Internal distribution code:

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

Datasheet for the decision of 30 April 2015

Case Number: T 1455/12 - 3.3.08

Application Number: 07109688.7

Publication Number: 1847608

IPC: C12N15/12, C12N15/19, C07K14/705, C07K14/52, C07K16/24, C07K16/28, G01N33/68, A61K38/19

Language of the proceedings: EN

Title of invention:
Member of the TNF ligand family

Applicant:
Glaxo Group Limited

Headword:
D7-ligand BLYS TALL1 THANK BAFF TNFSF13B antagonist antibody/ GLAXO

Relevant legal provisions:
EPC Art. 123(2), 114(2)
RPBA Art. 12(4), 13(1)

Keyword:
"Main Request - added subject-matter (no);
remittal to the first instance for further prosecution (yes)"

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

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 1455/12 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 30 April 2015

Appellant: (Applicant)	Glaxo Group Limited 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 27 December 2011 refusing European patent application No. 07109688.7 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	M. Wieser
Members:	P. Julià
	D. Rogers

Summary of Facts and Submissions

I. In a decision dated 27 December 2011, the examining division refused to grant a patent on the European patent application no. 07 109 688.7, a divisional application of European patent application no. 99 950 598.5, which was published as International patent application WO 00/39295 (referred to as "*the application as filed*"). The examining division considered the Main Request and Auxiliary Requests I and II to contravene Article 123(2) EPC.

II. An appeal was lodged by the applicant (appellant). With its statement setting out the Grounds of Appeal, the appellant maintained the Main Request and Auxiliary Requests I and II filed in the first instance proceedings and filed new Auxiliary Requests III and IV, together with new documentary evidence.

III. In a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) annexed to summons to oral proceedings, the appellant was informed of the board's preliminary, non-binding opinion on issues concerning Article 123(2) EPC.

IV. In reply thereto, the appellant filed an Auxiliary Request V.

V. Oral proceedings were held on 30 April 2015. At these proceedings, the appellant withdrew all its previous claim requests and filed a new Main Request. Claim 1 of the **Main Request** read as follows:

"1. An antibody which is specific for a trimeric protein selected from the group consisting of:

(a) a trimeric protein having the amino acid sequence of SEQ ID NO: 1; and

(b) a trimeric protein having an amino acid sequence at least 98% identical to SEQ ID NO: 1 and capable of binding to B-cells;

for use in treating an autoimmune disease, rheumatoid arthritis, inflammation or cancer;
wherein said antibody is an antagonist of the binding of said trimeric protein to its receptor on B lymphoma cell line RPMI 8866."

Claims 2 to 6 were preferred embodiments of claim 1. Claim 6 characterized the claimed antibody as an antagonist of the binding of a trimeric protein having the amino acid sequence of SEQ ID NO: 1 to B-cell lines RPMI 8866, RPIM 8226 and Raji.

VI. The arguments of the appellant, insofar as relevant to the present decision, may be summarized as follows:

The D7 ligand (amino acid sequence SEQ ID NO: 1) was identified in the application as filed as a member of the TNF ligand family. Members of this family were known in the prior art to bind (in a trimeric form) to cell-surface receptors of the TNF receptor family, starting thereby a chain of events that resulted in diverse functional responses. The binding of the (soluble) D7 ligand to its receptor on (and exclusively restricted to) B-cell lines disclosed in Example 6 (Figure 13) of the application as filed, together with the results shown in Examples 2, 5 and 7-8, suggested a role of the (soluble) D7 ligand on B-cell growth and differentiation. Screening methods for identifying modulators of this binding interaction and their use in

therapy, such as for the treatment of the diseases referred to in the claims, were disclosed in the application as filed as central embodiments of the invention. Antagonists were disclosed as preferred modulators of the binding interaction between the D7 ligand and its receptor.

Antibodies specific for the D7 ligand and their use as therapeutic agents were described in the application as filed. There was documentary evidence on file showing that antibodies binding a ligand protein of the TNF superfamily and thereby modulating the receptor binding interaction, were exclusively known in the prior art as having the function of antagonizing this binding interaction, i.e. they were antagonist antibodies. Thus, there was a direct and unambiguous disclosure of antibodies that antagonized the binding of the D7 ligand to its receptor on B-cells, such as on the B-lymphoma cell lines RPMI 8866, RPMI 8226 and Raji, shown in Example 6.

As also discussed in the application as filed, antibodies specific to the D7 ligand were described in document D7 (A. Mukhopadhyay et al., J. Biol. Chem., 4 June 1999, Vol. 274, No. 23, pages 15978 to 15981). These antibodies modulated the interaction of the D7 ligand to its receptor and prevented the generation of a signal and the resulting functional responses.

VII. The appellant (applicant) requested that the decision under appeal be set aside and that the case be remitted to the department of first instance for further prosecution upon the basis of claims 1 - 6 of the Main Request filed at the oral proceedings before the board on 30 April 2015.

Reasons for the Decision

Main Request
Amissibility into the appeal proceedings

1. The Main Request, filed at oral proceedings before the board, is based on Auxiliary Request I filed in the first instance proceedings. This Auxiliary Request I was maintained with appellant's Grounds of Appeal and withdrawn only at oral proceedings before the board (cf. points II and V *supra*). The new Main Request differs from Auxiliary Request I only by the deletion of a part of former claim 1 which related to an amino acid sequence SEQ ID NO: 2. This amendment was made in direct reply to issues raised and discussed for the first time at oral proceedings before the board. The amendment does not change the subject-matter of the appeal, it does not introduce new issues or objections into the appeal proceedings or render the appeal more complicated but, on the contrary, contributes to the efficiency of the procedure.

2. Thus, the board, in exercising its discretion under Article 114(2) EPC and Article 13(1) RPBA, decides to admit the Main Request into the appeal proceedings.

Article 123(2) EPC

3. The disclosure in the application as filed is concerned with the D7 ligand, a type II membrane protein with a single transmembrane domain near the N-terminus and a protease cleavage site at a specific position within its amino acid sequence. The D7 ligand is identified as a member of the tumour necrosis factor (TNF) ligand superfamily (cf. *inter alia*, pages 1-2 of the

application as filed). Whereas the full-length amino acid sequence of the human D7 ligand is shown in Figure 2 (SEQ ID NO: 2), the soluble, extracellular domain of the human D7 ligand is shown in Figure 1 (SEQ ID NO: 1) of the application as filed (cf. *inter alia*, page 15, lines 15-22 and page 17, lines 9-11). The relevance of a trimer form of this ligand is acknowledged in the application as filed which states that "*the proteins of the invention will bind to their receptor as a trimer*". Further experimental evidence is provided by demonstrating that the soluble D7 ligand "*is able to assemble correctly into a homotrimer*" (cf. *inter alia*, page 3, lines 22-27, page 22, Example 8 and claims 4-5).

4. With reference to "*other* [known] *members of the TNF ligand family*", the application states that "(t)*he interaction between a TNF ligand and its receptor is the key signal to start a chain of events leading to a range of responses as diverse as T-cell proliferation, apoptosis and induction of cytokine production*". It is further acknowledged that "(t)*he interaction between these ligands and their receptors provides an attractive target for the development of novel therapies*" (cf. page 1, lines 11-19). Indeed, the screening methods disclosed in the application as filed, and used to "*identify compounds which act as modulators of the interaction between proteins of the invention and their receptor*", are all based on measuring - in the presence or absence of a test compound (modulator) - the increase or decrease in the level of binding of the D7 ligand to its receptor or in measuring a response (such as NF-κB activation) associated thereto (cf. paragraph bridging pages 7-8 and claim 11 of the application as filed). In Example 6 of the application as filed, several B-lymphoma cell

lines with the D7 ligand receptor on their surface are provided. This is demonstrated by the binding of the D7 ligand shown in Figure 13 (cf. page 16, lines 32-34, pages 20-21, Example 6). These are the B-cell lines cited in claims 1 and 6 of the Main Request (cf. point V *supra*).

5. The experimental evidence provided by the Examples of the application as originally filed supports a role of the D7 ligand in the regulation of the immune system and its disorders and, more particularly, of B-cell growth and differentiation (cf. pages 17-18, Example 2 and pages 20-22, Examples 5-7). Indeed, this experimental evidence, based on the use of soluble D7 ligand, also provides the technical basis for supporting the therapeutic use of the modulators identified by the screening methods described. In particular, for their use in the treatment of the specific diseases mentioned in the claims of the Main Request (cf. *inter alia*, page 8, lines 12-34 and claims 12-15 of the application as filed). Moreover, it is also explicitly stated in the application as filed that the preferred modulators are antagonists (cf. page 8, lines 19-21).

6. Antibodies specific for the D7 ligand are explicitly disclosed in the application as filed which also acknowledges, in an explicit manner, that they *"may also be used as therapeutic agents in their own right*" (cf. page 3, line 29 to page 4, line 17 and claim 10).

In the decision under appeal, the examining division considered the combination of this paragraph with the passage referring to modulators and their therapeutic use not to be a "*direct and unambiguous disclosure of*

the combination of an antibody and the function as decreasing the binding of the protein described in the application and its receptor" (cf. page 5, points 3.2 to 3.4 and page 7, point 5.5 of the decision under appeal).

Since the specific therapeutic uses disclosed in the application as filed are based and rely only on these modulators (cf. points 4-5 *supra*), the board takes the view that the antibodies, in an implicit manner, are thereby identified as "*modulators of the interaction between proteins of the invention and their receptor*". Moreover, since the application as filed identifies the preferred modulators as antagonists (cf. point 5 *supra*), it is also implicitly disclosed that antagonist antibodies are preferred embodiments of the invention.

7. This implicit disclosure is fully in line with the teaching in the prior art referring to the TNF ligand and receptor superfamily which is mentioned in the application as filed and documented by further evidence on file (cf. points VI and 3 *supra*). Indeed, in the reference to document D7 on page 13 of the application as filed, anti D7-ligand antibodies are described as "(m)*olecules that modulate the interaction of the protein of the invention with its receptor ... able to modulate the activation of NF-κB and ... useful in any diseases that are responsive to modulation of the level of activity of NF-κB ...*", in particular in all diseases mentioned in claim 1 of the Main Request. It is also stated that "*the presence of the antibody affects the binding of the protein of the invention to its receptor, thus preventing generation of a signal and consequently reducing NF-κB activation. These findings indicate that <u>other</u> compounds ... which*

modulate the interaction between the protein of the invention and its receptor can be identified in a screen and can be used to modulate NF-κB activation and other downstream effects" (emphasis added by the board; cf. page 13, line 20 to page 14, line 10 of the application as filed).

8. Thus, it follows from the above considerations that the Main Request fulfils the requirements of Article 123(2) EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance for further prosecution upon the basis of claims 1 - 6 of the Main Request filed at the oral proceedings before the board on 30 April 2015.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated