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D E C I S I O N
of 16 March 2005

Case Number: T 0020/04 - 3.3.8

Application Number: 94919120.9

Publication Number: 0699236

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:
Purified mammalian Flt3 ligands and agonists and antagonists thereof

Patentees:
SCHERING CORPORATION, et al

Opponent:
Immunex Corporation

Headword:
Flt3 ligands/SCHERING

Relevant legal provisions:
EPC Art. 54, 88, 123(3)
EPC R. 88

Keyword:
"Main request: extension of the protection (yes)"
"Auxiliary request 1: entitlement to the earliest priority date (yes)"
"Novelty (yes)"

Decisions cited:
G 0002/98, T 0081/87, T 0296/93

Catchword:
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Case Number: T 0020/04 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 16 March 2005

Appellant: (Opponent)
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and

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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 31 October 2003 concerning maintenance of European patent No. 0699236 in amended form.

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
C. Rennie-Smith

Summary of Facts and Submissions

I. The opponent (appellant) lodged an appeal against the interlocutory decision of the opposition division dated 31 October 2003, whereby the European patent No. 0 699 236 was maintained on the basis of the second auxiliary request (claims 1 to 21) filed at the oral proceedings on 16 September 2003. The patent had been granted on European application No. 94 919 120.9 which originated from an international application published as WO 94/26891. Seven priority dates were claimed, the earliest being 19 May 1993, ie the filing date of the US application with serial number 08/065,231 (denoted "P1" hereafter).

II. The patent had been opposed on the grounds in Articles 100(a), (b) and (c) EPC that the invention was neither new nor inventive, that it was not sufficiently disclosed, and that the patent contained added matter.

III. In reply to the statement of grounds of appeal filed by the appellant, the patentees (respondents) filed three new auxiliary requests. Then, the Board issued a communication pursuant to Article 11(1) RPBA containing provisional and non-binding opinions. In reply to the Board's communication, the appellant filed observations and the respondents filed on 16 February 2005 a main and six auxiliary requests (denoted 1 to 6; to replace the auxiliary requests on file). The main request corresponded to the set of claims accepted by the opposition division.

IV. Oral proceedings took place on 16 March 2005 at which the respondents filed a new auxiliary request 1 to replace previous auxiliary request 1.

V. Claim 1 as granted read:

"1. An isolated **mammalian** Fms-like tyrosine kinase 3 (Flt3) ligand which specifically binds to a Flt3 tyrosine kinase receptor, **or a fragment thereof which comprises at least 8 amino acid residues, which Flt3 ligand binds to an antibody produced against a murine Flt3 ligand** characterized by:

(a) an apparent molecular weight of about 30 Kd in SDS-polyacrylamide gel electrophoresis;

(b) presence in a 60-85% saturated pellet during ammonium sulfate precipitation at 4°C;

(c) elution at between 900-750 mM $(NH_4)_2SO_4$ in 20 mM Tris buffer, pH 7.5, during gradient hydrophobic interaction chromatography using a phenyl-5PW column;

(d) elution at between 130-250 mM in a NaCl gradient in 10 mM Tris buffer, pH 7.5, during Mono Q column cation exchange chromatography;

(e) elution at between 440-540 mM in a NaCl gradient in 10 mM citrate buffer, pH 3.0, during Mono S column cation exchange chromatography;

(f) an apparent molecular weight of 70 kD in SEPHACRYL® S200 gel filtration and chromatography; and

(g) elution between 32-35% acetonitrile during reversed phase HPLC using a water acetonitrile gradient in 0.1% TFA and a Poros R/H column."

(emphasis added by the Board to show the differences from claim 10 of auxiliary request 1)

VI. The **main request** consisted of twenty-one claims of which claim 10 read:

"10. An isolated **murine** Fms-like tyrosine kinase 3 (Flt3) ligand which specifically binds to a Flt3 tyrosine kinase receptor **said ligand being** characterized by:

(a) an apparent molecular weight of about 30 Kd in SDS-polyacrylamide gel electrophoresis;

(b) presence in a 60-85% saturated pellet during ammonium sulfate precipitation at 4°C;

(c) elution at between 900-750 mM $(NH_4)_2SO_4$ in 20 mM Tris buffer, pH 7.5, during gradient hydrophobic interaction chromatography using a phenyl-5PW column;

(d) elution at between 130-250 mM in a NaCl gradient in 10 mM Tris buffer, pH 7.5, during Mono Q column cation exchange chromatography;

(e) elution at between 440-540 mM in a NaCl gradient in 10 mM citrate buffer, pH 3.0, during Mono S column cation exchange chromatography;

(f) an apparent molecular weight of 70 kD in SEPHACRYL® S200 gel filtration and chromatography; and

(g) elution between 32-35% acetonitrile during reversed phase HPLC using a water acetonitrile gradient in 0.1% TFA and a Poros R/H column."

(emphasis added by the Board to show the differences from claim 1 as granted)

VII. **Auxiliary request 1** consisted of twelve claims.

Claims 1 to 9 were identical to claims 1 to 9 of the second auxiliary request as accepted by the opposition division.

Claim 1 read:

"1. An isolated Fms-like tyrosine kinase 3 (Flt 3) ligand, comprising the amino acid sequence of SEQ ID No: 19"

The subject-matter of claims 2 to 9 was concerned with a nucleic acid encoding the ligand of claim 1 (cf claims 2 and 3), a recombinant vector comprising such a nucleic acid (cf claim 4), a host cell comprising such a vector (cf claim 5), a method for making a Flt3 ligand comprising culturing such a host cell (cf claims 6 and 7), a pharmaceutical composition comprising a ligand of claim 1 (cf claim 8) as well as a ligand of claim 1 which had been fused to a polypeptide or labeled with a detectable group (cf claim 9).

Claim 10 read:

"10. An isolated murine Fms-like tyrosine kinase 3 (Flt3) ligand which specifically binds to a Flt3 tyrosine kinase receptor **which Flt3 ligand binds to an antibody produced against a murine Flt3 ligand** characterized by:

(a) an apparent molecular weight of about 30 Kd in SDS-polyacrylamide gel electrophoresis;

(b) presence in a 60-85% saturated pellet during ammonium sulfate precipitation at 4°C;

(c) elution at between 900-750 mM $(NH_4)_2SO_4$ in 20 mM Tris buffer, pH 7.5, during gradient hydrophobic interaction chromatography using a phenyl-5PW column;

(d) elution at between 130-250 mM in a NaCl gradient in **20 mM** Tris buffer, pH 7.5, during Mono Q column **anion** exchange chromatography;

(e) elution at between 440-540 mM in a NaCl gradient in 10 mM citrate buffer, pH 3.0, during Mono S column cation exchange chromatography;

(f) an apparent molecular weight of 70 kD in SEPHACRYL® S200 gel filtration chromatography; and

(g) elution between 32-35% acetonitrile during reversed phase HPLC using a water acetonitrile gradient in 0.1% TFA and a Poros R/H column."

(emphasis added by the Board to show the differences from claim 10 of the main request)

Claim 11 was directed to an antibody or binding fragment thereof which specifically bound to a ligand of claim 10. Claim 12 was dependent on claim 11 and directed to a preferred embodiment thereof.

VIII. The following document is referred to in the present decision:

(D1) EP-A-0 627 487 (filed on 19 May 1994, published on 7 December 1994 and claiming six priority dates the earliest being 24 May 1993)

IX. The submissions made by the appellant (opponent), insofar as they are relevant to the present decision, may be summarised as follows:

Main request (claim 10) - requirements of Article 123(3) EPC

In the patent as granted, claim 1 defined the invention in terms which necessitated the Flt3 ligand to bind to an antibody raised against a murine Flt3 ligand having characteristics (a) to (g). This latter feature was now omitted with the result that the murine Flt3 sequence now claimed in claim 10 could include a broader range of variant sequences because the only limitation was that the murine sequence bound the Flt3 receptor.

Auxiliary request 1 (claim 10) - requirements of Articles 54 and 88 EPC

The earliest priority document (P1) did not provide a disclosure sufficient to enable the skilled person to successfully isolate a biologically active murine Flt3-ligand. The isolation method described on page 55 of (P1), under the subtitle "Purification of the Flt3 ligand" was not enabling. One reason therefor was that the T4A cell line, which among multiple cell lines tested was the "one" cell line found to express the Flt3 ligand in its supernatant, had not been made available at the filing date of (P1) by way of a deposit with a recognised depositary institution. Another reason was that (P1) did not provide any demonstration that the reduced and denatured murine Flt3 ligand isolated on the SDS-PAGE gel was capable of binding a Flt3 receptor.

As the earliest priority date, ie the filing date of (P1), could not be validly claimed, the subject-matter of claim 10 was not new over document (D1) which in contrast was entitled to its earliest priority date.

X. The submissions made by the respondents (patentees), insofar as they are relevant to the present decision, may be summarised as follows:

Main request (claim 10) - requirements of Article 123(3) EPC

Claim 1 as granted defined mammalian Flt3 ligands in terms of their ability to bind an antibody raised against a murine Flt3 ligand characterised by features (a) to (g). Claim 10 of the main request was directed

to an embodiment of claim 1 as granted, namely to a murine Flt3 ligand having characteristics (a) to (g). The scope of claim 10 was therefore narrower than that of claim 1 as granted. The wording of claim 1 as granted, insofar as the Flt3 ligand was defined with reference to its capability of binding to an antibody, had not been retained in order to avoid any unnecessary redundancy. It was manifestly clear to the skilled person that a murine ligand would bind to an antibody prepared against itself. Therefore, this change in the wording did not extend the protection conferred.

Auxiliary request 1 (claim 10) - requirements of Articles 54 and 88 EPC

The availability of the T4A cell line was not necessary for enablement. Other mouse thymic stromal cell lines were known at the earliest priority date. The isolation of the murine Flt3 ligand from its natural environment in priority document (P1) had been disclosed with sufficient details.

XI. The appellant (opponent) requested that the decision under appeal be set aside and the European patent No. 0 699 236 be revoked.

XII. The respondents (patentees) requested that the appeal be dismissed or, in the alternative, that the decision under appeal be set aside and the patent be maintained on the basis of either auxiliary request 1 and the amended description filed during the oral proceedings or one of auxiliary requests 2 to 6 filed on 16 February 2005.

Reasons for the Decision

Main request (claim 10) - requirements of Article 123(3) EPC

1. Claim 10 of the main request has been derived from claim 1 as granted by carrying out the following three amendments: the term "mammalian" has been replaced by the term "murine" with the effect that only a ligand of murine origin is claimed; then, the phrase "or a fragment thereof which comprises at least 8 amino acid residues" has been deleted with the result that ligand fragments are no longer claimed; finally, the phrase "which Flt3 ligand binds to an antibody produced against a murine Flt3 ligand" has been replaced by the phrase "said ligand being" with the double effect that the claimed ligand has to satisfy itself the properties (a) to (g) and is no longer required to bind to an antibody produced against a murine Flt3 ligand characterised by the properties (a) to (g).

2. The first two amendments are of a restrictive nature. It cannot be disputed also that the newly-introduced requirement that the claimed ligand has to satisfy the properties (a) to (g) is of the same nature.

3. In stark contrast thereto, the third amendment, insofar as it implies that the claimed ligand is no longer required to bind to an antibody produced against a murine Flt3 ligand characterised by the properties (a) to (g), has resulted in an extension of the protection conferred. Indeed, whereas a ligand according to claim 1 as granted had necessarily to be capable of binding to a receptor and to an antibody, a ligand as

presently claimed has to bind only to a receptor. As a result, claim 10 encompasses a broader range of ligands, as it covers not only those which are capable of binding to both a receptor and an antibody, but also those which are capable of binding only to the receptor.

4. The respondents argue, in view of the ligand features (a) to (g), that the capability of such a murine ligand to bind to an antibody produced against the same is an inherent property of that ligand, with the consequence that the scope of protection has not been extended. While it can be accepted that a given structurally-defined murine ligand would normally be expected to bind to an antibody prepared against it, it cannot be absolutely excluded that a variant or derivative thereof (see description pages 10 to 12 under the heading "Functional variants" in the patent in suit) would not. The more so if account is taken of the fact that claim 10 at issue broadly defines the murine ligand on the basis of a series of general parameters and process features so that ligands of various structures fall within its scope. The omission of the limiting mandatory feature "binds to an antibody produced against a murine Flt3 ligand characterized by (a) to (g)" which was found in the granted claim offends against Article 123(3) EPC as it indeed extends the scope of protection to embodiments which were previously excluded from the scope of the claims by virtue of the omitted feature.

5. Therefore, the requirements of Article 123(3) EPC are not met by claim 10. Thus, the main request is refused.

Auxiliary request 1

Formal issues (Articles 123(2)(3), 84 and Rule 88 EPC)

6. Auxiliary request 1 differs from the main request in that former claims 11 to 15 and 18 to 21 have been deleted and in that claim 10 has been redrafted. Present claim 10 has the same wording as claim 1 as granted and differs therefrom essentially in that it is restrictively directed to a ligand of **murine** origin and does not encompass any fragment thereof. Furthermore, in said claim 10, property (d) has been corrected under Rule 88 EPC to refer to **20 mM** Tris buffer and an **anion** exchange chromatography, instead of referring to a **10 mM** Tris buffer and a **cation** exchange chromatography.

7. The amendment of property (d) has been made to remove mistakes, the correction of which is obvious in the sense that in view of the text of the description as filed (see page 9, lines 23 and page 58, line 1) nothing else would have been intended than what is offered as the correction. Thus, the correction is accepted under the provisions of Rule 88 EPC and the amendment is allowable.

8. The appellant has no formal objections under Articles 123(2)(3) and 84 EPC against this auxiliary request 1. Nor does the Board have any. Thus, the requirements of both articles are met.

Requirements of Articles 54 and 88 EPC (priority and novelty)

9. Subject to an appropriate adaptation of the description, the appellant does not raise any objection to lack of

novelty against claims 1 to 9 which relate to human Flt3 ligands characterised by a given amino acid sequence. Nor has the Board any such an objection against these claims.

10. Nevertheless, the appellant argues that claim 10 is not entitled to the priority date of 19 May 1993, which is the filing date of the earliest priority document (P1) of the patent in suit, and considers that consequently the claim lacks novelty over document (D1) which is a European patent application belonging to the state of the art according to Article 54(3) EPC and is entitled to its earliest priority date of 24 May 1993.

11. In view of decision G 2/98 (OJ EPO 2001, 413, Order) which explains the meaning of the requirement for claiming priority of "the same invention", referred to in Article 87(1) EPC, the relevant question at issue in the present case is whether the skilled person can derive the "same" subject-matter of claim 10 directly and unambiguously, using common general knowledge, from the previous application (P1) as a whole.

12. On pages 51 and 52 of (P1) a preparation of murine Flt3 ligand is described which has the biological activity of specifically binding to a Flt3 tyrosine kinase receptor and has the properties (a) to (g) (in this last respect, see also page 9, Table 2). On pages 22 to 25 antibodies which can be raised to "the various Flt3-ligands" (see page 22, line 5), ie including any of the ligands referred to throughout the description such as the afore-mentioned murine Flt3 ligand, are described. The Board regards this technical information as sufficient to enable the skilled person to derive

therefrom directly and unambiguously that in (P1) a murine Flt3 ligand is described which, as referred to in claim 10, specifically binds to a Flt3 tyrosine kinase receptor and also binds to an antibody produced against a murine Flt3 ligand characterised by the properties (a) to (g). The source of the Flt3 ligand, its assay and its biochemical characterisation are reported in the same way as in the European patent specification. Thus, the two documents relate to the "same" subject-matter.

13. The appellant argues that the priority document should provide an enabling disclosure of the invention of claim 10 for which the priority is claimed. The Board agrees that the priority document should be enabling in the sense that it should concern the "same" subject-matter and that there should be no missing technical elements (cf eg T 81/87 OJ EPO 1990, 250 and T 296/93 OJ EPO 1995, 627). As shown above, this is the case here as the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole.

14. Therefore, claim 10 is entitled to the priority date of 19 May 1993 which precedes the earliest priority date of document (D1), and, thus, is novel over that document. The same conclusion applies *de facto* to the subject-matter of claims 11 and 12 as they are directed to antibodies, or fragments thereof, which specifically bind to a ligand of claim 10.

15. Document (D1) is the only document cited by the appellant for the assessment of novelty. As none of the

other cited prior art documents are relevant in this respect, it is concluded that auxiliary request 1 as a whole meets the requirements of Article 54 EPC.

Conclusion

16. As inventive step has not been challenged in the present appeal proceedings, auxiliary request 1 is considered to meet the requirements of the EPC and, therefore, can form a basis for the maintenance of the patent in an amended form.

Adaptation of the description

17. The respondents have proposed amendments to the description pages 3 to 31 which have not been objected to by the appellant. The Board considers that those amendments result in an appropriate adaptation of the description to the claims of auxiliary request 1 and are in compliance with 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 first instance with the order to maintain the patent on the basis of the claims of auxiliary request 1 and the amended pages 3 to 31 of the description filed during the oral proceedings and pages 32 to 50 of the description as granted.

The Registrar: The Chairman:

A. Wolinski L. Galligani