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Datasheet for the decision of 6 July 2021

Case Number: T 0505/19 - 3.3.04

Application Number: 13719147.4

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Language of the proceedings: EN

Title of invention:
Antibodies against CD106 (VCAM-1)

Applicant:
Oxford University Innovation Limited

Headword:
VCAM-1 antibody/OXFORD UNIVERSITY

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (yes)

Decisions cited:
T 0645/02

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Case Number: T 0505/19 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 6 July 2021

Appellant: (Applicant)	Oxford University Innovation Limited Buxton Court 3 West Way Botley Oxford OX2 0JB (GB)
Representative:	J A Kemp LLP 14 South Square Gray's Inn London WC1R 5JJ (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 3 August 2018 refusing European patent application No. 13719147.4 pursuant to Article 97(2) EPC**

Composition of the Board:

Chair	G. Alt
Members:	A. Schmitt
	L. Bühler

Summary of Facts and Submissions

I. The appeal of the applicant (appellant) lies from the decision of the examining division refusing European patent application No. 13 719 147.4, which had been filed as an international patent application published as WO 2013/160676. The title of the application is "*Antibodies against CD106 (VCAM-1)*".

II. The examining division had decided that the subject-matter of claims 1 and 9 of the main request and claim 1 of each of auxiliary requests 1 and 2 lacked an inventive step (Article 56 EPC) and that the subject-matter of claim 1 of the main request and auxiliary request 1 was not clear (Article 84 EPC).

In its decision, the examining division selected document D3 as the closest prior art. The technical problem was formulated as the provision of "*an antibody binding to VCAM-1 which as in D3 can be used to target particles of iron oxide for in vivo imaging and which is suitable to use in humans*". The examining division considered it obvious to adapt the antibody disclosed in document D3 for human use, i.e. to provide a human or humanised antibody which binds to human VCAM-1.

The examining division identified two properties of the claimed antibodies as further differences in relation to the antibody disclosed in document D3, namely that they were "*non-neutralising*" and had a "*low affinity*", but held that these properties were not "*surprising*" in relation to the intended use of the antibody as a conjugate with iron-oxide microparticles.

The examining division took the view that the feature "non-neutralising" was not linked to a technical effect of the antibody when present in the conjugate because, due to the large size of the iron-oxide microparticles used for imaging, they would "*inevitably interfere with the binding of VLA-4*", i.e. be neutralising. Therefore, qualifying the antibody as "non-neutralising" was "*only an arbitrary choice*".

The examining division further considered that the selection of a "*low affinity*" antibody was, on the one hand, "*counter-intuitive*" but, on the other hand, not associated with a surprising advantage because the skilled person was also aware of the associated disadvantage, namely the need to use a higher dose.

Finally, the examining division stated that its reasoning also applied to claim 9, which recited, in option (a), the amino acid sequences of the light (SEQ ID NO: 4) and heavy (SEQ ID NO: 10) chain variable regions, and, in option (b), the amino acid sequences of the light (SEQ ID NO: 3) and heavy (SEQ ID NO: 9) chains of the claimed antibodies.

Claim 1 of the main request considered in the following is identical to option (a) of claim 9 of the main request underlying the decision under appeal.

III. With the statement of grounds of appeal, the appellant submitted sets of claims of a main request and auxiliary requests 1a, 1b, 2 and 3. With the reply to the board's summons to oral proceedings and a communication pursuant to Article 15(1) RPBA, the appellant submitted sets of claims of auxiliary requests 4 to 6.

IV. Oral proceedings were held on 6 July 2021 by videoconference, as requested by the appellant. During the oral proceedings, the appellant submitted a new main request comprising claims 1 to 8 and withdrew all other claim requests on file. At the end of the oral proceedings, the chair announced the decision.

Claims 1 to 8 of the sole claim request read as follows:

"1. A non-neutralising antibody or fragment thereof that specifically binds to human endothelial vascular cell adhesion molecule-1 (VCAM-1), wherein the VCAM-l is in its native state, wherein the antibody or fragment thereof binds to the extracellular domain of VCAM-1, wherein the antibody or fragment thereof binds to VCAM-1 when expressed on endothelial cells, wherein the antibody or fragment thereof is a human or humanized antibody, or fragment thereof, and comprises the light chain variable region of SEQ ID NO: 4 and the heavy chain variable region of SEQ ID NO: 10.

2. An antibody according to preceding claim 1, wherein the antibody is a monoclonal antibody.

3. An antibody or fragment thereof according to claim 1 or 2, wherein the antibody comprises a light chain of SEQ ID NO: 3 and the heavy chain of SEQ ID NO: 9.

4. An antibody or fragment according to any of the preceding claims wherein the antibody is conjugated to an iron oxide microparticle, preferably wherein the antibody is conjugated to an iron oxide microparticle which is covalently bonded to other iron oxide microparticles by linker groups to form a multimeric

particle, wherein at least a portion of said linker groups are cleavable *in vivo*.

5. An antibody or fragment according to any one of the preceding claims for use in an *in vivo* method of diagnosis of inflammatory disease in the central nervous system, preferably wherein said disease is multiple sclerosis.

6. A polynucleotide encoding an antibody or fragment thereof according to any one of claims 1 to 3.

7. An antibody or fragment according to any one of claims 1 to 3, for use in a method of diagnosing an inflammatory disorder in the central nervous system, said method comprising administering to an individual said antibody or fragment thereof and monitoring for binding of the antibody, preferably wherein the antibody is conjugated to an iron containing colloidal particle or multimeric metal containing particle, and wherein magnetic resonance imaging is used to monitor for binding of the antibody to VCAM-1.

8. An antibody or fragment according to any one of claims 1 to 3, for use in an *in vivo* method of diagnosis of tumour metastasis."

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

D1 Anonymous, 2001, Specification Sheet Monoclonal Mouse Anti-Human VCAM-1, Clone 1.4C3

D3 Serres S. *et al.*, 2011, FASEB J. 25, 4414-4422

VI. The appellant's arguments, where relevant to the decision, are summarised as follows.

Main request

Amendments (Article 123(2) EPC)

Claim 1 had a basis in claims 1, 2 and 12; the sentence bridging pages 1 and 2; lines 17 to 20 and 28 to 30 of page 3; and lines 24 to 25 of page 15 of the international application as filed. Claims 2 to 8 had a basis in claims 4, 13, 15 and 16, 17 and 18, 19, 20 and 21, and 22 of the international application as filed, respectively.

Clarity (Article 84 EPC)

The claims of the main request complied with the requirements of Article 84 EPC since they did not comprise the features objected to for lack of clarity by the examining division in the decision under appeal.

Novelty (Article 54 EPC)

The claims complied with the requirements of Article 54 EPC since none of the cited prior art doucments disclosed an antibody or a fragment of one comprising the light chain variable region of SEQ ID NO: 4 and the heavy chain variable region of SEQ ID NO: 10.

Sufficiency of disclosure (Article 83 EPC)

The appellant did not comment on the sufficiency of the disclosure of the claimed invention.

Inventive step (Article 56 EPC)

Document D3 constituted the closest prior art since it disclosed a VCAM-1 antibody and its use for *in vivo* diagnosis by magnetic resonance imaging. The claimed antibodies differed from the monoclonal rat antibody against mouse VCAM-1 disclosed in document D3 in that they were human or humanised and comprised the light chain variable region of SEQ ID NO: 4 and the heavy chain variable region of SEQ ID NO: 10, resulting in human VCAM-1 as the target, a low affinity and low on/off-rates for their target, and cross-reactivity with VCAM-1 from rodents and primates, and in that they were non-neutralising.

The technical effect of the combination of these characteristics was that the claimed antibodies were particularly useful for *in vivo* diagnostic imaging in humans since they provided an optimal window for imaging while minimising toxicity. Furthermore, the cross-species reactivity allowed testing in rodents and/or primates prior to their use in humans.

The objective technical problem was thus the provision of an antibody binding to VCAM-1 useful for *in vivo* imaging in humans.

The provision of an antibody having the combination of these characteristics was not obvious to the skilled person.

Firstly, no human or humanised anti-human VCAM-1 antibody for *in vivo* imaging in humans had been known in the art.

Secondly, in the study disclosed in document D3, a neutralising VCAM-1 antibody with a higher affinity was used for *in vivo* imaging in a mouse model without recognising the potential toxicity associated with the use of such neutralising antibodies in humans. Hence, the provision of a non-neutralising VCAM-1 antibody for *in vivo* imaging in humans was not obvious to the skilled person from the teaching of document D3.

Thirdly, providing an antibody with a lower binding affinity in *in vivo* imaging than the one used in document D3 was counter-intuitive to the skilled person in view of the blood flow forces in the blood vessels. The provision of such a low-affinity antibody was therefore also not obvious to the skilled person from the teaching of document D3.

Document D1 disclosed a non-neutralising mouse anti-human VCAM-1 antibody for use as a control antibody in *in vitro* assays. Document D1 did not provide any guidance on how to develop an antibody suitable for *in vivo* imaging in humans, in particular as regards the low affinity.

Thus, documents D3 and D1, alone or in combination, contained no prompt for the skilled person to provide a VCAM-1 antibody having the combination of characteristics of the antibodies of claim 1. Thus, the skilled person would not have provided the claimed antibodies in an obvious manner. Hence, the subject-matter of claim 1 involved an inventive step.

VII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request filed during the oral proceedings.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is admissible.

Main request

Amendments (Article 123(2) EPC)

2. Claim 1 has a basis in claims 1, 2 and 12; the sentence bridging pages 1 and 2; and lines 17 to 20 and 28 to 30 of page 3 of the international application as filed. Furthermore, claims 2 to 8 have a basis in claims 4, 13, 15 and 16, 17 and 18, 19, 20 and 21, and 22 of the international application as filed, respectively. Consequently, claims 1 to 8 of the main request meet the requirements of Article 123(2) EPC.

Clarity (Article 84 EPC)

3. The board does not have any objections to the clarity of the claims of the main request and therefore considers that claims 1 to 8 of the main request comply with the requirements of Article 84 EPC.

Novelty (Article 54 EPC)

4. The subject-matter of claims 1 to 8 is novel at least for the reason that antibodies or their fragments comprising the light chain variable region of SEQ ID NO: 4 and the heavy chain variable region of SEQ ID NO: 10 do not form part of the state of the art. Consequently, the main request meets the requirements of Article 54 EPC.

Sufficiency of disclosure (Article 83 EPC)

5. The board is satisfied that the skilled person can provide antibodies falling within the scope of claim 1 without undue burden. Furthermore, in view of study 11 of the application that discloses that such antibodies are able to bind to VCAM-1 on isolated human brain microvessels stimulated with TNF under the shear and flow conditions expected in flowing blood, the board is satisfied that the claimed antibodies can be used for *in vivo* imaging and diagnosis in humans. The main request thus meets the requirements of Article 83 EPC.

Inventive step (Article 56 EPC)

6. The application discloses that non-neutralising anti-VCAM-1 antibodies, i.e. antibodies that do "*not interfere with the activity of VCAM-1*" are "*useful in the diagnostic context, in particular where such antibodies are being used in vivo for targeting of contrast agents in order to avoid interference with the normal signaling/binding biological effects of VCAM-1*" (see page 5, lines 10 to 15). Hence, the purpose for which the claimed, non-neutralising antibodies are used, and which is derivable from the application, is *in vivo* imaging for diagnosis.

Closest prior art

7. Document D3 discloses *in vivo* magnetic resonance imaging of brain lesions in a mouse model for experimental autoimmune encephalomyelitis using a rat anti-mouse VCAM-1 antibody conjugated to iron-oxide microparticles. The VCAM-1 antibody used in the study of document D3 is hence suitable for *in vivo* imaging and diagnosis and therefore constitutes a suitable

starting point for the assessment of inventive step of the claimed antibodies. The antibody of document D3 blocks the binding of VCAM-1 to its ligand VLA-4. It is, in other words, neutralising, i.e. it interferes with the biological activity of VCAM-1.

8. Document D1, in contrast, discloses a non-blocking (i.e. non-neutralising) mouse anti-human VCAM-1 antibody for use in *in vitro* detection of VCAM-1 or as a control antibody in adhesion assays. Thus, document D1 is not concerned with an antibody for an *in vivo* use, which is the object of the application (see point 6 above). The antibody of document D1 is therefore not a suitable starting point for the assessment of inventive step.

The objective technical problem

Differences

9. The claimed antibodies differ from the rat anti-mouse VCAM-1 antibody used in the study of document D3 in that they are characterised in claim 1 as being human or humanised, non-neutralising, and as comprising the light chain variable region of SEQ ID NO: 4 and the heavy chain variable region of SEQ ID NO: 10. These light and heavy chain variable regions provide, *inter alia,* the antibodies with the properties that they (i) bind to human VCAM-1; (ii) have cross-species reactivity with mouse, rat and primate VCAM-1 (Study 5 of the application); and (iii) have a 2-fold lower binding affinity with a 4-fold slower on-rate and a 2-fold slower off-rate than the rat anti-mouse antibody disclosed in document D3 (Study 6 of the application).

Technical effects of the differences and objective technical problem

Non-neutralising

10. The examining division considered that the non-neutralising characteristic of the claimed antibodies did not result in a technical effect when the antibodies were used as intended, i.e. conjugated to iron-oxide microparticles (see section II above).

11. The examining division reasoned that, due to their large size, the iron-oxide microparticles conjugated to the antibodies for *in vivo* imaging would inevitably interfere with the binding of VCAM-1 to its ligand VLA-4 (see section II. above). The board understands this to mean that because the conjugate as a whole would be neutralising, it was irrelevant if the antibody itself was non-neutralising.

12. However, while it may be a theoretical possibility that the iron-oxide microparticle-part of the conjugate interferes with VCAM-1 such as to abolish the binding of VCAM-1 to its ligand VLA-4, there is no evidence on file that such an interference actually takes place.

13. By definition, however, in contrast to a neutralising antibody, a non-neutralising antibody does not, as such, interfere with the biological activity of its target (see point 6. above). Therefore, a non-neutralising anti-VCAM-1 antibody is less likely to have undesired side effects during *in vivo* diagnosis than an antibody that blocks VCAM-1 activity.

14. Avoiding undesired side effects is relevant for any product intended for *in vivo* use in humans. Hence, in

contrast to the examining division, the board accepts that the non-neutralising property of the claimed antibodies has a technical effect contributing to their suitability for *in vivo* use in humans.

Low affinity

15. The examining division further considered that the selection of a "*low affinity*" antibody was "*counter-intuitive*" but not associated with a surprising advantage because the skilled person was also aware of the associated disadvantage, namely the need to use a higher dose (see section II above).

16. However, according to the application, "*low affinity*" antibodies are useful for the intended application in view of the "*potential high density of the target antigen*" and the use in a "*multivalent setting*" (page 5, lines 2 to 6 of the application). Furthermore, a slower off-rate of the human VCAM-1 antibody provides an increased window for imaging, and antibodies were specifically selected for these properties (page 5, lines 20 to 23; page 32, lines 2 to 3 and Table 1 of the application). If necessary, the lower affinity could be compensated by increasing the binding time rather than the antibody concentration (page 32, lines 3 to 5 of the application).

17. Thus, in light of the passages referred to above, the board concludes that the claimed antibodies were considered to be advantageous for *in vivo* imaging in particular due to their slower off-rate, whereas the overall affinity would not necessarily need to be compensated by increased antibody concentration. Study 11 of the application indeed confirms that such antibodies are able to bind to VCAM-1 on isolated human

brain microvessels stimulated with TNF under the shear and flow conditions expected in flowing blood despite their lower affinity.

18. Hence, in contrast to the examining division, the board accepts that the affinity of the claimed antibodies, in particular their specific off-rate, has a technical effect contributing to their suitability for *in vivo* imaging in humans.

Cross-species reactivity

19. Furthermore, the claimed antibodies have cross-species reactivity with mouse, rat and primate VCAM-1. This allows conducting *in vivo* tests of products comprising the antibodies in laboratory animals prior to human use. This property thus facilitates pre-clinical studies, but it does not directly contribute to the suitability of the claimed antibodies for *in vivo* imaging in humans. Therefore, the technical effect of this distinguishing feature is connected to a purpose different from the one to which the two other technical effects are connected.

In view of the considerations below, the cross-species reactivity will not be considered in the following.

20. To sum up, the claimed antibodies differ from the antibody disclosed in document D3 not only by the fact that they are human or humanised and recognise human VCAM-1, but in addition by a combination of two advantageous properties which contribute to making them suitable for *in vivo* imaging in humans.

21. The objective technical problem can therefore be formulated as the provision of an antibody binding to VCAM-1 that is useful for *in vivo* imaging in humans.

Obviousness

22. For assessing the obviousness of the claimed subject-matter, the question to be asked is whether the skilled person, faced with the problem formulated in point 21. above, would have provided antibodies as claimed, i.e. antibodies uniting several advantageous properties which make them useful for *in vivo* imaging in humans.

23. In the study disclosed in document D3, VCAM-1 expression was detected *in vivo* in mice using a neutralising, monoclonal, rat anti-mouse VCAM-1 antibody, which has a higher affinity than the antibodies of claim 1 (see points 7. and 9. above). Document D3 identifies, as the most important hurdle in the translation of the results observed in mice to a clinical application in humans, "*the development of fully biodegradable MPIO and anti-human analogues of the targeting antibodies, together with full toxicological testing of humanized and biodegradable agent*" (page 4421, right-hand column, second paragraph).

24. Thus, while discussing the need for toxicologically testing any humanised anti-human VCAM-1 antibody, the skilled person is not made aware of a potential disadvantage of using a neutralising anti-VCAM-1 antibody for *in vivo* imaging in humans, namely its interference with the biological activity of VCAM-1.

25. Document D1 discloses a non-neutralising mouse anti-human VCAM-1 antibody (see point 8. above). Yet, it is

used *in vitro* - in detection assays of VCAM-1 or as a control antibody in adhesion assays. Given the different purpose (see also point 8. above), the skilled person would not be aware from document D1 of the advantage of using a non-neutralising antibody for *in vivo* imaging in humans.

26. Similarly, as for the potential disadvantage of using a neutralising antibody, considerations are absent from document D3 regarding affinity requirements of a VCAM-1 antibody intended for *in vivo* imaging in humans. Hence, the skilled person seeking to provide such an antibody would not have thought of modifying the affinity and would thus have provided an antibody having the same affinity as the antibody used in document D3 and shown to successfully bind to VCAM-1 *in vivo*.

27. Consequently, the skilled person, in view of documents D1 and D3, alone or in combination, would not have provided anti-human VCAM-1 antibodies as recited in claim 1 uniting several properties which are advantageous for *in vivo* diagnostic imaging in humans, i.e. antibodies which are not only humanised and bind to human VCAM-1 but which are also non-neutralising and have a particular low affinity and off-rate.

28. Hence, considering that the claimed antibodies are precisely defined by the amino acid sequences of their heavy chain and light chain variable domains and possess a combination of properties which was not known in the art and which, in particular, was not recognised as being advantageous for an antibody to be used in *in vivo* imaging in humans (see point 20. above), the board concludes that the skilled person would not have provided such antibodies in an obvious manner.

29. The board finds support for its view in decision T 645/02 (16 July 2003), where the board in question, taking into account that the subject-matter of the independent claims was precisely defined, considered that the provision of an antibody with defined properties not known in the prior art possessed elements of surprise, this justifying the recognition of an inventive step (points 7 to 9 of the Reasons).

30. Consequently, the subject-matter of claim 1 and claims 2 to 8, which are either dependent on claim 1 or refer to the antibody of claim 1, involve an inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the examining division with the order to grant a patent based on the set of claims of the main request, filed at the oral proceedings, and a description and figures possibly to be adapted.

The Registrar: The Chair:

I. Aperribay G. Alt

Decision electronically authenticated