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D E C I S I O N
of 11 April 1995

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Case Number: W 0006/94 - 3.3.4
International Application No. PCT/US 93/04717

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 11 April 1995

Applicant: GENENTECH INC.
460 Point San Bruno Boulevard
South San Francisco, CA 94080-4990 (US)

Representative: -

Subject of the Decision: **Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicant against the invitation (payment of additional fees) of the European Patent Office (International Searching Authority) dated 30 September 1993.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: L. Galligani
R. Teschemacher

Summary of Facts and Submissions

I. International patent application PCT/US 93/04717 was filed on 17 May 1993 with fifty-two claims.

Claims 1 to 4, 8 and 11 read as follows:

"1. A method for receptor activation comprising (a) providing a conjugate comprising the direct fusion of a first ligand and a second ligand capable of binding to first and second receptors, respectively, wherein said first and second receptors are capable of oligomerization with each other, and are selected from the group consisting of receptors with tyrosine kinase activity, cytokine receptors, and members of the nerve growth factor receptor superfamily, and (b) contacting the conjugate with the first and second receptors whereby the first ligand binds to the first receptor and the second ligand binds to the second receptor."

"2. The method of Claim 1 wherein said first and second ligands are variants of native ligands."

"3. The method of Claim 2 wherein said first and second ligands are variants of the same native ligand."

"4. The method of Claim 3 wherein said native ligand is capable of binding to a receptor with tyrosine kinase activity."

"8. The method of Claim 3 wherein said native ligand is capable of binding to a receptor selected from the hematopoietin receptor superfamily."

"11. The method of Claim 3 wherein said native ligand is capable of binding to a member of the nerve growth factor receptor superfamily."

Claims 5 to 7, 13 to 33, 35 to 40 and 43 to 52 concerned embodiments of the invention in respect of receptors with tyrosine kinase activity.

Claims 9 to 10 (dependent upon Claim 8) concerned embodiments of the invention in respect of the receptors of the hematopoietin receptor superfamily.

Claim 12 (dependent upon Claim 11) concerned embodiments of the invention in respect of receptors of the nerve growth factor receptor superfamily.

Claims 34 and 41 to 42 concerned embodiments of the invention in respect of receptors with tyrosine kinase activity, cytokine receptors, and members of the nerve growth factor receptor superfamily.

II. On 30 September 1993 the European Patent Office (EPO), acting as an International Search Authority (ISA), invited the Applicant to pay within a time limit of 45 days two additional search fees pursuant to Article 17(3)(a) and Rule 40.1 PCT and issued a partial search report on Claims 1 to 3 (partially), 4 to 7, 13 to 33, 34 (partially), 35 to 40, 41 to 42 (partially), 43 to 52.

III. The invitation stated that the problem underlying the application was the activation of receptors belonging to the families of receptors with tyrosine kinase activity, cytokine receptors, and members of the nerve growth factor receptor superfamily and that the solution was the use of fused receptor ligands which activated the receptors due to their oligomerisation-inducing activity. In view of the prior art cited in the partial search report, namely:

(1) Cell, Vol. 61, 20 April 1990, pages 203 to 212,

which disclosed the activation of receptors with tyrosine kinase activity by oligomerisation induced with heterodimeric ligands, there was no longer a technical relationship among the inventions involving a special technical feature which defined their contribution over the prior art, the three receptor families mentioned in Claim 1 being of essentially different nature. Thus, the application related to the following groups of inventions which were not linked by a single inventive concept:

1. Claims 1 to 3 (partially), 4 to 7, 13 to 33, 34 (partially), 35 to 40, 41 to 42 (partially), 43 to 52.

2. Claims 1 to 3 (partially), 8 to 10, 34 (partially), 41 to 42 (partially).

3. Claims 1 to 3 (partially), 11 to 12, 34 (partially), 41 to 42 (partially).

IV. On 30 October 1993, the Applicant paid the additional fees under protest pursuant to Rule 40.2(c) PCT and at the same time filed amended Claims 1 and 13. In support of the protest, the Applicant submitted that:

- the practice of the ISA to carry out an *a posteriori* examination of an international application and to find non-unity based on the discovery of document(s) allegedly anticipating one or more of the generic claims was at the borderline of the ISA's authority and highly questionable;

- the single inventive concept in the present case was the recognition that receptors of certain families could be activated by linking two or more domains (ligands) capable of binding the receptor to be activated. It was found that this was generally applicable to the receptors of the indicated families, irrespective of whether they were known to have naturally occurring dimeric or heterodimeric ligands, these latter not being covered by the claims as amended. Nothing in the cited prior art document suggested that this could be done because the reference to "heterodimeric" ligands therein related to a specific naturally occurring isoform of native platelet-derived growth factor (PDGF), namely PDGF-AB. The ISA had failed to show why the existence of homo- and heterodimeric ligands for subclass III tyrosine kinase receptors would suggest that tyrosine kinase receptors in general could be activated by a large variety of structurally diverse molecules, provided they comprised at least two domains capable of binding the tyrosine kinase receptor to be activated.

V. On 25 January 1994 the ISA issued a complete search report and communicated to the Applicant the result of its review under Rule 40.2(e) PCT, giving the reasons why its invitation to pay additional search fees was completely justified. The Applicant was invited to pay within one month the protest fee.

VI. The protest fee was paid by the Applicant on 23 February 1994.

Reasons for the Decision

1. The protest is admissible.

2. According to Rule 13.1 PCT, the international patent application shall relate to one invention only or to a group of inventions so linked as to form a single inventive concept. If the ISA considers that the claims lack this unity, it is empowered, under Article 17(3)(a) PCT, to invite the Applicant to pay additional fees.

3. Lack of unity may be directly evident "a priori", i.e. before considering the claims in relation to any prior art. Alternatively, having regard to decision G 1/89 of the Enlarged Board of Appeal, dated 2 May 1990 (OJ EPO 1991, 155), the ISA is also empowered to raise an objection *a posteriori*, i.e. after having taken the prior art into consideration. This practice is laid down in the PCT Search Guidelines, Chapter VII-9 (PCT Gazette 30/1992, 10425) which are the basis for a uniform practice of all International Searching Authorities. The Enlarged Board of Appeal indicated that this represented only a provisional opinion on novelty and inventive step which was in no way binding upon the authorities subsequently responsible for the substantive examination of the application (point 8.1 of the Reasons for the decision).

   However, the Enlarged Board in point 8.2 of the Reasons mentioned that such invitation to pay additional fees should always be made "with a view to giving the Applicant fair treatment" and should only be made in clear cases.

4. Since the present examination by the Board according to Rule 40.2(c) PCT relates to the protest against the invitation by the ISA to pay additional search fees,

said invitation being based on the claims as originally filed, and there is no opportunity for the Applicant to amend the claims in the international phase until he has received the complete international search report [Article 19(1) PCT], there is no room for taking into account any later amendments of these claims (cf., for example, W 3/94 of 15 December 1994, to be published in the OJ EPO, in particular point 3 of the Reasons). Thus, the present decision is based on the claims as originally filed.

5. According to Rule 13.3 PCT, the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

6. The present application relates to methods and means for the activation of receptors with tyrosine kinase activity, cytokine receptors, and members of the nerve growth factor receptor superfamily. For the activation of these three groups of receptors, Claim 1 proposes a method which is essentially based on the recognition that activation can be achieved by mediation of dimer formation through a dimeric ligand. The claimed method consists in contacting receptors selected from the quoted groups with a conjugate that comprises the direct fusion of a first ligand and a second ligand, i.e. a dimeric ligand, said conjugate being capable of binding to first and second receptors which are capable of oligomerisation.

However, the concept underlying the claimed method, namely the activation of certain receptors by mediation of dimer formation through a dimeric ligand, is known from prior art document (1). As correctly observed by the ISA, this document discloses that the activation by

oligomerisation of receptors with tyrosine kinase activity, in particular of subclass III receptors, may occur by mediation of dimer formation through a dimeric ligand, in particular through a heterodimeric ligand such as PDGF-AB (see page 203, right-hand column, paragraphs 2 and 3 and Figure 2).

Therefore, Claim 1 which concerns as one alternative receptors with tyrosine kinase activity cannot considered to be novel having regard to document (1). Novelty is lacking also in respect of Claim 13 which concerns only receptors with tyrosine kinase activity. In view of this objection, the question arises whether the subject-matter of the application is based on a single general inventive concept.

7. In support of unity of invention, the Applicant puts forward arguments based essentially on the fact that Claim 1 (and Claim 13) **as amended** exclude(s) from its (their) ambit the disclosure of document (1). The Applicant maintains that the "single inventive concept" lies in the finding that the dimer-induced activation of receptors is generally applicable to all receptors of the indicated families.

However, as already indicated (see point 4, above), the proposed amendments have to be disregarded.

8. It is general knowledge that a common feature of many receptors is that they need to be oligomerised to become active or that their activity is enhanced by oligomerisation [in this respect, see pages 1 to 5 of the present application and page 203 of document (1)]. It is also known that oligomerisation can be induced by monomeric ligands or by bivalent ligands (ibid.).

Document (1), in particular, illustrates this concept in respect of receptors with tyrosine kinase activity (see point 6, second paragraph, above).

In the light of document (1), the technical problem to be solved can be seen in the provision of an alternative method for the activation of receptors selected from the groups of receptors with tyrosine kinase activity, cytokine receptors, and members of the nerve growth factor receptor superfamily.

As a solution thereto, Claim 1 proposes for the groups of receptors in question an activation method which is based on the approach of the dimeric ligand-induced activation. This would constitute *a priori* the "special technical feature" providing the link between the claimed alternatives in the sense of Rule 13.2 PCT. However, in the present situation, due to the fact that the said feature is known from document (1) in which for the receptors with tyrosine kinase activity an identical activation method is disclosed (cf. novelty objection in point 6, above), the alternatives within Claim 1 are left *a posteriori* without a common inventive concept.

9. It should, therefore, be investigated whether another "special technical feature" in the sense of Rule 13.2 is available which could link the three alternatives so as to form a single general inventive concept. In this respect it is observed that the finding that a **known** concept underlying a **known** method applicable to a given group of receptors (here: receptors with tyrosine kinase activity) can also be applied in an analogous manner to other groups of receptors (here: cytokine receptors and nerve growth factor receptors) per se is not sufficient to achieve unity of invention between the resulting

analogous methods, if no further "special technical feature" is available for establishing a technical relationship between them.

The sole feature which defines for each of the separate alternatives within Claim 1 the contribution over the prior art is the reference to the group of receptors to which the approach known from document (1) is applied. This, however, cannot be considered to be a "special technical feature" sufficient to form a single general inventive concept in the sense of Rule 13.2 PCT because of the marked structural and functional differences between the three groups of receptors. Failing such feature, the problem of providing an alternative activation method becomes a distinct - although analogous - problem for each group of receptors which is solved in each case by a separate - although analogous - way. Nor can any of the features referred to in the dependent claims, such as, for example, the fact that the first and second ligands are variants of native ligands (cf. Claim 2) or that the first and second ligands are variants of the same native ligand (cf. Claim 3), be considered as a "special technical feature" sufficient to establish an inventive link between the claimed alternatives in the sense of Rule 13.2 PCT. In fact, being recognised in the prior art [see document (1)] that the activation of receptors by oligomerisation can be achieved by means of binding of a native homo- and heterodimeric ligand, the mere reference to the use of variants of such ligands is not enough to establish a technical relationship between the claimed alternatives so as to reconstitute a single general inventive concept, especially in view of the marked structural and functional differences between the three groups of receptors.

10. For the foregoing reasons, in the Board's judgement, the international application does not comply with the requirement of Rule 13.1 PCT and the invitation to pay the additional fees was justified.

Order

For these reasons it is decided that:

The protest according to Rule 40.2(c) PCT is dismissed.

The Registrar: The Chairwoman:

L. McGarry U. Kinkeldey