

Internal distribution code:

- (A) [-] Publication in OJ
- (B) [-] To Chairmen and Members
- (C) [-] To Chairmen
- (D) [X] No distribution

**Datasheet for the decision
of 17 March 2015**

Case Number: T 1602/10 - 3.3.04

Application Number: 03723627.0

Publication Number: 1467759

IPC: A61K39/395, C07K16/28

Language of the proceedings: EN

Title of invention:

Compositions and methods related to TIM-3, a Th1-specific cell surface molecule

Applicant:

The Brigham and Women's Hospital, Inc.
Dana-Farber Cancer Institute, Inc.

Headword:

Anti-TIM-3 antibodies for the treatment of cancer/BRIGHAM

Relevant legal provisions:

EPC Art. 83

Keyword:

Sufficiency of disclosure - (no)

Decisions cited:

T 0609/02, T 1616/09, T 1492/09, T 1918/06

Catchword:



**Beschwerdekammern
Boards of Appeal
Chambres de recours**

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 1602/10 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 17 March 2015

Appellant: The Brigham and Women's Hospital, Inc.
(Applicant 1) 75 Francis Street
Boston, MA 02115 (US)

Appellant: Dana-Farber Cancer Institute, Inc.
(Applicant 2) 450 Brookline Avenue
Boston, MA 02215 (US)

Representative: Krauss, Jan
Boehmert & Boehmert
Anwaltspartnerschaft mbB
Patentanwälte Rechtsanwälte
Pettenkoferstrasse 20-22
80336 München (DE)

Decision under appeal: **Decision of the Examining Division of the
European Patent Office posted on 11 February
2010 refusing European patent application No.
03723627.0 pursuant to Article 97(2) EPC.**

Composition of the Board:

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

Summary of Facts and Submissions

- I. An appeal was filed by the patent applicant (appellant) against the decision of the examining division to refuse European patent application No. 03 723 627. The application, entitled "*Compositions and methods related to TIM-3, a Th1-specific cell surface molecule*" was filed as an international patent application and published as WO 03/063792.
- II. The examining division dealt with a main and an auxiliary request. Claims 5 and 6 of the main request were held to concern an invention which was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, contrary to Article 83 EPC. The same objection was held to apply to the subject-matter of claim 5 of the auxiliary request. These were the sole objections leading to the refusal of the application. The reason given for the refusal was that, although the application disclosed that mice with experimental autoimmune encephalomyelitis (EAE) treated with anti-TIM-3 antibodies exhibited exacerbated disease, this was not a therapeutic benefit and did not enable the skilled person to carry out the claimed invention.

It was held that post-published evidence of reduction of tumour growth in a tumour model by treatment with anti-TIM-3 antibody could not remedy the deficiency because sufficiency of disclosure had to be established at the filing or priority date of the application, as the case may be. Post-published documents could only be used to back up disclosures already made in the patent application but could not establish sufficiency of disclosure on their own.

III. With the statement of grounds of appeal, the appellant submitted a main and three auxiliary claim requests.

IV. With a letter dated 16 February 2015, in response to a communication of the board, the appellant filed a new main claim request replacing all previous claim requests.

V. Oral proceedings before the board were held on 17 March 2015. At the end of these proceedings, the chairwoman announced the decision of the board.

VI. The final request of the appellant was that the decision of the examining division be set aside and that a patent be granted on the basis of the set of claims filed as main request together with the letter dated 16 February 2015.

VII. Claims 1 and 2 of the sole request read:

"1. A TIM-3 binding molecule wherein the TIM-3 binding molecule is an antibody specific for TIM-3 or is a fragment of an antibody specific for TIM-3, for use in the treatment of cancer in a subject.

2. The TIM-3 binding molecule for use as claimed in claim 1, wherein said TIM-3 binding molecule binds to an extracellular region of TIM-3."

VIII. The following documents are cited in this decision:

D1: Janeway C. A. et al., Immunobiology, 4th edition, 1999, Section 8 - 25.

D2: Williams M. A. et al., Leukemia & Lymphoma, 1999, 34(3-4), 207 - 230.

D3 : Ngiow S. F. et al., Cancer research, 15 May 2011, 71 (10), 3540 - 3551.

D4: Dardhalon V. et al., The Journal of Immunology, 1 August 2010, vol. 185(3), 1383 - 1392.

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

The experimental results disclosed in the application related to administering an antibody against TIM-3 *in vivo* in a mouse model of experimental autoimmune encephalitis (EAE) which is a model of the human autoimmune disorder multiple sclerosis. In an autoimmune disease a subject's own antibodies react with host tissues or the immune effector T cells are autoreactive to endogenous self-peptides and cause destruction of tissue, i.e. an anti-self response.

The inventors discovered that administration of an antibody against TIM-3 resulted in more severe clinical disease and increased mortality in the EAE model. The inventors further found that these animals had increased inflammation in the central nervous system (CNS), and that the demyelinating lesions in the mice treated with antibody to TIM-3 were filled with activated macrophages (Example 6).

Further examination of immune cell populations taken from the EAE model mice led to the inventors' discovery that macrophages from mice administered TIM-3 antibody showed increased proliferation and expressed increased levels of MHC Class II antigens, these being indicative of increased ability to present antigen. Both these parameters were measurements of the activation status

of a macrophage, which is a type of antigen-presenting immune cell.

Together, these data would have been understood by a person skilled in the art to be clearly indicative of an enhanced or increased immune response in animals treated with an anti-TIM-3 antibody. The application therefore demonstrated the suitability of a TIM-3 specific antibody for enhancing an immune response which includes an immune response mounted against a cancer antigen. The enhancement of the immune response by administration of anti-TIM-3 antibodies was of a general and non-specific nature.

In the case of cancer, the skilled person knew from the prior art, for example from document D1, that macrophage activation was critical for the induction of immune responses to microbes as well to certain tumor cells. From document D2 (page 207, "Introduction") the skilled person knew that *"the monocyte/macrophage system exhibits a wide array of powerful effector mechanisms that may be harnessed for therapeutic effect against infection and malignancy."* The specification would have been considered in the light of the knowledge that monocyte-mediated immunity was active against malignancy.

Post-published evidence also supported an inherent effect of the TIM-3 inhibitor in cancer models (WT3 sarcoma, TRAP-C1 prostate sarcoma) and some PD-1 blockade synergy (document D3) and EL4 lymphoma (document D4, see page 1386, Fig. 2B). The skilled person would have therefore had no doubt that the invention could be carried out as claimed.

On the subject of whether the generation of a *de novo* immune response by anti-TIM-3 treatment was sufficiently disclosed, the appellant argued that, in fact, no generation of a *de novo* immune response was needed. The immune system carried out constant immune-surveillance, nascent cancers being naturally disposed of by activated macrophages. Disease was said to arise only when this surveillance failed. Administration of anti-TIM-3 antibodies acted to release a kind of "brake" on the immune system.

Finally, it was pointed out that similar claims to second medical uses of compounds for the treatment of cancer in general had been accepted as meeting the requirements of Article 83 EPC, for instance in decisions T 1616/09 of 27 August 2014 and T 1492/09 of 9 January 2014 and T 1918/06 of 10 March 2010.

Reasons for the Decision

Main request

Admissibility of the claim request - Article 114(2) EPC and Article 13(1) RPBA

1. The main request comprising an amended independent claim 1, filed with a letter of 16 February 2015 in reply to a communication of the board according to Article 15(1) RPBA, represents an amendment to the appellant's appeal case because it was filed after the filing of the grounds of appeal.
2. The admissibility of an amendment to an appellant's case is subject to the board's discretion which is to be exercised in view, *inter alia*, of the complexity of

the new subject-matter submitted, the current state of the proceedings and the need for procedural economy (Article 13(1) RPBA).

3. The present amendment is a straightforward one, consisting only of the deletion of subject-matter from the previously pending claim request. The main request is therefore admitted into the appeal proceedings.

Claim 1

Subject-matter of the claim

4. The subject-matter of claim 1 is an antibody specific for TIM-3 or a TIM-3 specific fragment thereof, for the specific use of "treatment of cancer in a subject". The claim is therefore directed to a second medical use as foreseen by Article 54(5) EPC.
5. TIM-3 is a transmembrane protein which is preferentially expressed on differentiated Th1 cells and is termed "*T cell Immunoglobulin and Mucin domain-containing molecule-3*" (see the description of the application, page 1, paragraph 1 and page 2, paragraph 3).
6. The antibody of claim 1, specific for TIM-3 or a TIM-3 specific fragment thereof, may bind different epitopes of the target protein. For instance, claim 2 specifies that the antibody binds to an extracellular region of TIM-3.
7. Antibodies may have different biological effects, depending on their particular binding specificity, for instance, they may be agonistic or antagonistic. The description of the application on page 59 provides several possible explanations of the effect of anti-

TIM-3 treatment on a subject: "[...] a cognate interaction between non-T cells and TIM-3-expressing Th1 cells is affected by anti-TIM-3 treatment, resulting in the expansion and activation of CD11b+/F4/80+ macrophages. Several possible mechanisms may explain this finding: a) Anti-TIM-3 may cross-link TIM-3 protein on the surface of differentiated Th1 cells in vivo and amplify the production of pro-inflammatory cytokines (e. g., IFN- γ and TNF), which in turn may induce activation of macrophages ; b) anti-TIM-3 antibody could enhance migration of differentiated Th1 cells into the brain where these cells may increase the cellular influx of macrophages from the circulation; c) anti-TIM-3 could block a cognate interaction of TIM-3 with its potential inhibitory ligand on macrophages, thus leading to enhanced macrophage activation in the presence of pro-inflammatory cytokines produced by Th1 cells".

8. The mechanism set out under (a) may be seen as an agonistic type mechanism, in which anti-TIM-3 binding triggers a signalling cascade, while that given under (b) is an antagonistic mechanism with the effects due to the blocking of the interaction of a ligand with its receptor.
9. The antibodies of the claim are for the treatment of cancer in a subject. Cancer is not a single disease with a single underlying mechanistic cause but is a collective term for a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body, see the description of the application, page 20, last paragraph: "Cancers include, but are not limited to, basal cell carcinoma, biliary tract cancer; bladder cancer; bone cancer; brain and CNS cancer; breast cancer; cervical cancer;

choriocarcinoma; colon and rectum cancer; connective tissue cancer; cancer of the digestive system; endometrial cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer; intra-epithelial neoplasm; kidney cancer; larynx cancer; leukemia; liver cancer; lung cancer (e.g. small cell and non-small cell); lymphoma including Hodgkin's and non-Hodgkin's lymphoma; melanoma; myeloma; neuroblastoma; oral cavity cancer (e.g. lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer; prostate cancer; retinoblastoma; rhabdomyosarcoma; rectal cancer; cancer of the respiratory system; sarcoma; skin cancer; stomach cancer; testicular cancer; thyroid cancer; uterine cancer; cancer of the urinary system, as well as other carcinomas and sarcomas."

10. In summary, claim 1 is directed to an anti-TIM-3 antibody or a TIM-3 specific fragment thereof, with any type of specificity for treatment of any type of cancer.

Sufficiency of disclosure - Article 83 EPC

11. Article 83 EPC requires that the claimed subject-matter is disclosed in the application "*in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art*".
12. The experimental evidence provided in the application relates *inter alia* to mice having experimental autoimmune encephalomyelitis (EAE), a Th1-dependent autoimmune disease being a widely accepted model for multiple sclerosis. The data provided in the examples show that the Th1-specific cell surface protein TIM-3 is involved in regulating the level of T-cell

trafficking to target tissues and macrophage activation in these mice (description of the application, page 1, lines 5 to 11 and Examples 5 to 16). Example 6 shows that an existing autoimmune reaction triggered by immunisation with encephalitogenic proteolipid protein (PLP) is exacerbated by administration of an anti-TIM-3 antibody.

13. The board concludes that, from the evidence provided in the application, the skilled person would have considered it plausible that an extant immune reaction, such as that existing in the EAE mice, could be amplified by administration of anti-TIM-3 antibodies.
14. The evidence provided in the application does not concern establishment of a *de novo* immune response to a tumour antigen or to any other antigen.
15. The skilled person at the priority date knew that i) cancer cells were "self" cells, ii) an immune response to self antigens was the exception to the rule (cf. description of the application, page 40, lines 7 to 29) and iii) there were a wide range of different cancers with diverse underlying causes (see point 9. above).
16. In view of the above it is considered that the skilled person would not have considered that the disclosure of the application makes it plausible that it would be possible to generate a *de novo* immune response to cancers where there was no established native response. Moreover, the skilled person would not have believed that substantially all cancer types inherently generate a Th1, TIM-3 mediated immune response and be treatable

by administration of anti-TIM-3 antibodies. It is noted that the post-published documents submitted by the appellant support this conclusion, see point 23. below.

17. Thus, the subject-matter of claim 1 does not meet the requirements of Article 83 EPC with respect to the whole scope claimed in relation to the disease to be treated.
18. Secondly, anti-TIM-3 antibodies do not all have the same specificity or functionality (see points 6. and 7. above). The particular antibodies used in the examples of the application are termed "8B.2C12" and "25F.1D6" (see Example 1) and were not deposited with a recognised depositary institution according to Rule 31(a) EPC. It was not disclosed in the application whether the interaction of TIM-3 with its not yet identified ligand (see Example 17) was blocked or activated by the antibody to achieve the claimed therapeutic effect. In view of the potentially opposite actions of anti-TIM-3 antibodies, the skilled person would not have considered it plausible that substantially all embodiments of the invention defined in claim 1 were capable of being realised (c.f. Case Law of the Boards of Appeal of the EPO, 7th edition, II.C.6.1.2).
19. Thus, the subject-matter of claim 1 lacks sufficient disclosure to be carried out by the skilled person over the entire claimed scope with respect to the specificity of the anti-TIM-3 antibody to be used in the claimed medical use.
20. At oral proceedings the appellant argued that the immune system carried out constant immune-surveillance *inter alia* for cancer cells, nascent cancers being

naturally disposed of by activated macrophages. Disease was said to arise only when this surveillance failed (see also description of the application, page 28, paragraphs 2 and 3). The administration as claimed was said to release a "brake" in the immune system. In support of these statements it was pointed out that the application disclosed that TIM-3 was specifically expressed on the majority of CD4+ and CD8+ T cells present in the CNS. Since it was known e.g. from documents D1 and D2, that these cell types are involved in macrophage activation and in tumour immunity, the skilled person would have realised that any cancer could be treated by administration of anti-TIM-3 antibodies which would result in amplification of the macrophage response.

21. It was also argued that the disclosure of post-published documents D3 and D4 supported an inherent effect of an inhibitory anti-TIM-3 antibody, which was present already at the priority date.
22. With respect to the assertion concerning immune surveillance against all cancers, the board notes that there is no documentary evidence on file to support the assertion concerning immune surveillance.
23. With respect to the evidence provided in the form of post-published documents, the board notes that document D3 provides evidence which confirms the board's earlier conclusion (see point 17. above) on the insufficiency of disclosure of the application with respect to *de novo* carcinogenesis. Document D3 reports "*an extensive characterization of the therapeutic activity and mechanism of action of an anti-mouse TIM-3 mAb [monoclonal antibody] against experimental and carcinogen-induced tumors*" (see the abstract). The

anti-TIM-3 antibodies used were specifically antagonistic antibodies (see page 3541, "*Tumor models*"). Anti-TIM-3 was reported to display **only modest** prophylactic (page 3546, column 2, final paragraph) and therapeutic activity (page 3547, paragraph 1) against **a small fraction** of carcinogen-induced sarcomas (13%). In the discussion section (page 3550, column 1) it is stated "*We have shown that dramatic therapeutic effects are not observed with monotherapies (including anti-PD1 or anti-TIM3) in this model [of de novo carcinogenesis]. This is despite the fact that anti-PD1 is an extremely promising therapeutic in some human cancers*".

24. In summary, document D3 discloses that anti-TIM-3 antibodies fail to successfully treat the majority (87%) of induced sarcomas (see the sentence bridging pages 3546 and 3547).
25. Document D4 reports *inter alia* that "*treatment of EL-4 tumor-bearing mice with anti-TIM-3 Ab resulted in delayed tumor progression coincident with lower frequency of CD11b⁺Gr-1⁺ cells (Fig. 2B)*" (see page 1386, column 2, penultimate sentence).
26. However, in view of the diversity of cancer types (see point 9. above), evidence of successful treatment of one tumour type with a specific antibody ("*clone 5D12*") does not provide evidence in support of the entire scope claimed. Moreover, even if the disclosure of document D4 were to be considered as evidence of the successful treatment of cancer, a particular post-published disclosure relating to a particular antibody and a specific type of cancer cannot remedy a problem of general lack of sufficient disclosure at the

priority date (see also decision T 609/02 of 27 October 2004, Reasons 9).

27. The appellant also argued that similar claims to second medical uses of compounds for the treatment of cancer in general have been accepted by the boards in the past, citing decisions T 1616/09 of 27 August 2014 and T 1492/09 of 9 January 2014 and T 1918/06 of 10 March 2010, in particular.
28. The board recalls that the merits of every case must be assessed on the basis of its own legal and factual situation. In the present case the board has, on analysis of the specific circumstances of the case, concluded that the application does not contain a disclosure sufficient for the skilled person to carry out the invention over the entire scope claimed.
29. In view of the above, the board concludes that the subject-matter of claim 1 is not disclosed in the application in a manner sufficiently clear and complete for it to be carried out by the skilled person and therefore does not meet the requirements of Article 83 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairwoman:



P. Cremona

G. Alt

Decision electronically authenticated