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Datasheet for the decision of 7 July 2022

Case Number: T 0813/19 - 3.3.04

Application Number: 12154124.7

Publication Number: 2559705

IPC: C07K16/22, A61K39/395, C12N15/13, A61P5/06, A61P9/10, A61P35/00, A61P37/00, A61P43/00

Language of the proceedings: EN

Title of invention:
Anti-activin A antibodies and uses thereof

Patent Proprietor:
Amgen Inc.

Opponent:
Regeneron Pharmaceuticals, Inc.

Headword:
Anti-activin A antibodies/AMGEN

Relevant legal provisions:
EPC Art. 56, 111(1), 113(1)
EPC R. 106

Keyword:
Inventive step - (no)
Obligation to raise objections - objection dismissed

Decisions cited:
R 0001/08, R 0013/09

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Case Number: T 0813/19 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 7 July 2022

Appellant: (Opponent)	Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown NY 10591 (US)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Respondent: (Patent Proprietor)	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799 (US)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 10 January 2019 rejecting the opposition filed against European patent No. 2559705 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chair	R. Morawetz
Members:	A. Chakravarty
	R. Romandini

Summary of Facts and Submissions

I. European patent No. 2 559 705, entitled "*Anti-activin A antibodies and uses thereof*" was opposed by a single opponent under Article 100(a) EPC in combination with Articles 54 and 56 EPC and Articles 100(b) and (c) EPC.

II. The opposition division rejected the opposition. The opponent (appellant) filed an appeal against this decision. The patent proprietor is respondent to this appeal.

III. In its statement of grounds of appeal, the appellant raised objections under Articles 100(a) and (b) EPC of lack of novelty, lack of inventive step and lack of sufficient disclosure against the patent as granted. It also objected under Article 123(2) EPC, Article 56 EPC and Article 83 EPC to auxiliary requests 1 and 2 as pending before the opposition division.

IV. The respondent replied to the statement of grounds of appeal. With this reply, it requested, as its main request, the maintenance of the patent as granted and re-submitted the sets of claims of auxiliary requests 1 and 2, as on file in the proceedings before the opposition division.

V. Claim 1 as granted reads:

"1. An isolated antibody, or an antigen binding fragment thereof, that specifically binds to a cysteine knot region of human activin A, said region spanning amino acids C11-S33 and amino acids C81-E111 of the sequence set forth in SEQ ID NO:225, and inhibits binding of human activin A to human activin A

receptor".

Claim 1 of auxiliary request 1 reads:

"1. An isolated antibody, or an antigen binding fragment thereof, that specifically binds to a cysteine knot region of human activin A, said region spanning amino acids C11-S33 and amino acids C81-E111 of the sequence set forth in SEQ ID NO:225, and inhibits binding of human activin A to human activin A receptor, for use in therapy".

Claim 1 of auxiliary request 2 reads:

"1. An isolated antibody, or an antigen binding fragment thereof, that specifically binds to a cysteine knot region of human activin A, said region spanning amino acids C11-S33 and amino acids C81-E111 of the sequence set forth in SEQ ID NO:225, and inhibits binding of human activin A to human activin A receptor, for use in a method of treating cachexia".

VI. The board issued a summons to oral proceedings as requested by the parties and subsequently issued a communication under Article 15(1) RPBA setting out its preliminary opinion on some of the issues in the appeal case. It informed the parties that it was in preliminary agreement with the appellant that the subject-matter of claim 1 of the main request was obvious. With respect to the sets of claims of auxiliary requests 1 and 2, the board observed that the appellant had raised objections under Articles 123(2), 56 and 83 EPC and stated that the parties would be heard on whether or not these claim requests met the requirements of the EPC at the oral proceedings, as

necessary.

VII. With letter dated 7 June 2022, the respondent confirmed that it requested remittal of the case to the opposition division if its main request, that the appeal be dismissed, was not found allowable and any discussion of the auxiliary requests was needed.

VIII. Oral proceedings took place as scheduled. At the oral proceedings, the board heard the parties' submissions on whether to remit the case to the opposition division for further prosecution. It then heard the parties' submissions on inventive step of the subject-matter of auxiliary request 2. After this, the board informed the parties of its opinion on the inventive step of the subject-matter of auxiliary request 2 and also informed them that it had decided not to remit the case to the opposition division for further prosecution. Subsequently, the respondent raised an objection under Rule 106 EPC to the effect that its right to be heard under Article 113 EPC had not been respected. The objection was submitted to the board by email. The board dismissed the objection. At the end of oral proceedings the chair announced the board's decision.

IX. The following documents are referred to in this decision:

D2: Vitt U.A. *et al.*, Molecular Endocrinology, 1 May 2001, 15(5), 681-694.

D4: Harrison C.A. *et al.*, TRENDS in Endocrinology and Metabolism, 27 January 2005, 16(2), 73 to 78.

X. The appellant's arguments relevant to the decision are summarised as follows.

Remittal (Article 111(1) EPC)

The case should not be remitted to the opposition division for further prosecution. No special reasons for remitting the case to the opposition division, in the sense of Article 11 RPBA existed. The same document, document D4 that was relevant for inventive step of claim 1 of the main request, was relevant for inventive step of claim 1 of auxiliary requests 1 and 2. The respondent had already relied on therapeutic properties of the claimed antibodies in its argumentation on inventive step for claim 1 of the main request and had provided little further argumentation in writing as to why claim 1 of auxiliary requests 1 and 2 should be inventive if claim 1 of the main request was not.

Main request - claim 1
Claim construction

The claimed antibody bound to a cysteine knot region of human activin A. This region spanned amino acids C11-S33 and amino acids C81-E111. Figure 1 of document D2 [reproduced below] showed that the cysteine knot region of activin A included three disulphide bonds formed from six cysteine residues and ran from amino acid position 11 (first cysteine) to amino acid position 115 (last cysteine), covering over 90% of the activin molecule. Domains formed as a result of the cysteine knot included two "fingers" or "loop regions" and a single "heel".

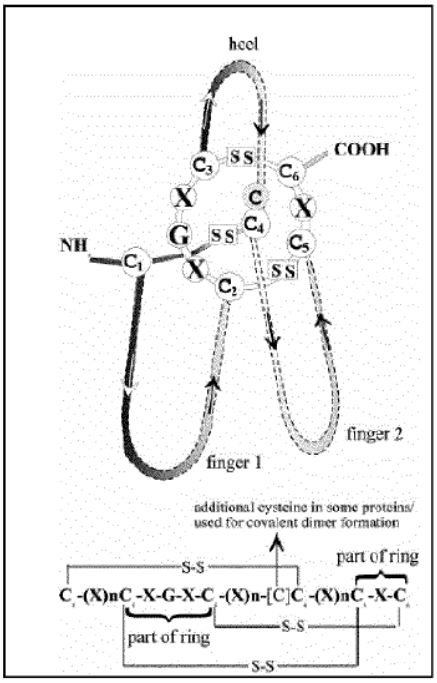

Figure 1 of document D2

The residues recited in claim 1 all fell within the two "fingers" or loop regions, as could be seen from Figure 2 of document D4. The regions recited in the claim only included three cysteine residues and therefore did not include all of the cysteine residues involved in the formation of the cysteine knot.

Therefore, antibodies binding to the cysteine knot region included those binding to residues outside the regions specified in claim 1 and also those binding between the regions specified in claim 1. Thus, claim 1 should properly be construed as requiring that the claimed antibody binds anywhere in the cysteine knot region of the human activin A protein. There was no need to bind to all, or even any, of the specified residues, nor to bind to both of the specified regions. Moreover, the claimed antibody did not need to bind a conformational epitope only present when both recited regions were present in their native form or

conformation. Furthermore, not all antibodies falling within the scope of claim 1 would inhibit binding of activin A to its receptor and would therefore not all be useful therapeutically, e.g. for treating cachexia. In addition, as the claim did not impose a minimum threshold level of inhibition; inhibiting the binding of activin A to its receptor by even a small amount, would satisfy the claim limitation, but most likely not result in any therapeutic benefit.

Inventive step (Article 56 EPC)

The closest prior art

The closest prior art was represented by document D4 which was a review of antagonists of activin signalling and disclosed anti-activin A antibodies for blocking binding of activin A to its receptors (see passage spanning pages 76 and 77).

The technical problem

The objective technical problem formulated by the opposition division in the decision under appeal, "the provision of an alternative neutralising anti-activin A antibody", was correct, although it could also have been framed as the provision of an alternative anti-activin A antibody for inhibiting binding of activin A to is receptor.

In the decision under appeal, the opposition division had erred in taking into account the alleged therapeutic effect of the A1 antibody, as demonstrated in the patent, since they had indicated that the technical effect was merely the ability to inhibit binding of activin A to its receptor. If the opposition

division had thought that the technical effect was in fact a therapeutic effect of the claimed antibody (e.g. on cachexia), they should have framed the objective technical problem differently.

Obviousness

The claimed antibody was obvious in view of Figure 2 in document D4. This Figure showed that all the residues that were important for binding of human activin A to its type II receptors were present in the two regions recited in claim 1. Therefore, it would have been obvious to a person skilled in the art at the priority date that an antibody that binds to these residues of activin A, which were known to be important for interaction with its receptor, would inhibit binding of human activin A to the human activin A receptor. Moreover, claim 1 when construed correctly, did not require the antibody to bind to all or even to any of the residues recited in the claim. In view of the teaching of document D4 it would have been obvious to a person skilled in the art to generate an antibody that binds to the cysteine knot region of human activin A.

In addition, it would have been obvious to a person skilled in the art to use an anti-activin A antibody that binds the cysteine knot region of human activin A therapeutically to treat cachexia, as document D4 disclosed that an increase in activin signalling was responsible for cachexia (weight loss) symptoms in mice and identified activin A as an important target for treating cachexia; i.e. document D4 suggested the use of activin A antagonists to treat cachexia and would have motivated the skilled person to use anti-activin A antibodies to treat cachexia. Thus, even if utility in treating cachexia were taken into account in assessing

the inventive step of the claimed antibody, the subject-matter of claim 1 lacked an inventive step.

Auxiliary request 1 - claim 1
Inventive step (Article 56 EPC)

Closest prior art

Document D4 represented the closest prior art for the claimed subject-matter, as explained for the main request.

The technical problem

The technical problem to be solved was the provision of an anti-activin A antibody for use in therapy.

Obviousness

As explained for claim 1 of the main request, it would have been obvious to a person skilled in the art to generate an antibody that binds to the cysteine knot region of human activin A as this region was known to be important for binding to its receptor. Furthermore, it would have been obvious for the skilled person to use such an antibody in therapy, e.g for treating cachexia, because document D4 disclosed that an increase in activin signalling was responsible for cachexia (weight loss) symptoms in mice and identified activin A as an important target for treating cachexia. In other words, document D4 suggested the use of activin A antagonists for treating cachexia and motivated the skilled person to use anti-activin A antibodies for this purpose. On page 77, under the heading 'Cachexia', the Coerver *et al*. reference showed that it was the increase in activin signalling via

ActRII that was responsible for the cachexia symptoms in mice with tumours. Given that all the residues known to be important in activin signalling via ActRII were present in the regions recited in claim 1 (see Figure 2 of D4), it would have been obvious to a person skilled in the art to generate an antibody binding to these regions to treat cachexia.

Auxiliary request 2 - claim 1
Claim construction

The claim was for a specific medical use of the antibody mentioned in claim 1 of the main request, where the specific medical use was treatment of cachexia.

Inventive step (Article 56 EPC)

The closest prior art

Document D4 represented the closest prior art for the claimed subject-matter, as explained for the main request.

The technical problem

The objective technical problem was the provision of an anti-activin A antibody for treating cachexia.

Obviousness

As explained for claim 1 of the main request, it would have been obvious to a person skilled in the art to generate an antibody that binds to the cysteine knot region of human activin A. Furthermore, as explained for claim 1 of auxiliary request 1, it would have been

obvious for the skilled person to use such an antibody to treat cachexia.

XI. The respondent's arguments relevant to the decision are summarised as follows.

Remittal

The case should be remitted to the opposition division if the main request, the dismissal of the appeal, were found not to be allowable and any discussion of the auxiliary requests were needed. As set out in Article 12(2) RPBA, the primary object of the appeal proceedings was to review the decision under appeal in a judicial manner. As the opposition division had only dealt with the claims as granted, consideration by the board of the auxiliary requests would not be in keeping with the judicial nature of the appeal proceedings.

Main request - claim 1
Claim construction

The opposition division's construction of the claim was correct: the claimed antibody had to bind to the native form of the cysteine knot region of human activin A, said region spanning amino acids C11 to S33 and amino acids C81 to E111 of the sequence set forth in SEQ ID No: 225. The antibody had to bind to at least a single residue in both specified regions to meet the claim limitation.

In spite of the "comprising" used in the claim, a construction according to which the antibody did not have to bind any amino acid residues in the recited stretches C11 to S33 and C81 to E111 of the sequence set forth in SEQ ID No: 225 or to include antibodies in

the scope of the claim that bound exclusively outside of these regions was not technically sensible. A skilled reader would not disregard explicitly mentioned regions. The claims had to be interpreted in light of the description and with a mind willing to understand. The opposition division had also correctly noted that inhibition of binding of human activin A to any human activin A receptor was a feature of the claimed antibody.

Inventive step (Article 56 EPC)
The closest prior art

Document D4, taken as closest prior art in the decision under appeal and by the opponent, was a review article concerned with antagonists of activin signalling. It discussed activin's potential involvement in a variety of physiological processes such as cell proliferation and differentiation, immune responses, wound repair and various endocrine activities. The article considered potential biological applications of activin antagonists, focusing on the known endogenous activin antagonists.

The technical problem

The claimed antibody differed from the antagonists described in document D4 in that it specifically bound to the cysteine knot region of human activin A, said region spanning amino acids C11 to S33 and amino acids C18 to E111 of the sequence set forth in SEQ ID NO: 225. The technical effect provided by this difference, was that the antibodies of the invention inhibited binding of human activin A to human activin A receptor and exerted significant biologically-relevant

effects.

Data provided in the patent showed that the antibodies of the invention inhibited binding of human activin A to human activin A receptor and that this led to real improvements in modulating the receptor *in vivo*. Examples 9 to 12 illustrated these surprising biological effects. For example, the body weight data of Example 10 showed that treatment with anti-activin A antibodies A1, A2 and A3 significantly improved survival rates in a mouse xenograft model, with antibodies A1 and A2 also completely preventing body weight loss. These data indicated that the claimed anti-activin A antibodies were effective in neutralising activin A activity *in vivo* (see paragraph [0268] of the patent). In addition to these significant effects on body weight and mass, antibodies A1 and A2 were shown at paragraph [272] of the patent to reduce xenograft tumour formation. The patent showed for the first time that targeting activin A with an antibody that specifically binds to the cysteine knot region defined by amino acids C11-S33 and/or C81-E111 of SEQ ID NO:225 of human activin A was able to inhibit activin A from binding to its receptor, and resulted in surprising biologically relevant effects *in vivo*.

In view of the above, the objective technical problem was the provision of a biologically and therapeutically useful antagonist against activin A.

Obviousness

There was no disclosure in the prior art of antibodies that bound to the region of human Activin A identified in the claim that exhibited the biologically and therapeutically relevant effects mentioned above.

There was no objective reason why a person skilled in the art, starting from document D4 would have selected the specific claimed region for raising an antibody to activin A with the intention of generating a molecule capable of inhibiting binding to an activin A receptor with the expectation of obtaining the surprising biological effects observed in the patent.

Document D4 in general and in Figure 2 of that document in particular suggested a very large number of possible antagonists and target molecules as potentially able to inhibit activin signalling. However, document D4 did not propose the use of antibodies for this purpose, let alone an antibody that had the specific binding properties required by the claim.

The authors of document D4 concluded that certain antagonists of activin A activity could perhaps be suitable therapeutic agents. Follistatin and the small molecule antagonist Met108Ala were proposed at page 77, final paragraph, as "*particularly attractive drug candidates*". Thus, the person skilled in the art would have turned to these rather than to antibodies when faced with the technical problem.

Even if, for the sake of argument, it was accepted that the skilled person would have chosen to investigate antibody antagonists, they would have found no guidance in the art which directed then towards the claimed subject-matter.

Auxiliary request 1 - claim 1

Claim 1 was for the first medical use of the antibody defined in claim 1 of the main request.

Inventive step (Article 56 EPC)

Document D4 was also closest prior art for claim 1 of this request. Contrary to what was alleged by the appellant, document D4 did not suggest anti-activin A antibodies as potential therapeutic agents. This was clear from reading document D4 as a whole: document D4 disclosed that certain antagonists of activin A activity could be suitable therapeutic agents but the promising candidates were follistatin and the small molecule antagonist Met108Ala. There was no suggestion to use anti-activin A antibodies, let alone the specifically claimed antibodies in the treatment of any disorders.

Auxiliary request 2 - claim 1
Claim construction

The antibodies defined in the claim was the same as defined in claim 1 of the main request.

Inventive step (Article 56 EPC)

Closest prior art

Document D4, already discussed for the higher ranking claim requests, could also be taken to represent the closest prior art for this claim, in particular the passage on page 77 relating to cachexia.

The technical problem

The claimed antibody differed from the antagonists described in document D4 in that it specifically bound to the cysteine knot region of human activin A, said region spanning amino acids C11 to S33 and amino acids

C18 to E111 of the sequence set forth in SEQ ID NO: 225. The technical effect provided by this difference, was that the antibodies of the invention inhibited binding of human activin A to human activin A receptor and exerted significant biologically-relevant effects in treating cachexia in particular.

Obviousness

As already set out for claim 1 of auxiliary request 1, the skilled person would have found no suggestion in document D4 that antagonists of activin were potential therapeutic agents for any disorder, let alone for the treatment of cachexia. In its submissions on inventive step, the appellant quoted a short passage from document D4 out of context so that it did not properly reflect the contents of document D4 as a whole. Moreover, its arguments used hindsight knowledge to argue that the claimed invention would have been obvious to the skilled person. The authors of document D4 considered that certain antagonists of activin A activity could be suitable therapeutic agents and the promising candidates were described as follistatin and the small molecule antagonist Met108Ala. There was no motivation for the skilled person to try an antibody-based therapeutic. Instead, this would have been a huge unqualified leap. Document D4 gave the skilled person no reasonable expectation of success that an anti-activin A antibody could serve as a therapeutic agent, let alone an antibody specific to the exact region specified in the claims. There was no objective reason why the skilled person would ignore the clear teaching in document D4 and try a different, untested approach.

Objection under Rule 106 EPC

A fundamental violation of the right to be heard under Article 113(1) EPC had occurred for the following reasons: i) the board had not remitted the case to the opposition division for further prosecution of auxiliary requests 1 and 2 as requested, ii) the board had decided on auxiliary requests 1 and 2 in spite of the lack of a first instance decision on these requests and iii) the board had decided on auxiliary requests 1 and 2 in spite of the lack of a preliminary opinion of the board on auxiliary requests 1 and 2.

The lack of a preliminary opinion on the auxiliary requests meant that the respondent was not able to properly prepare its case. All of the above led to an objection under Rule 106 EPC being raised.

The objection was submitted in writing and read:

"*We have not discussed the Opposition Division's decision at today's hearing, which is the fundamental purpose of the Appeal. The oral proceedings comprised a discussion of our request for remittal to the OD to consider AR1 and AR2, and a discussion of Article 56 EPC for AR2. The discussion of Article 56 EPC contained a discussion of claim interpretation. The Chair then announced that the claims of AR2 do not comply with Article 56 EPC, and that this also applies to AR1 and the MR. Our request for remittal was denied.*

When discussing Art 56 EPC for claim 1 of AR2, the Board instructed us to limit our submissions to those that had been made in writing.

AR1 and AR2 were not discussed at first instance, where the OD maintained the patent as granted.

We reserve the right to file a petition for review".

XII. The requests of the appellant, relevant to the decision, were that the decision under appeal be set aside and that the patent be revoked in its entirety. Furthermore, it requested that the case not be remitted to the opposition division for further prosecution in the case the main request was found not to be allowable.

XIII. The requests of the respondent, relevant to the decision, were that
- the appeal be dismissed, and the patent be maintained as granted (main request),
- alternatively, that the patent be maintained on the basis of one of auxiliary requests 1 and 2, re-filed with the reply to the statement of grounds of appeal, and within the context of this request, that the case be remitted to the opposition division for consideration of the auxiliary requests.

Reasons for the Decision

Remittal

1. The board decided not to remit the case to the opposition division for further prosecution on the basis of auxiliary requests 1 and 2.

2. The board agrees with the respondent that the primary object of appeal proceedings is the review of the decision under appeal in a judicial manner (Article 12(2) RPBA). However, according to established

case law, parties have "*no absolute right to have each and every matter examined at two instances*". Moreover, Article 111(1), second sentence, EPC, leaves it to the board's discretion to decide on an appeal either by exercising any power conferred on the department of first instance or by remitting the case to that department (see Case Law of the Boards of Appeal, 9th Edition, 2019, V.A.7.2.1).

3. In deciding not to remit the case, the board took into account that the legal and factual framework established by the decision under appeal (which dealt with the main request) was not significantly altered by dealing with auxiliary requests 1 and 2. This is because the opposition division had already taken the therapeutic use (which is a feature of claim 1 of both auxiliary requests but not of claim 1 of the main request) into account when considering the obviousness of the subject matter set out in claim 1 of the main request (see point 42 of the decision under appeal, which reads as follows: "*...In fact, there is no clear suggestion [in document D4] to generate and use anti activin A antibodies in therapy*" and "*there is no clear teaching that said epitope would be particularly suitable for the generation of antibodies to inhibit the binding of activin A to its receptor and particularly effective in therapy*").

4. Moreover, in its submissions on inventive step of the subject-matter of claim 1 of the main request, the respondent already relied on the "*surprising biological effects*" of the claimed antibody. It stated that "*the body weight data of example 10 show that treatment with anti-activin A antibody A1, A2 and A3 significantly improved survival rates in a mouse xenograft model, with antibodies A1 and A2 also completely preventing*

body weight loss. These data indicating that the claimed anti-activin A antibodies were effective in neutralising activin A activity in vivo (see [0268] of the patent). In addition to these significant effects on body weight and mass, Antibodies A1 and A2 are shown at paragraph [272] of the patent to reduce xenograft tumour formation" (see reply to the statement of grounds of appeal, paragraphs 92 to 104 and section XI. above). Indeed, it formulated the problem to be solved as "*the provision of a biologically and therapeutically useful antagonist against activin A*" (*ibid.*).

5. Furthermore, the respondent's arguments relating to the subject-matter of claim 1 of auxiliary requests 1 and 2 were similar to the arguments presented in relation to the subject-matter of the main request, (see section XI. above). This was an additional reason why the board considered that a remittal of the case was not warranted.

6. Finally, Article 11 RPBA 2020, which applies in the present case according to Article 25(1) RPBA 2020, provides that "the board shall not remit the case to the department whose decision was appealed unless special reasons present themselves for doing so. As a rule, fundamental deficiencies which are apparent in the proceedings before that department constitute such special reasons".

7. Dealing with claim requests not dealt with in the decision under appeal does not necessarily constitute such special reasons. In the present case, the respondent had the opportunity to study and reply to the appellant's relevant objections on these requests, as these were set out in the statement of grounds of appeal. Although the board had given no preliminary

view on the inventive step of auxiliary requests 1 and 2, it had in its communication under Article 15(1) RPBA, informed the parties that "*[they] will be heard on whether or not these claim requests meet the requirements of the EPC at the oral proceedings, as necessary*" (see point 31 of the communication and section VI. above). Furthermore, the appellant's case on inventive step of the subject-matter of claim 1 of the main request, auxiliary request 1 and auxiliary request 2 had already been made in writing and the appellant did not change it during the oral proceedings. Such a change of case might have constituted special reason for remittal to the opposition division for further prosecution. However, this situation did not arise here.

8. In view of all of the above considerations, the board decided that there are no special reasons justifying a remittal in the present case.

Auxiliary request 2 - claim 1
Inventive step (Article 56 EPC)

Claim construction

9. The subject-matter of claim 1 is a purpose-limited product under Article 54(5) EPC. The product is an antibody (or antigen binding fragment thereof) defined by two functional features:

a) the ability to specifically bind to a so-called "cysteine knot region" of human activin A, and

b) the ability to inhibit binding of human activin A to human activin A receptor.

The therapeutic purpose is "treating cachexia".

10. The "cysteine knot region" is defined in the claim as "spanning amino acids C11-S33 and amino acids C81-E111 of SEQ ID NO: 225". In the board's view, the "cysteine knot region" comprises these amino acids but must contain other amino acids, since the first and second regions are not contiguous. The claimed antibody therefore binds activin A (which is a βA-subunit homodimer, see paragraph [0010] of the patent), anywhere in the "cysteine knot region", i.e. not necessarily at the recited amino acids. In agreement with the appellant, the board is of the view that the "cysteine knot region" may be understood as encompassing almost the entire molecule.

11. According to the respondent, the claimed antibody bound (contacted) the native form of human activin A, only within two regions, the first being defined by amino acids C11 to S33 and the second defined by amino acids C81 to E111 of the sequence set forth in SEQ ID No: 225. Moreover, it was of the view that the antibody defined in the claim need bind at minimum only a single residue in each of the specified regions.

12. From a technical point of view, as already noted above, amino acids C11-S33 and amino acids C81-E111 are not contiguous in the activin molecule, thus a region that spans them must either stretch between them or include them.

13. Also from a semantic point of view the word "spanning" could mean either that the recited amino acid segments are at either end of the region, where spanning means to stretching across or the term may be understood to more loosely mean 'including', so that the region

comprises the recited amino acids. Contrary to the respondent's view, the skilled person with a mind willing to understand would not have understood that the antibody must bind to, at minimum, one amino acid residue in each of the amino acid segments mentioned in the claim, since there is nothing in the wording of the claim to indicate this.

14. There is no support for the claim construction offered by the respondent in the patent either. Paragraph [0171] referred to by the respondent i) concerns a fully human antibody, whereas the claim is not directed to a fully human antibody and ii) discloses "*an isolated fully human antibody that specifically binds to the cysteine knot region (amino acids C11-S33 and/or amino acids C81-E111) of activin A*". Even if were accepted that the two amino acid regions mentioned were the only binding sites of the antibody, the use of "and/or" makes it clear that the antibody disclosed here does not need at minimum, bind to one amino acid residue in **each** of the regions mentioned in the claim, but instead may bind to only one of these regions. This differs from the construction put forward by the respondent.

15. Example 6, also referred to by the respondent as supporting its claim construction, is concerned with "*Activin A binding region mapping for monoclonal antibodies*" (see paragraph [0253]) and gives the results of experiments done to determine the binding site on activin A of specific neutralising antibodies including antibody A1 in particular. The skilled reader however, has no reason to consider that the binding properties of these specific embodiments are limiting features of the claim.

16. In view of the above considerations, the board cannot agree with the respondent's view that the claimed antibody must bind at least one amino acid from C11-S33 and one amino acid from C81-E111 of SEQ ID NO:225.

The closest prior art

17. It was common ground between the parties that document D4 could represent the closest prior art for the claimed subject-matter. This document was also taken to represent the closest prior art in the decision under appeal. The board sees no reason to differ from this opinion.

18. Document D4 is a review article entitled "*Antagonists of activin signaling: mechanisms and potential biological applications*". The structure and function of activins is reviewed and it is explained that "*they possess a cysteine knot scaffold and are secreted as homo- or heterodimers of related β-subunits. Although four β-subunit genes (βA, βB, βC and βE) have been described in human, only dimers of βA and βA (activin A), βB and βB (activin B), and βA and βB (activin AB) have been shown to be biologically active*" (see page 73, left column). Furthermore, Figure 2 shows "*the activin-A dimer, highlighting residues involved in interactions with its receptors and binding proteins*".

19. The involvement of activin-A in cachexia is set out under the heading "*Potential biological applications of activin antagonism*" (see page 77, left column). As the entire paragraph is relevant it is reproduced below in full:
"*Mice deficient in the inhibin a-subunit develop sex-cord stromal tumors at an early age [8]. Tumor*

development is associated with a cachexia-like wasting syndrome, characterized by severe weight loss, hepatocellular necrosis around the central vein, and depletion of the parietal cells in the glandular stomach [9]. In inhibin-deficient mice with tumors, activins are increased tenfold in the serum. Coerver et al. [50] have shown that it is the increase in levels of activin signaling via ActRII that is responsible for the cachexia symptoms in these mice. Notably, the related ligand myostatin has been also implicated in the induction of cachexia. Myostatin is expressed almost exclusively in cells of the skeletal muscle lineage and signals via activin type II receptors (Table 1). Zimmers et al. [51] have shown that systemic overexpression of myostatin in adult mice induces profound muscle and fat loss analogous to that seen in human cachexia syndromes. These studies suggest that activin and myostatin might be useful pharmacological targets for treating cachexia. Indeed, overexpression of follistatin has been shown to slow both activin- and myostatin-induced weight loss".

20. Of particular importance is the sentence "*these studies suggest that activin and myostatin might be useful pharmacological targets for treating cachexia*". It is apparent that this sentence refers to activin A, since the previous sentence concerns an increase in levels of activin signalling by the ActRII receptor and it is disclosed on page 73 (left column) of document D4 that this is a receptor for activin A.

The technical problem

21. The difference between the claimed subject-matter and the disclosure in document D4 is that the claim is for an agent for treating cachexia, directed to activin A

as a pharmacological target, whereas document D4 merely suggests activin A as a potential pharmacological target for this purpose.

22. In view of the claim construction adopted by the board (see point 10. above), antibody binding to the amino acid residues mentioned in the claim is not a feature of the claimed antibody and is therefore not taken into account in the formulation of the technical problem.

23. The technical effect of the above mentioned difference is the provision of an agent useful for treating cachexia. In view of this effect, the technical problem can be seen as the provision of an agent for treating cachexia.

Obviousness

24. In the assessment of obviousness, the question to be answered is whether a person skilled in the art, starting from the disclosure in document D4 and seeking a solution to the above formulated technical problem, would have provided the claimed antibody for treating cachexia.

25. The board considers that the skilled person knew from the disclosure in document D4 that there were a number of potential pharmacological targets for treating cachexia, including activin. They would also have known from document D4 that "*it is the increase in levels of activin signalling via ActRII that is responsible for the cachexia symptoms in these mice*" (see page 77, first full paragraph), from which they would have realised that the desired pharmacological agent would have to block the binding of activin A to its ActRII receptor. Furthermore, they would have considered that

antibodies (amongst other molecule types) would be suitable for achieving this aim, *inter alia,* because neutralising antibodies were shown as agents for blocking binding between activin A and its receptor in Figure 1 of document D4. Thus, the skilled person starting from document D4 seeking an agent for treating cachexia would have generated antibodies able to block the binding of activin A to its receptor. There is no evidence on file to indicate that the skilled person had any reason to doubt that routine techniques would not allow the production of such antibodies.

26. The respondent argued that the skilled person seeking a solution to the technical problem would not have chosen antibodies capable of binding activin A, for the following reasons:

i) because document D4 suggested other solutions to the technical problem and in fact taught away from the claimed solution: the skilled person reading document D4 would have turned to follistatin or the small molecule antagonist Met108Ala since they were both described as the most promising candidates. In the section of document D4 relating to cachexia, overexpression of follistatin was again suggested as potentially useful for treating cachexia;

ii) even if the skilled person had considered making antibodies directed to activin A, they would not have had a reasonable expectation that these would solve the technical problem.

27. The board is not persuaded by these arguments. While it is true that both follistatin and the small molecule antagonist Met108Ala are suggested in document D4 as attractive drug candidates, this does not detract from

the obviousness of the claimed activin A specific antibodies. According to the case law of the Boards of Appeal, a selection from a number of obvious solutions to a technical problem does not generally involve an inventive step (cf. Case Law of the Boards of Appeal of the European Patent Office, 9th edition 2019, I.D.9.19.9). Rather, to conclude that a proposed solution would have been obvious, it is sufficient that the board is convinced that a person skilled in the art would have considered the claimed subject-matter to be a solution to the technical problem. In the present case, the skilled person is also deemed to have had a reasonable expectation that antibodies would successfully solve the problem, as there is nothing in any of the cited art to suggest otherwise and moreover, antibodies specific for activin A that block the activin-induced stimulation of FSH secretion from pituitary cells and the induction of erythrocyte differentiation (and therefore the interaction of activin A with its receptor) were known (see page 77, right column, paragraph 1 of document D4).

28. The board notes that many of the respondent's submissions on inventive step rely on a claim construction under which the antibody defined in the claim must bind (contact) a minimum of a single residue in each of the specified amino acid sequences. Since the board does not adopt this construction, these submissions cannot succeed. As noted in point 10. above, the board agrees with the appellant that the antibody defined in the claim need not bind to all or even to any of the residues recited in the claim and certainly not to amino acids in both regions. However, even if a claim construction which requires that the antibody claimed specifically binds to the residues mentioned in the claim were adopted, the board

considers that such antibodies would also have been obvious to the skilled person. This is because these regions include the amino acids known to be involved in the binding of activin to its type II receptors (see document D4, Figure 2, amino acid residues highlighted in red).

29. In conclusion, the subject-matter of claim 1 lacks an inventive step in view of disclosure in document D4 alone.

Main request and auxiliary request 1 - claim 1

30. The conclusions reached above on the obviousness of the subject-matter of claim 1 of auxiliary request 2 apply equally to the subject-matter set out in claim 1 of the higher ranking main request and auxiliary request 1. Indeed, these claims are directed to the antibody defined in claim 1 of auxiliary request 2 as a product and to the first medical use of that antibody, respectively. Since it was obvious to provide the antibody for treating cachexia, the provision of the same antibody for use in therapy generally (claim 1 of auxiliary request 1) as well as provision of the antibody itself (claim 1 of main request) was obvious *a fortiori*.

Objection under Rule 106 EPC

31. During the hearing before the board, the respondent raised an objection under Rule 106 EPC. The objection was also submitted by email during the oral proceedings, see point XI., above.

32. The objection concerned the fact that the board did not separately consider the main request, i.e. the claim

request found allowable by the opposition division. In the respondent's view, i) not remitting the case to the opposition division for further prosecution of auxiliary requests 1 and 2, ii) the lack of a first instance decision on these requests and iii) the lack of a preliminary opinion of the board on auxiliary requests 1 and 2, all infringed the respondent's right to be heard under Article 113(1) EPC.

33. The board dismissed the objection for the following reasons: the respondent was given extensive opportunity during the oral proceedings to comment on whether or not the case should be remitted to the opposition division for further prosecution on the basis of auxiliary request 1 or auxiliary request 2, according to its request for remittal if the main request were held not to be allowable. The reasons why the board decided not to remit are set out in points 1. to 8. above.

34. Furthermore, the respondent was heard both on the question of remittal and on the topic of inventive step of the subject-matter of claim 1 of auxiliary request 2 before the board decided on the question of remittal. The board decided to deal with the subject-matter of claim 1 of auxiliary request 2 at the oral proceedings first, *inter alia* for reasons of procedural economy, since any successful objection of lack of an inventive step against it would apply *mutatis mutandis* to the subject-matter of claim 1 of the higher ranking claim requests.

35. In response to the respondent's written objection that "*When discussing Art 56 EPC for claim 1 of AR2, the Board instructed us to limit our submissions to those that had been made in writing*", the board observed, at

the oral proceedings, that it had merely been drawing the parties' attention to Article 12(3) RPBA, under which "the statement of grounds of appeal and the reply shall contain a party's complete appeal case" and any amendment to a party's case would be subject to the provisions in Article 13(1) and (2) RPBA. Furthermore, after raising the objection, the respondent was given an additional opportunity to make any submissions which it might have omitted. However, it chose not to make any further submissions because it considered that not knowing the reasons for the board's conclusions on inventive step meant that it could not address them. Finally, the board took all submissions made by the respondent during the oral proceedings into account, including those which went beyond those included in the reply to the statement of grounds of appeal. Indeed, the respondent was informed of this before the board announced its opinion on inventive step in the oral proceedings.

36. According to the established case law of the Boards of Appeal, the right to be heard does not require that a Board of Appeal must provide a party with all foreseeable arguments in favour of or against a request in advance (see e.g. R 1/08, Reasons, point 3.1 and R 13/09, Reasons, points 2.6.3 and 2.6.4.). More precisely, the right to be heard does not include the right to know in advance why a request is not allowable and which of the arguments made by another party was considered convincing by the board. In the case at hand, the board reached its conclusion on inventive step based on objections validly raised by the appellant in its statement of grounds of appeal. Accordingly, these were all known to the respondent.

37. It was therefore the board's judgement that the respondent's right to be heard under Article 113(1) EPC had not been violated either by the board's decision to hear the parties on inventive step of claim 1 of auxiliary request 2 first or by the board's decision not to allow the respondent's request to remit the case to the opposition division in case the main request were held not allowable.

38. Finally, the lack of a preliminary opinion of the board on auxiliary requests 1 and 2 does not constitute a violation of the respondent's right to be heard as prescribed in Article 113(1) EPC either. Firstly, the board is not required to provide a preliminary opinion, see Article 15(1) RPBA under which "The Board may also provide a preliminary opinion". Secondly, as already set out in point 36. above, the respondent was aware of the grounds and evidence on which this decision is based from the appellant's written submissions and had the opportunity to present its comments on these, both in writing and at the oral hearing.

39. Thus, the board concluded that the respondent's right to be heard had been respected and that the objection according to Rule 106 EPC was unfounded and had to be dismissed.

Conclusion

40. Since no claim request is allowable, the patent must be revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chair:

I. Aperribay R. Morawetz

Decision electronically authenticated