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**Datasheet for the decision
of 23 April 2009**

Case Number: T 0929/07 - 3.3.08

Application Number: 97932526.3

Publication Number: 0912734

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:
Chimeric heteromultimer adhesins

Applicant:
Genentech, Inc.

Headword:
Adhesins/GENENTECH

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main request - inventive step - yes"

Decisions cited:
T 0606/89

Catchword:
-



Case Number: T 0929/07 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 23 April 2009

Appellant: Genentech, Inc.
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 7 November 2006
refusing European application No. 97932526.3
pursuant to Article 97(1) EPC 1973.

Composition of the Board:

Chairman: L. Galligani
Members: F. Davison-Brunel
C. Heath

Summary of Facts and Submissions

- I. European patent application No. 979332526.3 with the title "Chimeric heteromultimer adhesins" filed as International application PCT/US 97/11825 was published under No. WO 98/02540. It was refused by the examining division in a decision dated 7 November 2006.
- II. The decision of the examining division was taken on the ground that claim 1 of each of the main request and auxiliary requests 1 to 3 then on file (all filed on 19 June 2006 as requests 1 to 4) did not meet the requirements of Article 56 EPC, mentioning in this respect the relevance of documents (1), (2), (3) and (4) taken in various combinations (see *infra*).

Claim 1 of the main request read as follows:

"1. An isolated recombinant chimeric heteromultimer adhesin comprising:

 a first amino acid sequence comprising an extracellular domain of an ErbB2 receptor monomer, lacking a transmembrane domain, and a first heterologous multimerization domain;

 an additional amino acid sequence comprising an extracellular domain of an ErbB3 or ErbB4 receptor monomer, each lacking a transmembrane domain, and a second heterologous multimerization domain;

 wherein the multimerization domain of the first amino acid sequence and additional amino acid sequence each comprise an immunoglobulin IgG constant region or fragment thereof;

wherein the extracellular domain of the first amino acid sequence and the extracellular domain of the additional amino acid sequence are brought together via interaction of the multimerization domain of the first amino acid sequence and the multimerization domain of the additional amino acid sequence to form a binding domain of a chimeric heteromultimer adhesin having 10^{-1} to 10^6 fold affinity for a ligand relative to a ErbB3 or ErbB4 monomer or a homodimeric ErbB3 or ErbB4 receptor; and
wherein the chimeric heteromultimer adhesin is soluble in an aqueous solution."

- III. The appellant (applicant) lodged an appeal against this decision and filed a statement setting out the grounds of appeal together with the main and auxiliary requests refused by the examining division.
- IV. The examining division did not rectify its decision and the case was remitted to the board of appeal (cf. Article 109(2) EPC).
- V. On 10 September 2008, the board sent a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA), making known its preliminary, non-binding opinion that a claimed subject-matter restricted to recombinant chimeric heteromultimer adhesins made of ErbB2/ErbB3-Ig monomers or ErbB2/ErbB4-Ig monomers could be acknowledged as inventive.
- VI. On 4 March 2009, the appellant filed further submissions in answer to this communication together

with a new main request (claims 1 to 10) taking into account the board's preliminary opinion.

VII. In a telephone conversation on 15 April 2009, the rapporteur informed the appellant that a patent could be granted on the basis of the main request filed on 4 March 2009 provided that amendments were carried out in, respectively, claims 1 and 10.

VIII. On 16 April 2009, the appellant sent a fax letter together with a new main request wherein claims 1 and 10 had been amended to take into account the board's opinion. Oral proceedings were, then, cancelled.

Claims 1 and 10 of the new main request read as follows:

"1. An isolated recombinant chimeric heteromultimer adhesin comprising:

 a first amino acid sequence comprising an extracellular domain (ECD) of an ErbB2 receptor monomer, lacking a transmembrane domain, and a first heterologous multimerization domain; wherein the ECD is fused to the multimerization domain;

 an additional amino acid sequence comprising an extracellular domain of an ErbB3 or ErbB4 receptor monomer, each lacking a transmembrane domain, and a second heterologous multimerization domain;

 wherein the multimerization domain of the first amino acid sequence and additional amino acid sequence each comprise an immunoglobulin IgG constant region;

 wherein the extracellular domain of the first amino acid sequence and the extracellular domain of the

additional amino acid sequence are brought together via interaction of the IgG constant region of the multimerization domain of the first amino acid sequence and the IgG constant region of the multimerization domain of the additional amino acid sequence to form a binding domain of a chimeric heteromultimer adhesin; and

wherein the chimeric heteromultimer adhesin is soluble in an aqueous solution.

10. The chimeric heteromultimer adhesin of claim 1 or the pharmaceutical composition of claim 9 for use in a method of treatment of the human or animal body by therapy for any one or more of the following disease states: inflammatory disorder; cancer; neurofibromatosis; peripheral neuropathologies."

Dependent claims 2 and 3 related to nucleic acids encoding the adhesin of claim 1 whereas claims 4 and 5 were respectively directed to vectors and host cells comprising said nucleic acids/vectors. Claims 6 and 7 related to methods of forming a chimeric heteromultimer adhesin-ligand complex wherein the adhesin of claim 1 was used. Claim 8 related to a method of inhibiting activation of a naturally occurring ErbB heteromultimer receptor wherein the adhesin of claim 1 was used. Claim 9 was directed to a pharmaceutical composition comprising the chimeric heteromultimer adhesin of claim 1 and a pharmaceutically acceptable carrier.

IX. The following documents are mentioned in the present decision:

- (1) : Sliwowski, M.X. et al., The Journal of Biological Chemistry, Vol.269, No.20, pages 14661 to 14665, 20 May 1994;
- (2) : Horan, T. et al., The Journal of Biological Chemistry, Vol.270, No.41, pages 24604 to 24608, 13 October 1995;
- (3) : Chen, X. et al., The Journal of Biological Chemistry, Vol.271, No.13, pages 7620 to 7629, 29 March 1996;
- (4) : Chamow, S.M. and Ashkenazi, A., Tibtech, Vol.14, pages 52 to 60, February 1996;
- (5) : WO-A-95/25795 filed on 17 March 1995 with a publication date of 28 September 1995;
- (6) : WO-A-95/27061 filed on 4 April 1995 with a publication date of 12 October 1995;
- (7) : US-A-5428130 published on 27 June 1995.

X. The appellant's arguments in writing insofar as relevant to the present decision may be summarized as follows:

- Document (4) related to the provision of bivalent ErbB molecules which may be bivalent homodimers or bispecific heterodimers. It did not provide any suggestion of adapting the technology for non-ligand binding extracellular domains. In contrast, ErbB2 used to obtain the molecule in accordance with claim 1 did

not bind ligand and the molecules of the invention were not bivalent.

Document (3) taught weaker binding for ErbB3 and ErbB4 homodimers compared to monomers whereas the patent application showed stronger binding for monovalent heterodimers compared with bivalent homodimers.

Document (2) taught that Her2/Her3 extracellular domains did not dimerize to provide a ligand binding receptor. It further taught that transmembrane and/or intracellular domains or additional unidentified components might be required for ligand binding.

Document (1) related only to the expression of full-length ErbB polypeptides in the intracellular environment and its teachings that other factors might be required within that environment in order to generate functional binding multimers supported the findings in document (2).

- If document 2 or 3 was taken as closest prior art, it was not obvious from either document in combination with any of the other cited documents that an ErbB2/ErbB3 or ErbB2/ErbB4 heterodimer should be made as claimed nor that such molecules would exhibit enhanced binding affinity for a ligand compared with ErbB3 or ErbB4 homodimers. The enhanced binding affinity of the heterodimer provided the molecules with the ability to compete for a ligand with a naturally occurring receptor.

If document (1) was taken as closest prior art, there was no other single document that could be combined with it to render the claimed invention obvious.

Furthermore, the finding in accordance with the invention that the monovalent heterodimer of the

invention bound a ligand more strongly than bivalent homodimer was not obvious from any of the documents, whether taken alone or in combination. In fact, both documents (3) and (2) taught away from this.

For these reasons, the claimed subject-matter fulfilled the requirement of Article 56 EPC.

XI. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed on 16 April 2009.

Reasons for the decision

1. The claimed subject-matter finds a basis in the application as filed in particular on pages 5 to 7 (claims 1 to 5) and on pages 8 to 10 (claims 6 to 10). The claimed subject-matter is clear and supported by the description. The requirements of Articles 123(2) and (84) EPC are fulfilled.
2. Novelty is not at stake (Article 54 EPC). In the course of examination procedure, an objection for lack of sufficient disclosure was raised in relation to subject-matter which is no longer claimed. The board is satisfied that the now claimed subject-matter can be reproduced on the basis of the teachings of the application, in particular of the examples (Article 83 EPC). The industrial applicability of the claimed subject-matter is seen e.g. in its capacity to regulate biological mechanisms taking place in certain disease states (page 25), which may ultimately result in therapeutic applications (Art.57 EPC).

3. The issue to be decided is that of inventive step. Taking the problem-solution approach to inventive step requires in the first place that the prior art closest to the claimed subject-matter be determined. Here, the subject-matter of claim 1 is a chimeric heteromultimer adhesin comprising the fused ErbB2 receptor extracellular domain-IgG constant region monomer (ErbB2-IgG) bound to either the ErbB3 receptor extracellular domain-IgG constant region monomer (ErbB3-IgG) or to the ErbB4 receptor extracellular domain-IgG constant region monomer (ErbB4-IgG), by virtue of interactions taking place between the IgG regions.

4. Seven prior art documents are on file. Documents (1) and (2) are studies of the natural transmembrane receptors/parts thereof of the ErbB family. They do not involve immunoadhesins. In document (3), homodimeric ErbB3-IgG adhesin and homodimeric ErbB4-IgG adhesin are described which have been isolated with the aim of investigating their ability to bind the heregulin ligand (identified as NDF- β 1, page 7622). It is shown that ErbB3-IgG or ErbB4-IgG homodimers have less affinity for NDF than the corresponding monomers (Fig.1). Heteromultimeric adhesins are not mentioned nor any potential therapeutic benefits. Document (4) is a review on immunoadhesins. The immunoadhesin is defined as a molecule which combines the Fc region of e.g. an IgG heavy chain with the molecular entity to be studied, it being, most frequently but not necessarily, the extracellular domain of a cell receptor (page 52, right-hand column).

It is taught that several structural variations on the basic immunoadhesin are possible; in particular the production of bispecific heterodimeric immunoadhesins with a general structure such as now claimed is mentioned on page 56, left-hand column. On page 58, left-hand column, the therapeutic potential of immunoadhesins is strongly emphasized. Thus, it is mentioned that "... immunoadhesins can be used in a similar manner to some mAbs to modulate biochemical interactions that play key roles in pathological processes".

Documents (5) to (7) are patent documents relating to various heterodimeric immunoadhesins comprising the external domains of different ligand-binding molecules or receptors, and their potential therapeutic uses. ErbB2, ErbB3 and ErbB4 receptors are not mentioned.

5. In accordance with the case law, the closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common (see e.g. T 606/89 of 18 September 1990). In the board's judgment, the closest prior art is, thus, document (4) as it provides a general teaching on immunoadhesins and their therapeutic roles. This teaching reflects and includes the kind of work described in documents (5) to (7).

6. Starting from document (4), the problem to be solved can be defined as enlarging the family of immunoadhesins.

7. The solution provided is the isolation of specific **heterodimeric** adhesins comprising ErbB2 extracellular domain-IgG adhesin linked to either ErbB3 extracellular domain-IgG adhesin (ErbB2/ErbB3-IgG) or to ErbB4 extracellular domain-IgG adhesin (ErbB2/ErbB4-IgG). These heterodimeric adhesins have the property to bind the heregulin ligand with high affinity, some 300-700 fold more than the corresponding homodimeric species, (cf. Example 3 of the patent application).

8. At the priority date, it was known in the art (cf. document (1), summary, page 14661 and page 14662, left-hand column) that the association of the natural ErbB2 and ErbB3 receptors (that is, receptors comprising the external, transmembrane and cytoplasmic natural domains) constituted a **heterodimeric** receptor with a higher affinity to the ligand heregulin than **homodimeric** ErbB2 receptor (no binding observed) or **homodimeric** ErbB3 receptor (low affinity). Yet, studies of the ErbB3 external domain as such (document (2), page 24604, abstract) had not shown any increase in affinity to heregulin (identified as NDF) upon addition of the external ErbB2 domain to the external ErbB3 domain. For the authors of document (2), this finding suggests that:

"... transmembrane and/or intracellular domains of receptor family members or perhaps additional unidentified components may be involved in NDF induced dimerization and autophosphorylation or, alternatively that dimerization is not the mechanism for Her3 autophosphorylation and signal transduction."

Furthermore, prior art document (3) reports that monomers of ErbB3 or ErbB4-Ig adhesins have a higher

affinity for the heregulin (NDF) ligand than the homodimers (Fig.1, page 7622).

9. The only conclusion which can be drawn from these data, is that the process of heterodimerization (cf. document (2)) or the process of homodimerization (cf. document (3)) confers levels of complexity to the interaction of the receptor with the ligand which do not allow any reasonable expectation as to the binding capacity of structurally different receptor-like molecules.
10. Accordingly, it is non-obvious that the claimed specific ErbB2-Ig/ErbB3-IgG and ErbB2/ErbB4-IgG heterodimers would bind to the heregulin ligand, let alone with high efficiency. And, thus, inventive step is acknowledged.

Order:

For these reasons, it is decided that:

1. The decision of the examining division is set aside.
2. The case is remitted to the first instance with the order to grant a patent on the basis of claims 1 to 10 filed on 16 April 2009 and a description and figures to be amended accordingly.

The Registrar

The Chairman

G. Nachtigall

L. Galligani