tests were set up and designed, did not involve an inventive step but would be performed automatically by the skilled person.

– Claim 1 was directed to the role of the α4β1 receptor and to the use of antibodies against that receptor. However, blocking the binding to the counter-receptor on the endothelial cells was not a feature of claim 1 so that the Patentee's statements with regard to fibronectin were irrelevant. What was claimed was the inhibition of any binding via the α4β1 receptor irrespective of the counter-receptor. Claim 1 only concerned binding to the endothelium, not binding to the endothelium via fibronectin. However, it had been known in the art that α4β1 binds to the endothelium as such and also that said binding could be inhibited by antibodies against the α4β1 receptor, in particular by antibodies against the α4 chain.

Substantial procedural violation

– The opposition division had disregarded a relevant prior art document, i.e. document (D10), under Article 54(3) EPC because no proof had been provided that the priority documents of document (D10) had been filed with the EPO. The filing of priority documents did not however constitute a

prerequisite or condition for a document being prior art under Article 54(3) EPC. The conditions to be fulfilled in this regard were rather determined by Article 158(1),(2) EPC as well as Article 54(3),(4) EPC, conditions which had all been met in the case of document (D10).

– The decision to disregard the opponent's submissions with regard to the relevance of document (D10) as well as to disregard document (D10) as valid prior art under Article 54(3) EPC was thus based on criteria not provided for by the EPC. This represented a substantial procedural violation, so reimbursement of the appeal fee was equitable.

X. The arguments of the respondent (patentee) in the case can be summarised as follows:

Admissibility of the requests filed on 10 February 2010

– The board usually arranges oral proceedings by sending a communication, which did not happen in the present case. After receiving the appellant's submission of 8 January 2010, the respondent replied in a few days by filing new requests. Regardless of the PCT form, the best way was for the respondent to indicate what it would do. Document (D10) was a key prior art document which raised both legal and substantive questions and the respondent was entitled to deal with those issues. The amendments were clear and limiting and the appellant had time to consider them. The respondent had done nothing beyond what could be

expected of a party which had been successful at first instance and wanted to protect its position.

Added matter - Article 123(2) EPC

– The basis for the amendments of the wording of the independent claims as compared to the granted claims could be found in the application as filed: as regards the monoclonal antibodies, on page 17, lines 20 to 23, the sentence spanning pages 17 and 18 and page 19, lines 28 to 20; as regards the antibody binding to the α4 subunit, on page 52, lines 5 to 11 and page 54, lines 4 to 19; and as regards the lymphocyte adherence, on page 1, paragraph 1, in particular lines 7 to 12.

Article 123(3) EPC

– The amendment in the independent claims to refer now to "the immune response" as compared to "an immune response" in the claims as granted, resulted in a limitation rather than in an extension of the scope of protection of the claims as granted.

Clarity

– The fact that claim 1 mentioned that the antibody suppressed the immune response as well as the medical use being to suppress the immune response was the result of the proper formulation of the claim in the required format. Therefore, it did not introduce unclarity in the wording of the claim.

– The reference in the independent claims to "the immune response", instead of to "an immune response" as in the patent as granted, removed a possible ambiguity.

– The wording "for use in a human to suppress the immune response" was in compliance with the requirements for proper wording of a second medical use claim (see decision G 2/08, Reasons, point 5.10.5).

Novelty

– Only one document had been cited by the appellant to argue lack of novelty, i.e. document (D10). Document (D10) was only citable under Article 54(3) EPC if and insofar as it was entitled to benefit from the claimed priority dates. Seeing however that the disclosure in document (D10) could not benefit from these dates, document (D10) did not constitute prior art pursuant to Article 54(3) EPC.

– Nevertheless, even if document (D10) was contained in the prior art pursuant to Article 54(3) EPC, it was not detrimental to the novelty of the claimed subject-matter.

– Document (D10) lacked a clear and unambiguous disclosure of the claimed invention. The skilled person was required to choose from several possible alternatives described in document (D10) in respect of the majority of the features of the

claims. To arrive at the claimed invention required mosaicing.

– The claimed invention explicitly required that the selected antibodies were used bind to the α4β1 intergrin, i.e. the human molecule. These molecules therefore also had to inhibit the adherence of human lymphocytes to human vascular endothelial cells. The functional assays used in document (D10) to identify relevant antibodies (pages 45 and 46) were conducted using murine tissue. Document (D10) therefore did not teach the skilled person to use an adhesion assay involving human lymphocytes and human endothelial cell tissue. The only antibody identified in document (D10) as being capable of inhibiting cell adhesion was monoclonal antibody R1-2. This antibody however had subsequently been shown not to cross-react with human α4β1 (document (D36)). Document (D10) therefore did not provide an enabling disclosure of the invention as claimed.

Inventive step

– The patent in suit disclosed two very significant scientific findings. First, the patent demonstrated that, far from being an organ-specific adhesion molecule relevant only to the Peyer's patch, α4β1 played a wider role in mediating adhesion to non-specialized endothelial cells. Non-specialised endothelial cells were morphologically and functionally distinct from the specialised HEV cells present in Peyer's patch. Non-specialized endothelial cells were

ubiquitously present along the vasculature, providing a cellular barrier between the circulatory system and other tissues, and mediated extravasation of leukocytes from the circulation in disorders of the immune system. Second, the patent in suit revealed the ability of α4β1 to bind not only to endothelial cells but also to fibronectin. Fibronectin formed part of the extracellular matrix underlying the vascular endothelium representing a second tissue barrier to lymphocytes infiltrating tissue during, for example, inflammation. By revealing the binding of α4β1 to both non-specialized endothelial cells and fibronectin, the patent in suit implicates α4β1 as having an important role in facilitating the egress of leukocytes/lymphocytes from the circulation in immune disorders, and in turn implicates antibodies to α4β1, particularly, the α4 subunit thereof, for use in suppressing such disorders.

– The problem to be solved by the claimed invention was the provision of means to inhibit the homing of lymphocytes to endothelial cells in a human (in vivo) thereby suppressing the immune response. The solution to this problem was provided by the patent which disclosed the use of antibodies which bound α4β1 and which inhibited adherence of human lymphocytes to human vascular endothelial cells.

– At the priority date the skilled person considered lymphocyte-HEV interactions within the context of the prevailing and dogmatic "lock and key" model, according to which lymphocytes and homing

receptors interacted in a restricted tissue and organ-specific manner.

– Document (D27), like documents (D1) and (D4), discussed the characterisation of a monoclonal antibody R1-2 which bound LPAM-1 and which was shown capable of inhibiting adherence of mouse lymphocytes to mouse Peyer's patch tissue, but not to other lymphoid tissue, i.e. peripheral lymph nodes (Table I and page 47, second paragraph). On the basis of these results, LPAM-1 was said to be a molecule responsible for Peyer's patch specific homing. Such a conclusion was consistent with the theory of homing receptors at the time, according to which homing receptors acted in a tissue specific manner, also known as "lock and key" theory. In addition document (D27) reported the ability of antibodies to α4β1, i.e. P4C2 and P4G9, to inhibit the adherence of human lymphoma cells to mouse Peyer's Patch tissue.

– Also document (D41) characterised the MECA-79 antigen as a specific recognition element involved in lymphocyte binding to peripheral node HEV. The document concludes that the antigen either had to "function as a specific endothelial cell surface ligand for peripheral lymph node-homing receptors or had to be associated both physically and functionally with such a ligand" (page 1859, right-hand column).

– There was in particular no suggestion whatsoever in document (D27) that would lead the skilled person to consider using any of the antibodies

mentioned therein for suppressing the immune response in a human. In fact, the role for α4β1 in the binding of cells to human endothelial tissue was not assessed in document (D27). The binding assay disclosed in document (D27) relied on the use of murine Peyer's patch tissue. Thus, from document (D27) alone, the skilled person would not have been able to establish any role for α4β1 in mediating adherence to human endothelial tissue. If anything, the document made a distinction between mouse and human homing systems by suggesting that, in humans, an alternative 9OkDa receptor known as Hermes was responsible for adhesion to mucosal lymphoid tissue. On page 45, it was stated: "*In humans, it has been shown that distinct epitopes of M_r 90 000 glyocproteins are involved in the adhesion of lymphocytes to HEV in peripheral lymph node or appendix*" and "*However, unlike the human system, M_r 90 000 molecules that are involved in the adhesion of murine lymphocytes to Peyer's patch HEV have not been detected so far*". Without appreciating a role for α4β1 in mediating the adherence of human lymphocytes to human endothelial tissue, it would not have been obvious for the skilled person to consider a medical utility of antibodies to α4β1 in the in vivo suppression of the immune response in a human.

– Furthermore, even if the skilled person were to make an extrapolation from document (D27) to the possible role of α4β1 in humans, such an extrapolation would not render the medical use obvious.

– Document (D25) was a review on lymphocyte and lymphoma homing receptors and reiterated the theory of tissue specific homing, i.e. that distinct receptors were responsible for homing lymphocytes to distinct tissues and organs. Although document (D25) discussed using antibodies to inhibit selectively the migration of lymphocytes to sites of chronic inflammation, it neither discussed the presence of α4β1 at such sites nor proposed that antibodies to α4β1 be used for this purpose. Document (D25) also did not suggest inhibiting the migration of lymphocytes to the Peyer's patch. For example, document (D25) (see page 469, second paragraph) made a clear distinction between mechanisms responsible for the homing of lymphocytes to the peripheral and mucosal lymph nodes and mechanisms responsible for the homing of lymphocytes to sites of chronic inflammation (e.g. the inflamed synovium). Homing to these two sites was thought to be mediated by different receptors.

– The claimed subject-matter was, in view of the above considerations, not rendered obvious to the skilled person.

Reasons for the Decision

1. The appeal is admissible.

Admissibility of the requests filed on 10 February 2010

2. It is true that these requests were filed only a month before the oral proceedings but the amended claims they contained did not require more than that time to consider; the board was able to deal with them and, in the event, so was the appellant. While the board does not consider the requests as plausibly prompted by either the appellant's submission of 8 January 2010 or the absence of a communication, they none the less did mark a narrowing or limitation of the claims sought by the respondent and no adjournment of oral proceedings was necessary, or indeed sought by the appellant. The criteria in Article 13 RPBA being satisfied, the board held that these requests were admissible.

Added matter - Article 123(2) EPC

3. The amendment specifying that the antibodies according to the claim are monoclonal antibodies is supported by the following passages in the application as filed:

"*According to the present invention, an alternative fibronectin receptor was identified by preparing monoclonal antibodies that specifically inhibited the adhesion of T lymphocytes but not other cells to fibronectin*" (page 17, lines 20 to 23);

"*According to the present invention, T lymphocytes were found to attach only to CS-1 and monoclonal antibodies*

to α4β1 (P3E3, P4C2 P4G9) completely inhibited T lymphocyte adhesion to the 38 kDa fragment and to CS—1" (sentence spanning pages 17 and 18);

"*The monoclonal antibodies for therapeutic use may be human monoclonal antibodies or chimeric human—mouse (or other species) monoclonal antibodies*" (page 19, lines 28 to 30); and claim 2 as filed which read:

"2. The method of claim 1 in which the antibody is a monoclonal antibody".

4. Although the feature that the antibody binds to the α4 subunit of the α4β1 receptor was already present in claim 3 as granted, the appellant only objected to the amendment to introduce this into claim 1 for the first time during the oral proceedings before the board. The objection to the feature was based on the "binding" to the receptor and on the combination of this binding with the inhibition of the adherence of lymphocytes.

4.1 The board is however satisfied that the amendment, so far as it concerns the fact that the antibody "binds" to the α4 subunit of the α4β1 receptor, is supported by the passage on page 52, lines 2 to 12 of the application as filed which reads:

"*Using monoclonal antibody technology (...) we have identified a new fibronectin receptor α4β1. Monoclonal antibodies P3E3, P4C2 and P4G9 recognized epitopes on the α4 subunit and completely inhibited the adhesion of peripheral blood and cultured T lymphocytes to a 38 kDa tryptic fragment of plasma fibronectin containing the carboxy terminal Heparin II domain and part of the type*

III connecting segment (IICS). The ligand in IIICS for α4β1 was the CS—1 region previously defined as an adhesion site for melanoma cells."

Further support is found in the passage on page 54, lines 4 to 19 which reads:

"*Like α2β1, the α4 subunit is weakly associated with the β1 subunit. The data presented here (Figure 2) and our previous findings (...) show that the functionally defined monoclonal antibodies to α2β1 and α4β1 selectively interact with epitopes present on the α subunits, based on immune precipitated of α2 or α4 without β1 after subunit dissociation. These results suggest that the unique α subunit is responsible for determining the ligand—binding specificity of each α-β complex. This concept is now further support by the observations presented here that α5 and α4, which are both complexed with β1, mediate adhesion to distinct sites on fibronectin. This is not to suggest that the β subunit is not important in binding, but that the specificity of receptor-ligand interactions is determined by α or a unique α-β complex.*"

The passage on page 52 of the application as filed (see point 4.1 above) discloses monoclonal antibodies which recognise epitopes on the α4 subunit of the α4β1 receptor. Similar wording appears present in claim 16 as filed which read:

"*An antibody, fragment or derivative thereof which recognizes an epitope defined by monoclonal antibody P4C2*".

The Board is satisfied that, in order for an antibody to "recognise" an epitope, it must also "bind" to it and consequently to the molecule comprising the epitope. The Board furthermore notes that this is confirmed by claim 17 as filed which read:

"17. The antibody, fragment or derivative of claim 16, which competitively inhibits the binding of monoclonal antibody P4C2".

4.2 The board is also satisfied that the disclosure in the passages cited above, read in the light of the general disclosure of the patent application as exemplified in claims 1 and 3 of the application as published support the combination of the antibody which binds to the α4 subunit of the α4β1 receptor with the inhibition of the adherence of lymphocytes to endothelial cells. Those claims read:

"1. A method for inhibiting the adherence of lymphocytes to endothelial cells comprising exposing the lymphocytes to an effective amount of an antibody, or a fragment or derivative thereof, that binds to α4β1.

3. The method of claim 2 in which the antibody is P4C2, deposited with the ATCC and having the accession number HB—10215".

Article 123(3) EPC

5. The appellant has argued that, since the independent claims had been amended to refer to "the immune response" as compared to "an immune response" in the

claims as granted, this consisted of an *aliud* and meant that the scope of protection of these claims had changed, contrary to the requirements of Article 123(3) EPC. However, the board cannot see how this amendment results in an extension in the scope of protection over claim 1 as granted, nor could the appellant, when asked during the oral proceedings, show how this was the case. Therefore, since the objection under Article 123(3) EPC is a mere unsupported allegation, it must fail.

Clarity

6. The appellant has argued that claim 1 was unclear contrary to Article 84 EPC because of its "circular" format, whereby both the antibody and the medical use were defined by reference to "suppressing the immune response". The board considers however that the similar functional definition of the antibody and the intended use of the pharmaceutical composition both constitute appropriate technical features which are clear under Article 84 EPC and introduce neither contradiction nor ambiguity into the claim wording. The appellant's argument must therefore fail.

7. The appellant furthermore argued that it was unclear what the amendment in the independent claims changed in technical terms by referring to "the immune response" instead of to "an immune response". The board considers however that the appropriate question to answer under Article 84 EPC is whether or not the definition in the claim of the matter for which protection is sought, is clear. The board notes that the appellant has not argued that the term "the immune response" is as such unclear and the board sees no unclarity in it either.

Accordingly, this argument of the appellant must also fail.

8. It was also argued by the appellant that the wording "for use in a human to suppress the immune response" did not define a disease and lacked any instruction for a treatment. In particular the diseases of claim 4 were different from the conditions mentioned on page 27, lines 25 to 35 of the application as filed. The claim format was therefore not the appropriate one as allowed by the case law of the boards of appeal for second medical uses. The board notes however in this context that the case law on the so-called "Swiss-type" claims has been developed as an exception to the conventional novelty criteria provided for in the EPC. The appellant's objection however is to non-compliance with Article 84 EPC in respect of clarity of the claims, so that for this reason alone the argument must fail. For the sake of completeness however, the board also considers the wording "for use in a human to suppress the immune response" to be clear and to meet the requirements of Article 84 EPC.

Sufficiency of disclosure

9. The appellant had no objections against the claimed subject-matter under Article 83 EPC. The board has none either.

Novelty

10. The sole document on which the appellant has argued a lack of novelty of the claimed subject-matter is document (D10) being an international patent

application which was filed on 10 November 1989 and which claims priorities from the earlier applications US 07/289201 filed on 23 December 1988 and US 07/315736 filed on 24 February 1989. Both priorities of document (Dl0) antedate the priority date of the patent in suit. The appellant has confirmed that the priority claim for the patent in suit is valid. Accordingly, document (D10) is a document which is potentially detrimental for the novelty of the claimed subject-matter pursuant to Article 54(3) EPC.

11. In its decision the opposition division did not consider document (D10) to constitute prior art pursuant to Article 54(3) EPC. The appellant has contested this aspect of the decision and argued that document (D10) disclosed subject-matter which was embraced by the wording of claims 1 and 6 which accordingly lacked novelty pursuant to Article 54(3),(4) EPC over the disclosure.

12. Claim 1 of the main request concerns the use of a **monoclonal antibody** (or fragment thereof) which **binds to the α4 subunit** of the α4β1 receptor and which inhibits the adherence of lymphocytes to vascular endothelial cells thereby suppressing the immune response for the preparation of a pharmaceutical composition **for use in a human to suppress the immune response**, whereas claim 6 concerns a process for the preparation of a pharmaceutical **composition for suppressing the immune response in a human** containing the same antibody (emphasis added by the board).

13. Accordingly, for any disclosure to read on to these claims it must describe a monoclonal antibody which

a) binds to the α4 subunit of a α4β1 receptor and which
b) is able to suppress the immune response in a human.

14. Document (D10) describes in its claim 22 *inter alia* antibodies to the α4 subunit of an α4β1 receptor, i.e. antibodies to a so-called α_{4m} subunit of LPAM-1, a mouse integrin of which the structure is virtually identical to that of the human integrin VLA-4, i.e. the α4β1 receptor (page 6, lines 20 to 22) and which is "*capable of blocking binding to high endothelial venules*". Document (D10) exemplifies this antibody by R1-2, a rat monoclonal antibody recognising the α chain of LPAM-1 (see page 44, line 22 to 36) which was shown to be capable of inhibiting "the binding of lymphoma cells to high endothelial venules of Peyer's patch" (page 54, lines 26 to 28). Document (D10) furthermore establishes the analogy between the α4 subunit of LPAM-1, i.e. α_{4m}, and the α4 subunit of VLA-4, i.e. the human α4β1 receptor, by showing cross reactivity of a rabbit **polyclonal** antiserum specific for the α4 subunit of the human α4β1 receptor with α_{4m} (page 49, lines 8 to 34). However, document (D10) does not disclose explicitly that monoclonal antibody R1-2 binds to the α4 subunit of the human α4β1 receptor and nothing indicates to the board that the skilled person would derive such binding properties of the antibody R1-2 implicitly from the disclosure of document (D10). Accordingly, document (D10) cannot be read to disclose a monoclonal antibody which binds to the α4 subunit of a α4β1 receptor and which could therefore potentially be able to suppress the immune response in a **human**. Therefore, the disclosure in document (D10) cannot be considered to read on to either of the independent claims of the main request.

That monoclonal antibody R1-2 does not bind to the α4 subunit of a human α4β1 receptor was indeed established in post-published document (D36), which discloses in the sentence bridging pages 946 and 947 that R1-2 "*recognized mouse α4 but not human α4*".

15. The board notes that in view of the above finding, it is irrelevant to the outcome of the present decision whether or not, from a formal point of view, document (D10) constitutes prior art pursuant to Article 54(3) EPC or not.

Inventive step

16. 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.

17. The subject-matter of claims 1 and 6 pertains to the use of a inhibitory compound, i.e. a monoclonal antibody to the α4 subunit of the α4β1 receptor, to inhibit the adherence of lymphocytes to vascular endothelial cells thereby suppressing the immune response in a human (see section VI). The objective of

the claimed invention is the inhibition of so-called lymphocyte "homing", i.e. the inhibition of binding of lymphocytes to endothelial cells, thereby preventing lymphocyte entrance into tissues and suppressing the immune response (see *inter alia* paragraphs [0001] and [0049] of the patent in suit).

18. The parties have considered a number of prior art documents to represent the closest prior art for the assessment of inventive step.

18.1 The first such document was document (D27), which concerns integrin molecules involved in lymphocyte homing to mucosal lyphoid organs, in particular in murine Peyer's patches. It describes monoclonal antibody R1-2 (page 47, line 6 ff.) which recognises the α chain (α_{4m}) of a murine lymphocyte homing receptor specific for Peyer's patch high endothelial venules (HEV, page 47, lines 22 to 24) and which is shown to be capable of inhibiting, *in vitro*, the adhesion of murine lymphocytes to Peyer's patch HEV, i.e. endothelial cells. The document discloses furthermore that α_{4m} is homologous to the α_4 chain of the human integrin receptor VLA-4 (page 50, lines 26 to 27 and ff.), i.e. α4β1. The document demonstrates that the lymphocyte receptor systems for the recognition of and adhesion to HEV in mucosal lymphoid organs are similar in mouse and human in that two out of three antibodies directed against the α subunit of human VLA-4, including P4C2 which is also used in the patent in suit, inhibit the adhesion of human KCA B-cell lymphoma cells to murine Peyer's patch HEV (see e.g. Figure 2 on page 55).

Unlike document (D27) however, two other documents directly address the implication of interference with lymphocyte homing in immunosuppression.

18.2 Document (D25) is a review with the title "Human lymphocyte and lymphoma homing receptors" which discloses (page 469, last paragraph, to page 470, first paragraph), that:

"*These organ-specific lymphocyte homing mechanisms probably act not only to enhance the efficiency of immune responses in related tissues but, perhaps as importantly, to decrease opportunities for autoimmune cross reactions by preventing, for example, effector cells arising in response to mucosal or skin pathogens from entering unrelated tissues such as joints. Finally, these findings offer the exciting possibility that specific monoclonal antibodies or pharmacologic agents could be developed to inhibit selectively lymphocyte migration to inflamed synovium (or other specific tissues). This might provide a highly selective, organ-restricted immunosuppressive therapy for rheumatoid arthritis and other immune-mediated, tissue-specific disease processes*."

18.3 Similarly, document (D32) reviews "Mechanisms of human lymphocyte migration and their role in the pathogenesis of disease" (title) and concludes in the summary (page 128, lines 23 to 30) that:

"*Lymphocyte recirculation is an essential component of the functional immune system, providing a means for constant surveillance of the organism's tissues by immunocompetent cells and, moreover, facilitating*

interactions between different cell types engaged in the immune response. Adhesive interactions between recirculating lymphocytes and the wall of high endothelial venules (HEV) are thought to play a central role in this process. These interactions are mediated by lymphocyte homing receptors expressed on the lymphocyte cell surface which recognize tissue-specific molecules on the endothelium."

19. In view of the disclosures in the above cited documents, the board considers that, for the purpose of assessing inventive step in the present case and taking into account the principles established in the case law, the disclosure in document (D25), in the light of the general knowledge as e.g. disclosed in document (D32) in relation to lymphocyte homing, represents the closest prior art.

20. Based on this closest prior art the objective technical problem to be solved by the claimed subject-matter is the provision of specific agents that are capable of suppressing the immune response by inhibiting the adherence of lymphocytes to vascular endothelial cells in a human.

21. The board is satisfied that this problem has been solved by the claimed subject-matter, i.e. by using a monoclonal antibody or fragment thereof which binds to the α4 subunit of the human α4β1 receptor, in view of the technical detail disclosed in the patent in suit. The appellant has not contested this finding.

22. The board accepts that, when searching for a solution to the formulated technical problem, the skilled person

would consider the disclosure in document (D27). In the context of the assessment of inventive step therefore, the relevant question is whether the disclosure in document (D27) rendered the claimed subject-matter, i.e. the use of antibodies to the human α4β1 receptor, obvious to the skilled person when addressing a solution to the formulated problem.

22.1 Document (D27), as already partly stated above (point 18.1), discloses a monoclonal antibody R1-2 (page 47, line 6 ff.) which recognises the α chain of the murine lymphocyte homing receptor specific for Peyer's patch HEV and which is capable of inhibiting the adhesion of murine lymphocytes to Peyer's patch HEV, i.e. endothelial cells. The document further demonstrates that two antibodies directed against the α subunit of human VLA-4 inhibit the adhesion of human lymphoma cells to murine Peyer's patch HEV. On the basis of these experiments, the authors of document (D27) conclude (page 57, line 38 to line 58, line 9) that:

"*We further investigated whether VLA-4, the human analog of LPAM-2, can mediate adhesion of human lymphocytes to HEV on mucosal lymphoid organs. Two different monoclonal antibodies specific for the α chain of VLA-4, but none of the control antibodies strongly inhibited the binding of human lymphoma cells to Peyer's patch HEV. As the tissue-specific lymphocyte recognition mechanisms for HEV are conserved in evolution (Wu et al. 1988), these results suggest that the tissue-specific component of the lymphocyte receptor system mediating the recognition of and adhesion to HEV in mucosal lymphoid organs consists of*

at least two independent types of adhesion molecules: LPAM-1 and or LPAM-2/VLA-4-related integrin molecules acting in conjunction with the M_r 90000 homing receptors."

22.2 The board notes that although document (D27) may imply the human α4β1 receptor to be instrumental in the binding of human lymphocytes to murine HEV of mucosal lymphoid organs such as Peyer's patch, the document merely demonstrates a structural homology between the α_{4m} subunit of LPAM-1 and the α4 subunit of the human α4β1 receptor as well as a functional homology between the two receptors when it comes to prevent the binding of lymphocytes of murine origin by antibodies against LPAM-1 and of human origin by antibodies against α4β1 to murine Peyer's patch HEV. However, the document neither explicitly nor implicitly elaborates on the fact whether or not α4β1 is of primary importance for the binding of human lymphocytes to human Peyer's patch HEV, let alone whether antibodies to α4β1 can prevent such possible binding *in vivo* and, when therapeutically applied, the use of such antibodies can suppress the immune response in a human. If only for this reason the Board concludes that the claimed subject-matter was not rendered obvious to the skilled person by the available prior art.

23. The appellant has nevertheless argued that the solution to the formulated technical problem was immediately obvious to the skilled person because the use of the antibodies described in document (D27) for suppressing the immune response in a human was a concept that would have immediately occurred. The entire disclosure of document (D27) was concerned with lymphocyte homing and

antibodies interfering with this mechanism. Furthermore, document (D27) mentioned on page 45, lines 3 to 7 at least three antigenically and functionally distinct lymphocyte homing systems which had been identified, i.e. to peripheral lymph nodes, to mucosal tissues and to inflamed synovium. It would thus be immediately apparent to the skilled person that the inhibition of homing to, for instance, inflamed synovium would suppress the immune response in the synovium in the same way as the inhibition of homing to mucosal tissue. For the latter the Peyer's patch model was a model and suppression could be achieved with antibodies to the α4β1 receptor. It would thus suppress the immune response in such tissue.

24. The appellant has furthermore argued that at the relevant date the skilled person knew that HEVs were not only relevant for the extravasation of lymphocytes into Peyer's patches but also for the extravasation of lymphocytes into sites of chronic inflammation (document (D8)). Interfering with or preventing homing thus directly affected the immune response. Therefore test systems such as those described in document (D27) were concerned with the influence of test substances such as antibodies on the immune response. To derive from test results the function (namely suppression of an immune response) for which said tests were set up and designed, did not involve an inventive step but was a step taken automatically by the skilled person. The experiments contained in the patent in suit did not make any additional contribution over the prior art documents (Dl), (D4) and (D027) with regard to the claimed subject-matter.

25. The board notes however that these inferences made by the appellant stand in contrast to the general remarks expressed by the authors of document (D2) (page 1367, left-hand column, line 21 to 36) in their discussion of VLA-4 (α4β1) expression on human lymphocytes. In particular, the passage states that:

"*Because VLA-4 expression is widespread on leukocytes, and because a wide variety of specific and non-specific receptors and ligands have been identified which assist T cell-target cell interaction (...), it appears most likely that VLA-4 would be an accessory molecule rather than a highly specific receptor in this process. Furthermore, VLA-4 not only appears to mediate T-B cell interaction, but another recent study has implicated mouse VLA-4 in lymphocyte-endothelial cell interaction. Specifically, anti-mouse VLA-4 mAb selectively blocked organ specific homing to Peyer's patch high endothelial venules (...). At present it is difficult to understand how VLA-4 could have an organ-specific role in lymphocyte homing, considering the widespread distribution of VLA-4 on nearly all lymphocytes and its role on T-B cell interaction*".

The board considers that these statements in the prior art highlight the fact that for a skilled person, at the relevant date, it would not have been obvious, despite structural and possibly functional similarities of murine LPAM and human VLA-4 (α4β1), to treat the two molecules equivalently in a possible therapeutic immunosuppressive regime.

26. In view of the above considerations, the claimed subject-matter is not rendered obvious to the skilled

person by the prior art, and hence involves an inventive step (Article 56 EPC).

Substantial procedural violation

27. The board does not consider that the opposition division committed a substantial procedural violation by refusing to consider document (D10) as prior art. It is clear from the appellant's own submissions (see its statement of grounds of appeal, page 9, first full paragraph and page 10, first full paragraph) that the parties presented different submissions to the opposition division as to whether or not document (D10) should be considered and, as the appellant itself states, the opposition division "eventually followed the argumentation of the patentee" (statement of grounds of appeal, page 9, last paragraph). Deciding between competing submissions from parties who have both presented their cases is not a violation of procedure. That the decision may reflect an error of judgment, or be wholly wrong, is another matter and the purpose of appeal proceedings is to allow an unsuccessful party to challenge such a decision.

28. While the board has found, contrary to the view of the opposition division, that document (D10) is prior art of which account should be taken pursuant to Article 54(3) EPC (see point 10 above), it has also decided that the document is not novelty-destroying and is, strictly speaking, irrelevant to the outcome of the proceedings (see point 15 above). Further, the opposition division decided to maintain the patent in an amended form and thus held against the appellant (then, the opponent) on other grounds than the refusal

to consider document (D10) as prior art. Thus, quite apart from any issue relating to document (D10), the appellant would have had to appeal in order to challenge those grounds of the opposition division's decision. Accordingly, even if there had been a substantial procedural violation, it would be inequitable to allow the appellant a "fee-free" appeal against those grounds and the request for reimbursement of the appeal fee must be refused.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of claims 1 to 6 of the main request filed during the oral proceedings and the description and drawings to be adapted to.

3. The request for reimbursement of the appeal fee is refused.

The Registrar The Chairman

R. Schumacher C. Rennie-Smith