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**Datasheet for the decision
of 27 November 2017**

Case Number: T 0760/12 - 3.3.01
Application Number: 04754499.4
Publication Number: 1636593
IPC: G01N33/74, G01N33/68, C07K7/08,
A61K38/00
Language of the proceedings: EN

Title of invention:

MODULATING THE INTERACTION BETWEEN HGF BETA CHAIN AND C-MET

Patent Proprietor:

Genentech, Inc.

Opponents:

GLAXO GROUP LIMITED
Millennium Pharmaceuticals, Inc.
Galaxy Biotech, LLC

Headword:

HGF/Met modulation/GENENTECH

Relevant legal provisions:

EPC Art. 83
RPBA Art. 15(3)

Keyword:

Oral proceedings - held in absence of appellant
Sufficiency of disclosure - (no)

Decisions cited:

G 0004/92, G 0001/03, T 0609/02, T 0877/03, T 0431/96,
T 1466/05

Catchword:



Beschwerdekammern

Boards of Appeal

Chambres de recours

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Case Number: T 0760/12 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 27 November 2017

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Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted on
26 January 2012 concerning maintenance of
European patent No. 1636593 in amended form**

Composition of the Board:

Chairman A. Lindner
Members: T. Sommerfeld
 P. de Heij

Summary of Facts and Submissions

- I. European patent No. 1636593, based on European patent application No. 04754499.4, which was filed as an international patent application published as WO 2005/001486, was granted with 38 claims.
- II. Three oppositions were filed against the granted patent, all opponents requesting revocation of the patent in its entirety on the grounds of lack of novelty and inventive step (Articles 54(2) and 56 EPC and Article 100(a) EPC), lack of sufficiency of disclosure (Article 100(b) EPC) and added subject-matter (Article 100(c) EPC); additionally, opponent 2 invoked exclusion from patentability as a further ground for opposition (Articles 52 and 53 EPC and Article 100(a) EPC).
- III. In an interlocutory decision announced at oral proceedings, the opposition division decided that the patent was to be maintained in amended form on the basis of the second auxiliary request filed during oral proceedings (Articles 101(3)(a) and 106(2) EPC).
- IV. The patent proprietor and all opponents appealed against that decision.
- V. With its statement of grounds of appeal, the appellant-patent proprietor requested that the decision of the opposition division be set aside and that a patent be maintained on the basis of the main request or, alternatively, on the basis of any of auxiliary requests 1 to 5, all filed with the grounds of appeal.

VI. The appellant-opponents requested that the decision under appeal be set aside and that the patent be revoked.

VII. Replies to the grounds of appeal were submitted by the appellant-patent proprietor, appellant-opponent 2 and appellant-opponent 3. With its reply, dated 19 November 2012, the appellant-patent proprietor submitted a new main request and auxiliary requests 1 to 11.

Claim 6 of the **main request** reads as follows:

"6. Use of a substance that inhibits specific binding of HGF β chain to c-met in the preparation of a medicament for treating a pathological condition associated with activation of c-met in a subject, wherein the substance is:

(a) a peptide comprising an amino acid sequence having at least 60% sequence identity with the sequence VDWVCFRDLGCDWEL;

(b) a monoclonal antibody or a fragment thereof which specifically binds to said activated HGF β chain; or

(c) a combination thereof,

wherein the substance binds to activated HGF β chain and inhibits specific binding of said activated HGF β chain to c-met, and

wherein the pathological condition is a tumor or angiogenesis-related disorder."

Claim 7 is directed to the same subject-matter, but is in the form of a purpose-restricted product claim.

Claims identical to claims 6 and 7 are present in **auxiliary request 1** (as claims 3 and 4, respectively)

and in **auxiliary requests 2, 3, 4, 5 and 6** (as claims 6 and 7, respectively).

In **auxiliary request 7**, claims 3 and 4 (corresponding to claims 6 and 7 of the main request) are limited to "tumor" as pathological condition.

Auxiliary request 8 is based on auxiliary request 7, with further amendments in claims 3 and 4 as follows:
"...wherein the substance binds to activated HGF β chain and ~~inhibits~~ is capable of inhibiting specific binding to c-met of ~~said~~ activated HGF β chain ~~to c-met~~ in the absence of any HGF α chain,..."

Auxiliary request 9 is based on auxiliary request 8, with further amendments in claims 3 and 4 as follows:
"...wherein said HGF β chain contains a C604S mutation,..."

Auxiliary request 10 is based on auxiliary request 7, with amendments in claims 3 and 4 as follows:
"...wherein the substance binds to activated HGF β chain and ~~inhibits~~ is capable of inhibiting specific direct binding of said activated HGF β chain to c-met,..."

Auxiliary request 11 is based on auxiliary request 10, with further amendments in claims 3 and 4 as follows:
"...wherein said HGF β chain contains a C604S mutation,..."

VIII. Summons to oral proceedings before the board were issued, scheduling oral proceedings for 27 and 28 November 2017.

- IX. With letters dated 17 August 2017, 25 July 2017 and 17 May 2017, respectively, the appellants opponent 1, opponent 2 and opponent 3 informed the board that they would not be attending oral proceedings.
- X. The appellant-patent proprietor first sent a letter requesting a preliminary opinion of the board and the rescheduling of oral proceedings for the second day; with a further letter, dated 21 November 2017, he announced that he would not attend oral proceedings either.
- XI. Oral proceedings before the board took place on 27 November 2017 as originally scheduled. As announced in writing, none of the parties was present. At the end of the oral proceedings, the chairman announced the board's decision.
- XII. The documents cited during the proceedings before the opposition division and the board of appeal include the following:
- D5 Cao et al. 2001, PNAS 98(13), 7443-7448
 - D6 Product information sheet for mAb 24612.111 from Sigma-Aldrich
 - D7 Yamamoto et al. 1997, Jpn. J. Cancer Res. 88, 564-577
 - D9 Email from Abcam concerning HGF antibodies
 - D10 Extract from Abcam catalogue (website print-out)
 - D11 Burr et al. 1998, J. Pathol. 185, 298-302
 - D30 US 2008/0108565 (cover page and pages 25 to 27)
 - D35 Declaration of Dr K. Jin Kim
 - D36 R&D website print-out for MAB294
 - D41 Kim et al. 2006, Clin. Cancer Res. 12, 1292-1298

XIII. The submissions of the appellant-opponents (opponents 2 and 3) which are relevant to the present decision may be summarised as follows:

The patent did not describe the production of a single antibody having the claimed features, and it would be an undue burden to find antibodies suitable for the medical uses of claims 6 and 7. This was also apparent from D5 which, using an immunisation approach according to the patent, i.e. with an immunogen including activated HGF β chain (paragraph [0131]), isolated hundreds of HGF monoclonal antibodies, but none that could neutralise HGF as a single agent. The skilled person would thus have to embark on a research programme (T 1466/05) without any teaching in the application on how to achieve the desired specificity. Moreover, the description failed to show that the class of peptides or the class of antibodies mentioned in claims 6 and 7 had any effect which rendered the claimed medical use credible. The patent contained no examples falling within the scope of the claims and no data of relevance to the claimed medical uses.

XIV. The submissions of the appellant-patent proprietor which are relevant to the present decision may be summarised as follows:

The patent experimentally demonstrated the underlying properties of an HGF/c-met antagonist of the invention, namely the ability to bind HGF β chain and block binding of HGF β to c-met (page 4, lines 2 to 12 and 18 to 24; page 45, lines 6 to 7; examples on pages 52 to 58); therapeutic uses were made credible or plausible. Examples of suitable well-known types of antagonist molecules such as antibodies and peptides in addition to HGF mutants were given, as well as ways of producing

such molecules and testing them for the required properties using techniques known in the art (pages 45 to 51 and examples on pages 52 to 53). It was no undue burden to screen for antagonist antibodies where the target protein and binding interaction to antagonise had been provided along with suitable screening tests (T 877/03). The patent described a suitable antigen for preparing antibodies, namely one which included activated HGF β chain (paragraph [0131]); the activated HGF β chain was known and was also defined in the patent, and there was no requirement to use particular residues of HGF β chain to generate an antibody according to the invention. The opponents did not show evidence of unsuccessful attempts to produce and use antibodies according to the technical teaching of the patent. A specific failure in the prior art to produce an anti-HGF neutralising antibody had no bearing on the sufficiency of the patent disclosure, in particular in view of the fact that other such antibodies had been produced (D11, D36), and further neutralising antibodies against human HGF were known after the patent's disclosure (D30, D41).

The key disclosure of the patent was thus the demonstration of a new binding interaction between HGF β chain and c-met, blocking of which inhibited c-met biological activity. From the technical teaching in the patent, with his knowledge of the art, the skilled person would understand: (i) that a substance or molecule having the properties of binding to HGF β chain and inhibiting the binding of HGF β chain to c-met would have the desired technical effect of inhibiting c-met activity; (ii) how to produce and test for such substances or molecules; and (iii) how to use such substances or molecules in therapeutic applications relating to inhibition of c-met activity.

- XV. The appellant-patent proprietor requested in writing:
- that the decision under appeal be set aside and the patent maintained on the basis of the main request or one of auxiliary requests 1 to 11, filed with the letter dated 19 November 2012;
 - that the case be remitted to the opposition division for amendment of the description if the board were to find allowable any claim request other than auxiliary request 6 (the claims as maintained by the opposition division);
 - that, if the board were not to remit the case for amendment of the description, the patent be maintained on the basis of the amended description as filed with the letter dated 21 November 2017.

The appellant-opponents all requested in writing that the opposition division's decision be set aside and that the patent be revoked.

Reasons for the Decision

1. The appeals are admissible.
2. The oral proceedings before the board took place in the absence of the appellants, who had all been duly summoned but decided not to attend.

The present decision is based on facts and evidence put forward during the written proceedings and on which the appellants have had an opportunity to comment. Therefore the conditions set forth in Enlarged Board of Appeal opinion G 4/92, OJ EPO 1994, 149, are met.

Moreover, as stipulated by Article 15(3) RPBA the board is not obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral proceedings of any party duly summoned who may then be treated as relying only on its written case.

3. Main request

Claims 6 and 7: sufficiency of disclosure

- 3.1 Article 83 EPC stipulates that the application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. For the assessment of sufficiency of disclosure, the teaching of the application as a whole is relevant, taking into account the common general knowledge of the skilled person. At least one way of enabling the person skilled in the art to carry out the invention has to be disclosed, but this is sufficient only if it allows the invention to be performed in the whole range claimed.
- 3.2 Claims 6 and 7 are second medical use claims, either in the "Swiss-type" format (claim 6) or in the purpose-restricted product claim format (claim 7). The therapeutic compound is defined functionally as being a "substance that inhibits specific binding of HGF β chain to c-met" and that "binds to activated HGF β chain and inhibits specific binding of said activated HGF β chain to c-met"; it is further defined as being either "(a) a peptide comprising an amino acid sequence having at least 60% sequence identity with the sequence VDWVCFRDLGCDWEL" or "(b) a monoclonal antibody or a fragment thereof which specifically binds to said activated HGF β chain" or "(c) a combination thereof".

The therapeutic indication is "a pathological condition associated with activation of c-met in a subject", further defined as being "a tumor or angiogenesis-related disorder".

3.3 These being second medical use claims, the technical effect, which is the therapeutic effect, is expressed in the claim. When the technical effect is expressed in the claim, the issue of whether this effect is indeed achieved over the whole scope of the claim is a question of sufficiency of disclosure (G 1/03, OJ 2004, 413, Reasons 2.5.2). Hence, under Article 83 EPC, unless this is already known to the skilled person at the priority date, the application must disclose the suitability of the product to be manufactured for the claimed therapeutic application (T 609/02, Reasons 9). Thus, in order to establish whether the requirement of sufficiency of disclosure is met, it has to be assessed whether the application discloses the potential suitability of the substance as defined in the claim to exert a therapeutic effect on a tumour or angiogenesis-related disorder which is associated with activation of c-met.

3.4 One of the alternative substances to be used as a medicament in claims 6 and 7 is "a monoclonal antibody or a fragment thereof which specifically binds to said activated HGF β chain", wherein said substance also "inhibits specific binding of said activated HGF β chain to c-met". The patent however does not disclose any antibody with the claimed specificity and function. Hence, to assess sufficiency of disclosure in relation to this alternative it has to be decided whether the provision of such an antibody and its potential suitability to exert the claimed therapeutic effect are both enabled in the patent, account being taken of the

common general knowledge at the effective date of the patent.

3.5 As argued by the appellant-patent proprietor, the production of monoclonal antibodies against a known target protein may require perseverance, but *a priori* involves only widely known routine technical steps. Since the functional features characterising the antibody, namely the binding to activated HGF β chain and the inhibition of the binding of said activated HGF β chain to c-met, were readily testable in an assay, the skilled person seeking to provide antibodies as defined in the claim would simply have to use the activated HGF β chain as immunogen, test the obtained antibodies in an assay and use routine procedures to produce hybridomas secreting monoclonal antibodies. Hence, although possibly involving some tedious and time-consuming work, the provision of antibodies with the functional characteristics as defined in the claim would not require an undue burden (T 877/03, Reasons 23, also referring to T 431/96, Reasons 6).

3.6 It thus next has to be examined whether it is made plausible in the patent that monoclonal antibodies as defined in the claim are potentially suitable for exerting a therapeutic effect on tumour and angiogenesis-related disorders mediated by c-met activation.

3.7 It is *a priori* plausible that interference with the HGF/Met signalling pathway may result in a therapeutic effect in those pathological conditions where the activation of this pathway has been shown to play a role. It was known from the prior art that the HGF/Met signalling pathway was "implicated in invasive tumor growth and metastasis and as such represents an

interesting therapeutic target" (patent, paragraph [0002]), and it had also been disclosed that the β subunit of HGF, although not binding Met alone, was "crucial for the optimum activation of Met receptor induced by HGF/SF" (D5, page 7446, right column, lines 10 to 13; HGF/SF is another designation for HGF). Hence it would be expected that blocking the β subunit of HGF (e.g. by antibodies) would also interfere with the HGF/Met signalling pathway. The patent not only confirms the role of the HGF β chain in Met activation but also further elucidates the underlying mechanism, by showing that the activated β chain directly binds to the Met receptor (paragraphs [0107] and [0178]). Blocking of HGF or of its β subunit could of course plausibly be achieved by using antibodies directed thereto, and in fact D5 shows that neutralising monoclonal antibodies against HGF displayed anti-tumour activity in animal models.

- 3.8 However, it was also known from D5 that, while a rabbit *polyclonal* antibody had been shown to neutralise HGF, there was no single *monoclonal* antibody (mAb) which was able to significantly inhibit all of the biological activities of HGF (D5, page 7443, right column, second full paragraph); in fact, D5 (*supra*) teaches that "a minimum of three mAbs used in combination" were required to inhibit the HGF/Met pathway *in vitro* and to inhibit tumour growth *in vivo*. In the Discussion section, D5 concludes that "only certain mAbs that bind to specific epitopes of HGF/SF can inhibit biological activity, and that blocking three or more of the epitopes is required to inhibit HGF/SF activity" (page 7447, left column, lines 5 to 8); "multiple ligand binding surfaces must be blocked to completely inhibit receptor activation" (page 7447, left column, lines 29 and 30). In fact, according to D5, "among the hundreds

of mAbs derived from fusions from animals with HGF/SF-neutralizing serum, no single mAb displayed neutralizing activity" (page 7447, left column, lines 15 to 17).

3.9 As argued by the appellant-patent proprietor, the patent's contribution to the teachings of the prior art is that it shows that there is direct binding of the HGF β chain to the Met receptor. However, the board considers that this new teaching does not overcome the difficulties mentioned in D5 as regards the provision of a single monoclonal antibody against HGF which is capable by itself of completely inhibiting c-met activation and thus of exerting a therapeutic effect on its own. Since D5's mAbs were raised against the native HGF protein (page 7443, right column, last paragraph), the skilled person would assume that, among the "hundreds of mAbs derived from fusions from animals with HGF/SF-neutralizing serum" which were obtained in D5, some would be directed to epitopes in the β chain. However these antibodies did not have neutralising activity on their own. The discovery that there was direct binding between the β chain and c-met did not *per se* provide any teaching on how to overcome the above-mentioned difficulties, since the prior art suggested that inhibiting HGF/SF biological activity required blocking at least three epitopes.

3.10 Hence, the patent essentially teaches to antagonise the β chain in order to interfere with c-met activation, but this teaching was already derivable from the prior art, including D5, which had disclosed that the β subunit of HGF was "crucial for the optimum activation of Met receptor induced by HGF/SF" (D5, page 7446, right column, lines 11 to 13). However, the patent does not demonstrate that any monoclonal antibody with the

functional characteristics as defined in the claim (binding to activated HGF β chain and inhibiting the binding of said activated HGF β chain to c-met) would inhibit c-met activation. The skilled person would thus have to embark on a research programme without any teaching in the application on how to achieve the desired effect of inhibiting c-met activation with a single monoclonal antibody (T 1466/05, Reasons 16). Hence the board concludes that it is not sufficiently disclosed in the patent that a single monoclonal antibody as defined in the claim potentially exerts the therapeutic effect as claimed.

3.11 The appellant-patent proprietor essentially argued that the failure in D5 to produce an anti-HGF neutralising antibody had no bearing on sufficiency of disclosure, because it had already been overcome in the prior art, as evidenced by D10, D11 and D35/D36; moreover, further neutralising antibodies against human HGF had been provided after the patent's disclosure (D30, D41).

3.12 The board disagrees with these arguments. D10 is an extract from Abcam's online catalogue listing available HGF antibodies in 2009; among them, ab10678, described as a mouse monoclonal antibody against human HGF, corresponds to clone 24612.111, which was already available before the priority date, as evidenced by D7 (legend to Figure 3 on page 568). According to D6 (the Sigma-Aldrich product information sheet for this antibody), mAb 24612.111 "may be used in neutralization of bioactivity and immunoblotting" (first page, left column, second paragraph); also, D7 shows that there is "neutralization of the HGF effect on cell motility by anti-HGF monoclonal antibody 24612.111" (D7 supra; Figure 3B). There is however no evidence on file that this antibody actually "inhibits specific binding of

HGF β chain to c-met", as required by the claim. D9, an email response from Abcam to an enquiry about HGF antibodies, simply states that ab10678 "recognizes both the beta and alpha chain".

- 3.13 As to D11, it uses a HGF-neutralising antibody raised against an immunogen from the α chain and not from the β chain (page 299, left column, lines 5 to 25); moreover, it only shows an effect in liver cell proliferation, in the context of liver injury, and not in the pathological conditions as claimed, namely tumour or angiogenesis-related disorder.
- 3.14 On the other hand, D35 discloses that an antibody derived from the MAB294 of D36 does indeed bind to the activated β chain and inhibit its binding to c-met (D35, Figures), but does not show that it also inhibits activation of c-met, let alone in the context of tumour or angiogenesis-related disorders. Again, in view of D5's teaching that "multiple ligand binding surfaces must be blocked to completely inhibit receptor activation" (page 7447, left column, lines 29 and 30), it would not necessarily be expected that the MAB294 would be suitable for completely inhibiting activation of c-met.
- 3.15 As to D30 and D41, these are post-published documents and hence not available to the skilled person at the effective date of the patent. Moreover, they do not establish that the teachings of the patent enabled the production of antibodies with the functional characteristics as claimed, in particular the claimed therapeutic effect, because the antibodies disclosed therein are not directed against the activated β chain.

3.16 The board thus comes to the conclusion that the subject-matter of claims 6 and 7 is not sufficiently disclosed. Hence, at least for this reason, the main request is not allowable for lack of compliance with Article 83 EPC.

4. Auxiliary requests 1 to 11

Article 83 EPC

4.1 Auxiliary requests 1 to 6 all contain claims which are identical to claims 6 and 7 of the main request (see section VII). Hence, for the same reasons as discussed above in relation to the main request, these requests also contravene Article 83 EPC.

4.2 The same also applies to auxiliary request 7, wherein claims 3 and 4 differ from claims 6 and 7, respectively, of the main request only in that the pathological condition is restricted to a tumour. Auxiliary request 7 hence also contravenes Article 83 EPC.

4.3 In auxiliary requests 8 to 11, the substance is further characterised by functional parameters such as that it is capable of inhibiting specific binding to c-met of activated HGF β chain *in the absence of any HGF α chain* (auxiliary requests 8 and 9) or that it is capable of inhibiting specific *direct* binding to c-met of activated HGF β chain (auxiliary requests 10 and 11). Auxiliary requests 9 and 11 moreover add the feature that the HGF β chain contains a C604S mutation. The board fails to see how these amendments would overcome the deficiencies of the main request as regards sufficiency of disclosure, and the appellant-patent

proprietor has not submitted any arguments in that context.

- 4.4 The board thus concludes that none of auxiliary requests 1 to 11 is allowable for lack of compliance with Article 83 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:



M. Schalow

A. Lindner

Decision electronically authenticated