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Title of invention:
Apo-2 ligand variants and uses thereof

Applicant:
Genentech, Inc.

Headword:
Functional Apo-2 ligand variants suitable for PEGylation/ GENENTECH

Relevant legal provisions:
EPC Art. 82, 111(1)
EPC R. 137(4), 164(2)

Keyword:
Unity of invention - (yes)
Appeal decision - remittal to the examining divsion (yes)

Decisions cited:
T 0631/97

Catchword:

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Case Number: T 2248/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 29 October 2015

Appellant: (Applicant)	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 (US)
Representative:	Kiddle, Simon John Mewburn Ellis LLP City Tower 40 Basinghall Street London EC2V 5DE (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 8 May 2012 refusing European patent application No. 02766436.6 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	M. Montrone
	M.-B. Tardo-Dino

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division to refuse European patent application No. 02766436.6 with the title *"Apo-2 ligand variants and uses thereof".* It was filed as an international application and published as WO 03/029420.

II. The European supplementary search report in relation to the application under consideration was based on 51 claims filed upon entry into the regional phase.

Claim 1 reads:

"1. An isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1) and has one or more of the following amino acid substitutions at the residue position(s) in Figure 1 (SEQ ID NO:1): S96C; S101C; S111C; V114C; R11SC; E116C; N134C; N140C; E144C; N152C; S153C; R170C; R170K; R170S K179C; D234C; E249C; R255C; E263C; H264C."

III. The Supplementary European Search Report (SESR) was drawn up in 2005 and cited *inter alia* documents WO 01/00832 and Veronese F; *Biomaterials,* 2001; 22: 405-417, which are referred to in the present decision as documents D1 and D4 respectively.

IV. The search division considered that the application did not meet the requirements of unity of invention because the subject-matter of claim 1 related to 20 inventions, *i.e.* one for each of the mutation sites identified in claim 1 above.

The applicant (hereinafter the appellant), after receiving an invitation pursuant to Rule 112 EPC 1973, did not pay further search fees and the European supplementary search report was accordingly limited to the invention first mentioned in the claims, *i.e.* the Apo-2 ligand (Apo2L) variant "S96C".

V. The decision of the examining division was based on a main and an auxiliary request. Claim 1 of both requests related to Apo2L variants characterised by a cysteine (C) substitution of either arginine (R) at position 170 (R170C) and/or lysine (K) at position 179 (K179C).

Claim 1 of the main request reads:

"1. An isolated Apo-2 ligand variant polypeptide having at least 80% amino acid sequence identity to an Apo-2 ligand polypeptide having an amino acid sequence from residues 114 to 281 inclusive of Figure 1 (SEQ ID NO: 1), wherein the Apo-2 ligand variant polypeptide comprises an amino acid substitution of a cysteine amino acid at the position corresponding to R170 and/or K179 of Figure 1 (SEQ ID NO: 1) wherein the Apo-2 ligand variant polypeptide binds to a polypeptide selected from the group consisting of DR4 receptor and DR5 receptor."

Claim 1 of the auxiliary request differed from that of the main request in that the passage "having at least 80% amino acid sequence identity to an Apo-2 ligand polypeptide" had been deleted from it.

VI. The examining division took the view that "*claim 1* [of both requests] *contains subject-matter which is not unitary with invention 1 of the claim set on which the supplementary European search was based, contravening*

the provisions of Article 82 EPC in combination with Rules 137(5) [sic] *and 164(2) EPC*".

The reasons given for this finding were essentially that the closest prior art document D1 disclosed positions R170 and K179 as possible mutation sites of Apo2L. The technical problem to be solved was the provision of alternative Apo2L mutants, which was considered obvious because the pharmacological activity of Apo2L was disclosed in document D1 and the engineering of cysteine residues into pharmaceutical proteins for PEGylation was taught in document D4. In view of the combined teaching of both documents, the skilled person would have tried to find PEGylated Apo2L variants with retained receptor-binding activity, since PEGylation was known to distort protein-protein interactions.

Moreover, the three mutants S96C, R170C and K179C failed to provide a common unexpected technical effect in view of the data disclosed in Table I of the application as filed.

VII. With the statement of grounds of appeal, the appellant submitted a main and two auxiliary requests.

VIII. The appellant was informed of the preliminary opinion of the board that the two auxiliary requests, but not the main request, complied with the requirements of Article 82 EPC (communication of 22 May 2015). The appellant was also informed about the board's intention to decide the case in writing and to order its remittal to the first instance for further prosecution if the main request was withdrawn. Otherwise, oral proceedings were to be arranged.

IX. Subsequently, the appellant withdrew its main request and made its previous second auxiliary request - which was identical to the main request dealt with in the decision under appeal (see section V above) - its new main request.

X. The appellant's arguments submitted in writing may be summarised as follows:

Unity of invention (Article 82 EPC)

The Apo2L was a cytokine that upon interaction with a so-called death receptor (DR) induced apoptosis in cells.

The claimed Apo2L variants were engineered not only to retain their DR binding and apoptotic activity, but also to facilitate the conjugation to a polyol, such as polyethylene glycol (PEG). The sites for modification were selected using the X-ray crystal structure of the Apo2L-DR5 protein complex to identify residues that were outside of Apo2L's receptor contact site and had a high solvent accessibility. The native residues at the selected positions were then replaced by cysteine, which was readily conjugated to polyols like PEG. Therefore, the variants R170C and K179C of claim 1 shared significant structural and functional features with the variant S96C on which the European supplementary search report was based.

The examining division identified document D1 as the closest prior art but failed to take into account the technical difference between the alanine variants disclosed in this document and the claimed cysteine variants. The decision did not give reasons why the skilled person would have combined the positions

disclosed in Table I of document D1 with the general teaching about protein PEGylation of document D4.

The teaching of document D4 was more balanced than the examining division had conceded. In fact, it pointed to complications such as steric interference caused by PEGylation, which may abolish a protein's ability to bind to its substrate. However, this document did not disclose any specific information for solving the problem of engineering PEGylated ligands which remained biologically active upon interaction with TNF receptors, such as DR, let alone for Apo2L.

XI. The appellant requested in writing that the decision under appeal be set aside and that the case be remitted to the examining division for further prosecution.

Reasons for the Decision

Unity of invention (Article 82 EPC)

1. In the European grant procedure, the ultimate responsibility for establishing whether an application complies with the requirements of Article 82 EPC rests with the examining division, which has the duty to review the unity assessment made by the search division. The fact that the appellant has not paid further search fees does not prohibit this review (see e.g. decision T 631/97, headnote and points 3.6 to 3.8 and 3.9.2 of the Reasons).

2. Article 82 EPC states that "*The European patent application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept*".

The case law has established in this context that a "*single general inventive concept*" is present only when the concept underlying the invention is new and inventive (see Case Law of the Boards of Appeal, 7th edition 2013, II.B.4.2, page 291, third paragraph).

3. Rule 44(1) EPC further interprets the concept of unity of invention where a group of inventions is claimed. In such cases "*the requirement of unity of invention under Article 82 EPC shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those features which define a contribution which each of the claimed inventions as a whole makes over the prior art*".

4. The assessment of unity of invention requires as a precondition the analysis of the technical problem or problems underlying the respective groups of inventions, because only then is it possible to decide whether or not the same or corresponding special technical features exist for the different embodiments under consideration (see Case Law of the Boards of Appeal, 7th Edition, II.B.4.1).

5. In the decision under appeal, the examining division concluded that the two claimed Apo2L variants R170C and K179C which were not covered by the Supplementary European Search Report (SESR) lacked unity of invention *a posteriori* in view of the disclosure of the closest prior art document D1 in combination with that of document D4 with regard to the variant S96C covered by the search report (see section IV above), because the concept, *i.e.* the "*special technical features*" linking

the three variants, was not inventive. (Note added by the board: In the designation of the Apo2L variants, the number indicates the position of the amino acid in the Apo2L protein, the first letter indicates the amino acid at that position in the native protein and the last letter that in the variant. Moreover, in the standard one-letter abbreviation for amino acids, "C" stands for cysteine, "K" for lysine and "R" for arginine).

6. Document D1 discloses that the native cytokine Apo2L interacts with the two death receptors 4 (DR4) and 5 (DR5), thereby causing apoptosis of target cells, which recommends its use as a pharmaceutical compound (see page 4, lines 12 to 24). The document also reports on Apo2L variants with improved biological activity, including two having mutations in the positions cited in claim 1, *i.e.* 170 and 179 (see Table I).

7. The board notes that the claimed variants R170C and K179C differ from those disclosed in document D1 in that the native amino acid residue at each position is substituted by cysteine. The searched, but no longer claimed variant, S96C is not disclosed in this document.

8. The "*special technical features*" (see point 3 above) vis-à-vis the disclosure in document D1 common to the three variants S96C, R170C and K179C are that (i) the residues present at the three positions in the native protein are substituted by a cysteine, (ii) the three positions lie outside of the receptor contact region of Apo2L in a binding complex with DR5 and (iii) these positions display a high solvent accessibility. The technical effects resulting from these features are that the three variants are readily PEGylated, and yet substantially retain their biological activity, *i.e.* they bind to their receptors and induce apoptosis (see

Table 1 on page 47 and page 50, third paragraph of the application as filed). Consequently, the board considers that the technical problem underlying the three variants (see point 4 above) is the provision of Apo2L variants which are readily PEGylated and biologically active.

9. Document D1 is not concerned with revealing positions in Apo2L characterised by a high solvent accessibility allowing a PEGylation which does not significantly interfere with the biological activity of the protein but rather with the identification of positions affecting trimer formation and stability of Apo2L. Consequently, a potential substitution of the native residues at these positions with cysteine is not derivable from the document.

10. Document D4 discloses the advantages of PEGylation for therapeutic proteins in general and also that the amino acid cysteine is one of the possible linking partners. The document further draws the skilled person's attention to the potential risk of loosing the biological activity of a protein when trying to improve its pharmacokinetics by conjugation to PEG and reports in this context that *"[t]he same mechanism that prevents the approach of proteolytic enzymes or antibodies to PEGylated protein can also reject a substrate from the protein active site"* (see page 411, left-hand column). However, suggestions as to how the skilled person could avoid or minimise such a risk for therapeutic proteins known to be involved in protein-protein interactions, let alone for Apo2L in particular, are not derivable from the document.

11. Therefore, neither the teaching of document D1 alone nor that of a combination of documents D1 and D4 discloses or suggests the common concept underlying the three

variants under consideration, *i.e.* having modified cysteine residues at positions lying outside of the receptor contact region of Apo2L which concomitantly display high solvent accessibility and thereby allowing a ready conjugation to PEG without significantly reducing the biological activity of the proteins.

12. Thus, contrary to the examining division, the board arrives at the conclusion that the concept by which the three variants S96C, R170C and K179C are linked is new and inventive and is therefore to be considered as a "*single general inventive concept*" in accordance with Article 82 EPC. Hence, the three variants fulfil the requirements of unity of invention.

13. Accordingly, the subject-matter of claim 1 of the main request relating to the variants based on R170C and K179C fulfils the requirements of Article 82 EPC.

14. Moreover, although both claimed variants relate to unsearched subject-matter, both combine with the searched variant S96C to form a "*single general inventive concept".* Therefore, the requirements of Rule 164(2) EPC and Rule 137(4) EPC 2000 are also met. (Note added by the board: The examining division erroneously referred to Rule 137(5) EPC 2010 in the decision under appeal. However, since the SESR had been drawn up in 2005, it is in fact Rule 137(4) EPC 2000 that applies).

15. The appeal is thus allowable.

Remittal (Article 111(1) EPC)

16. The board considers that in a case such as the present one, where the decision under appeal has dealt with Article 82 EPC only, remittal to the first instance is the appropriate option. The board has therefore decided to exercise its discretion under Article 111(1) EPC and to remit the case to the examining division for further prosecution.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The case is remitted to the examining division for further prosecution.

The Registrar: The Chairwoman:

A. Wolinski G. Alt

Decision electronically authenticated