Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 20 June 2024

Case Number: T 1103/22 - 3.3.04

Application Number: 09766879.2

Publication Number: 2297207

IPC: A61K39/395, C07K14/745, C07K16/36

Language of the proceedings: EN

Title of invention:
Use of anti-factor XI antibodies for prevention or treatment of thrombus formation

Patent Proprietor:
Prothix BV

Opponent:
Mathys & Squire LLP

Headword:
Anti-factor XI antibodies/PROTHIX

Relevant legal provisions:
EPC Art. 83

Keyword:
Sufficiency of disclosure - (no)

Decisions cited:
T 0910/02, T 0663/10, T 0671/12, T 0166/17, T 1750/19, T 0435/20

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1103/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 20 June 2024

Appellant: (Opponent)	Mathys & Squire LLP The Shard 32 London Bridge Street London SE1 9SG (GB)
Representative:	Ford, Hazel Mathys & Squire The Shard 32 London Bridge Street London SE1 9SG (GB)
Respondent: (Patent Proprietor)	Prothix BV Warmonderweg 23 2334 AB Leiden (NL)
Representative:	Nederlandsch Octrooibureau P.O. Box 29720 2502 LS The Hague (NL)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 3 March 2022 concerning maintenance of the European Patent No. 22 97 207 in amended form**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	B. Rutz
	L. Bühler

Summary of Facts and Submissions

I. The appeal by the opponent (appellant) lies from the interlocutory decision of the opposition division that European patent No. 2 297 207, entitled "*Use of anti-factor XI antibodies for prevention or treatment of thrombus formation*", met the requirements of the EPC in amended form in accordance with the main request (set of claims originally submitted as auxiliary request 1 on 27 November 2019).

II. The opposition proceedings were based on the grounds of Article 100(a) EPC, in relation to inventive step (Article 56 EPC), and of Article 100(b) and (c) EPC.

III. With its statement of grounds of appeal the appellant filed document D46.

IV. With its reply to the appeal, the respondent (patent proprietor) indicated that its main request was that the patent be maintained in amended form as allowed by the opposition division. The respondent further filed sets of claims of auxiliary requests 1 to 7. Auxiliary requests 1 and 2 are identical to auxiliary requests 7 and 8, respectively, submitted on 3 December 2021. Auxiliary request 3 is a combination of auxiliary request 9 submitted on 3 December 2021 and the main request as maintained in opposition proceedings. Auxiliary request 4 is a combination of auxiliary request 6 submitted with the reply to the notice of opposition and the main request as maintained. Auxiliary requests 5 to 7 correspond to auxiliary requests 1 to 3 wherein claims 5 and 8 to 10 have been deleted.

V. The board summoned the parties to oral proceedings as requested, and informed them of its preliminary opinion in a communication under Article 15(1) RPBA.

VI. In this communication, the board indicated that it held the preliminary view that none of the requests met the requirements of Article 83 EPC.

VII. By letter dated 11 June 2024 the respondent informed the board that it would not be attending the oral proceedings.

VIII. With a communication dated 17 June 2024 the board informed the parties that the oral proceedings had been cancelled and that the proceedings would be continued in writing.

IX. Claim 1 of the main request and of auxiliary request 4 reads as follows:

"1. A binding molecule that specifically binds factor XI, for use in preventing or treating a pathological thrombosis or in preventing thrombosis in a subject who is at increased risk of developing thrombosis due to a medical procedure, wherein the binding molecule binds at the active site located in the light chain region of factor XI and inhibits the activity of factor XIa in chromogenic assay for factor XIa activity wherein L-pyroglutamyl-L-prolyl-L-arginine-p-nitroanilide is used as chromogenic substrate, and wherein the binding molecule is a monoclonal antibody or a factor XI-binding monoclonal antibody fragment."

Claim 1 of auxiliary requests 1 and 5 differs from claim 1 of the main request in that "the binding

molecule binds at the active site located in the light chain region of factor XI**a**" (highlighting added by the board).

Claim 1 of auxiliary requests 2 and 6 differs from claim 1 of auxiliary request 1 in that "the binding molecule binds factor XI and factor XIa when tested in an ELISA".

Claim 1 of auxiliary requests 3 and 7 differs from claim 1 of the main request in that the binding molecule "binds factor XI with a Kd that is equal to or less than 1 nM".

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

D5 WO 2017/162791 A1

D8 Declaration of Jonas Emsley dated 25 June 2019

D19 Y. Wu et al., "*Structural insight into distinct mechanisms of protease inhibition by antibodies*", PNAS 104(50), 2007, 19784-9

D20 R. A. Al-Horani and U. R. Desai, "*Designing Allosteric Inhibitors of Factor XIa. Lessons from the Interactions of Sulfated Pentagalloylglucopyranosides*", Journal of Medicinal Chemistry 57, 2014, 4805-18

D21 M. D. Argade et al., "*Allosteric Inhibition of Human Factor XIa: Discovery of Monosulfated Benzofurans as a Class of Promising Inhibitors*", Journal of Medicinal Chemistry 57, 2014, 3559-69

D41 WO 2016/207858 A1

D42 M. Schaefer et al., "*Allosteric Inhibition as a New Mode of Action for BAY 1213790, a Neutralizing Antibody Targeting the Activated Form of Coagulation Factor XI*", Journal of Molecular Biology 431, 2019, 4817-33 (including supplementary information obtained from https://doi.org/10.1016/j.jmb.2019.09.008)

XI. The appellant's submissions are summarised as follows.

Main request
Sufficiency of disclosure (Article 83 EPC)

The patent did not explain what was meant by "the active site", and there was no clear definition in the prior art of which amino acids formed the active site of factor XIa. Substantial further experimentation would be needed in order to obtain a clear definition of the active site before starting to screen for suitable antibodies. Such experimentation would have been further complicated by the need to identify the active site in the inactive zymogen protein factor XI as required by the claims.

The assays described in the Examples related to functional properties of the enzyme, but none of them necessarily and exclusively correlated with binding at the active site. In particular, the chromogenic assay mentioned in claim 1 did not necessarily show that binding was at the active site, a deficiency evidenced by the discussion of allosteric binders in e.g. documents D8, D19, D20, D21 and D42.

The respondent had failed to provide any evidence of any other method or assay that would have been known to

the skilled person at the relevant date and that could have been used to unequivocally show that binding was at the active site, particularly at the active site of an inactive zymogen as required by the claims.

The patent did not describe any antibodies meeting the requirements of the claim and produced by the filing date. There were no antibody sequences or detailed descriptions of antibodies that could be used as a starting point to produce further antibodies as claimed.

The provision of an antibody as claimed would require a research project well beyond routine experimentation, and amounting to an undue burden for the skilled person.

Auxiliary requests 1 to 7
Sufficiency of disclosure (Article 83 EPC)

The amendments did not overcome the deficiencies under Article 83 EPC. The same issues in relation to the scope and identification of the active site still applied.

XII. The respondent's submissions are summarised as follows.

Main request
Sufficiency of disclosure (Article 83 EPC)

Example 1 disclosed that antibodies that inhibited the active site of factor XIa could be selected by testing their ability to decrease the rate of conversion of the chromogenic substrate S-2366 (L-pyroglutamyl-L-prolyl-L-arginine-p-nitroanilide) by factor XIa in a chromogenic assay for FXIa activity.

Example 5 (pages 33 to 34 of the application as filed) disclosed how monoclonal antibodies against FXI and/or FXIa could be generated with standard hybridoma technology, using purified human FXI to immunise mice.

Example 6 (page 34 of the application as filed) disclosed how the antibodies produced by the hybridomas of Example 5 could be screened for their ability to specifically bind FXI or FXIa or both FXI and FXIa.

Example 8 (page 35 of the application as filed) in Table 2 presented an overview of the functional characterisation of the various possible antibodies in the different assays disclosed in the patent. The antibody type corresponding to the antibody claimed in claim 1 was mAb4, which had the functional characteristics of inhibiting the chromogenic activity of FXIa of Example 1 (assay 1) and specific binding to both FXI and FXIa in the ELISA of Example 5 (assay 6).

The disclosures were as clear and complete as a protocol in a laboratory manual. Unless the appellant produced verifiable facts that showed otherwise, the requirements of Article 83 EPC were thus met. There was no lack of sufficiency if a skilled person seeking to reproduce a monoclonal antibody did so by routine methods and tested them in an assay. Although this might possibly involve some tedious and time-consuming work, it was nothing out of the ordinary since the techniques for producing and selecting hybridomas were common routine techniques at the priority date of the patent.

Active site of the zymogen FXI

A skilled person reading claim 1 with a mind willing to understand would recognise that the "active site" of the FXI zymogen was formed by those parts of the FXI zymogen that would form the active site of the enzymatically active FXIa upon activation of the zymogen.

When screening for antibodies that bound to both FXI and FXIa and inhibited FXIa in the chromogenic assay, the skilled person would find antibodies that bound an epitope at the active site of FXIa, which epitope was common to both FXI and FXIa, without undue burden. No knowledge was required about exactly which amino acids formed "the active site" of FXI (the zymogen) and their rearrangement upon activation.

It was established case law that the EPC did not require experimental proof for patentability (see decisions T 578/06 and T 143/07). The fact alone that the patent did not disclose particular antibodies, either by sequence or by biological deposit, was in itself not a reason to deny sufficiency of disclosure.

The term "binding at the active site" was a functionally defined term, i.e. requiring inhibition of FXIa in the chromogenic assay. Therefore, even if the structure and amino acids involved in the active site were not known in the literature or disclosed in the patent, this would not raise any doubts about whether it would be possible to generate antibodies that bound the functionally defined active site by screening for their ability to inhibit FXIa in the chromogenic assay.

Figure C of document D8 showed that within the dashed oval and in its immediate vicinity there were a number of structural elements at the active site that were invariable between the FXI and FXIa conformations. Due to their size, antibodies binding to these invariable structural elements could be expected to block access to the active site even for a small substrate like S-2366, and thereby cause inhibition of FXIa in a chromogenic assay using this substrate.

In addition, Figure C of D8 demonstrated that while some of the amino acid sequences at the active site had moved between the two conformations, in either conformation they remained present and accessible. The skilled person would therefore conclude that perhaps some conformational epitopes made up of discontinuous amino acids might be lost between the two different conformations, but the majority of epitopes made up of continuous amino acid sequences remained available in either conformation.

Both post-published documents D5 and D41 disclosed antibodies (34.2 and NOV1401, respectively) that bound to the active site of FXI and inhibited FXIa in an assay for FXIa activity using the chromogenic S-2366 substrate or a similar small substrate.

Inhibitory effect in a chromogenic assay identifies antibodies binding at the active site

The appellant’s proposition of hypothetical antibodies inhibiting the chromogenic assay but not binding at the active site remained a purely theoretical exercise, for which the appellant had not produced convincing evidence.

No such allosteric antibodies inhibiting FXIa in a chromogenic assay had ever been described in the art, not even to date and not even for any amidolytic serine protease.

The observed allosteric effects of the small-molecule inhibitors of documents D20 and D21 could by no means be taken as an indication that similar effects could be achieved by the much larger anti-FXI antibody, because small-molecule inhibitors could interact at locations within the FXI molecules that antibodies, because of their size, could never reach.

The skilled person was well aware of the different types of enzyme inhibition and would know how to distinguish competitive inhibitors blocking the active site from allosteric inhibitors or other non-competitive inhibitors binding elsewhere by means of enzyme kinetics. The skilled person could thus have used enzyme inhibition kinetics, e.g. a Lineweaver-Burk plot, to exclude the hypothetical possibility that the antibody would exert its effect by allosteric means.

There was no more than a negligibly small chance that a skilled person, following the teachings of the patent, would ever end up with an antibody inhibiting the chromogenic assay but not binding at the active site of FXIa. Such extremely rare "occasional failures" would not impair the reproducibility of the claimed antibodies.

Antibodies of documents D19 and D42

Document D19 disclosed two inhibitory antibodies from a human Fab phage display library, termed Ab58 and Ab75,

selected for binding to a trypsin-like protease, hepatocyte growth factor activator (HGFA).

D42 was a post-published document disclosing the FXIa inhibitory antibody BAY 1213790, which inhibited FXIa activity in an assay using a small chromogenic tripeptide substrate similar to S-2366.

The skilled person would understand that binding "at the active site" meant binding at any epitope close enough to the active site cleft in such a way that the antibody sterically hindered access of a small chromogenic substrate detectable in an enzymatic assay using that substrate, wherein the antibody showed (at least partial) inhibition with competitive kinetics.

The Ab75 antibody in D19 bound to loops (the 99- and 60-loops) that in D19 itself were reported to "form[s] part of the substrate-binding cleft". Notwithstanding that Ab75 bound the "backside" of the 60- and 99-loops, "away from the substrate-binding cleft", this was still so close to the substrate-binding cleft that, given the size of an antibody, the skilled person would expect Ab75 to at least partially sterically hinder access to the substrate-binding cleft even for small chromogenic substrates (see also Figure 3A in D19).

Similar considerations applied to the BAY 1213790 antibody of D42.

Hence the antibodies disclosed in D19 and D42 were examples of antibodies that bound at the active sites of HGFA and FXIa respectively, and that inhibited the respective amidolytic activities in assays using a small peptide substrate, such as S-2366.

These disclosures were consistent with the teaching of the patent and also consistent with the general expectation of the skilled person that an antibody binding at the active site of a serine protease would inhibit the amidolytic activity of the protease with competitive kinetics.

The patent thus met the requirements of Article 83 EPC.

Auxiliary requests 1 to 7
Sufficiency of disclosure (Article 83 EPC)

Auxiliary requests 1 to 7 *inter alia* addressed the appellant's concern that claim 1 of the main request did not require the inhibition of FXIa activity to be caused by binding to the active site of the same molecule.

XIII. The appellant requested that the decision under appeal be set aside and the patent revoked.

The respondent requested that the appeal be dismissed, i.e. the decision of the opposition division be upheld and the patent be maintained on the basis of the main request (based on a set of claims first submitted as auxiliary request 1 on 27 November 2019), or alternatively on the basis of one of the sets of claims of auxiliary requests 1 to 7 filed with the response to the appeal. Document D46 should not be admitted into the proceedings.

Reasons for the Decision

Requests for oral proceedings (Article 116 EPC and Article 15(3) RPBA)

1. The board had summoned the parties to oral proceedings as requested. In its communication under Article 15(1) RPBA, the board informed the parties that it was inclined to set aside the contested decision and to revoke the patent. The respondent then indicated in a letter dated 11 June 2024 that it would not be represented at the oral proceedings.

2. In accordance with established case law, if oral proceedings are scheduled as a result of a party's request for such proceedings on an auxiliary basis, and if that party subsequently states that it will not be represented at the oral proceedings, the board is not obliged to hold oral proceedings in the party's absence. Rather, under these circumstances and irrespective of whether or not the appellant explicitly maintains its request for oral proceedings, it is within the discretion of the board to decide whether the scheduled oral proceedings are to be maintained or to be cancelled, since it cannot be the purpose of Article 116 EPC that a party can oblige a board to hold oral proceedings in its absence (see T 663/10, point 1.3 of the Reasons; T 910/02, point 6 of the Reasons; T 671/12, point 2 of the Reasons; T 166/17, point 1.2 of the Reasons; T 1750/19, point 2.2 of the Reasons).

3. Having been made aware of the board's preliminary view, the respondent announced its absence from the oral proceedings. In view of the above case law, the board

was thus in a position to make a final decision without holding oral proceedings, in accordance with Articles 113(1) and 116(1) EPC and Article 12(8) RPBA. Consequently, the scheduled oral proceedings were cancelled.

Admission of document D46 (Article 12(4)(6) RPBA)

4. As document D46 was not needed to come to a decision its admission has not been decided upon.

Main request - claim 1
Claim interpretation

5. The monoclonal antibody or monoclonal antibody fragment of claim 1 is "*for use in preventing or treating a pathological thrombosis or in preventing thrombosis in a subject who is at increased risk of developing thrombosis due to a medical procedure*". According to established case law, attaining the therapeutic or preventive effect is a functional feature of the claim.

6. The monoclonal antibody or monoclonal antibody fragment is defined by the further functional features in the claim:
   (a) it specifically binds factor XI (FXI),
   (b) it binds at the active site located in the light chain region of FXI, and
   (c) it inhibits the activity of FXIa in a chromogenic assay with L-pyroglutamyl-L-prolyl-L-arginine-p-nitroanilide (S-2366) as chromogenic substrate.

7. It was disputed whether the inhibition of the activity of the enzyme FXIa in an activity assay by an antibody or antibody fragment could be equated with the binding of said antibody or antibody fragment at the active

site of the corresponding zymogen (or pro-enzyme) FXI (see document D8, point 43).

8. The appellant refuted this because an antibody could inhibit the activity of an enzyme by modes other than binding at the active site of the pro-enzyme, e.g. through steric hindrance or by inducing a conformational change (allosteric inhibition), as evidenced by documents D19, D20 and D21.

9. Document D19 discloses inhibition of hepatocyte growth factor activator (HGFA), another trypsin-like protease, by an antibody as assayed with a chromogenic substrate while binding outside the substrate-binding cleft (see page 19788, left-hand column, third full paragraph: "*one* [of the antibodies] *applies an allosteric effect while binding outside the cleft* [...] *it is likely that analogous features across a wide range of protease targets can be exploited by conventional antibodies acting as inhibitors*").

10. Document D20 discloses small-molecule allosteric inhibitors of FXIa (see abstract and page 4806, right-hand column, first full paragraph: "*These* [heparin-binding] *sites are typically cooperatively linked to the catalytic site, as demonstrated particularly for FXIa, which affords the ability to allosterically inhibit the enzyme*"). Document D21 also discloses small-molecule allosteric inhibitors (see abstract).

11. The respondent counter-argued that the small-molecule allosteric inhibitors of FXIa in D20 and D21 were not evidence that similar effects could arise with anti-FXI antibodies, which because of their size could not access the same binding sites.

12. With regard to document D19, the respondent considered binding of the antibody Ab75 to the "backside" of the 60- and 99-loops, away from the substrate-binding cleft, still so close that, given the size of an antibody, it at least partially sterically hindered access to the substrate-binding cleft even for small chromogenic substrates. This was what was meant by "binds at the active site". Furthermore, the skilled person could measure enzyme kinetics to separate allosteric and competitive inhibitors and thus obtain an antibody having all the features required in the claim.

13. The board does not agree with this reasoning. The skilled person would not interpret "binds at the active site" as a mere functional requirement of inhibiting enzymatic activity, e.g. by steric hindrance. Such interpretation would disregard the clear requirement of "binding at", which is different from "binding near", "binding close to", or "inhibiting an activity". The board does not agree either that the allosteric inhibition by small molecules disclosed in documents D20 or D21 cannot also be expected for antibodies. Document D19, indeed, shows that antibodies are capable of allosterically inhibiting a trypsin-like protease structurally related to FXI (see also discussion in document D8, points 29 to 34).

14. The board therefore considers that, in the absence of a single example of an antibody which inactivates FXIa activity in a chromogenic assay (c) and is shown to bind at the active site of FXI (b) in the application, it is not possible to assume that complying with feature (c) would necessarily also lead to feature (b) being complied with.

Sufficiency of disclosure (Article 83 EPC)

15. It is undisputed that producing a monoclonal antibody which specifically binds FXI (feature (a)) is within the routine capabilities of a skilled person. It is also undisputed that identifying an antibody which inhibits FXIa activity in a chromogenic assay with S-2366 (feature (c)) does not pose any particular difficulties for the skilled person. It is further undisputed that an antibody inhibiting FXIa activity in a chromogenic assay credibly achieves a therapeutic or preventive effect on thrombosis.

16. The parties, however, disagree on whether the application as filed sufficiently discloses a monoclonal antibody which binds at the active site located in the light chain region of FXI (feature (b)).

17. In the following, it will be analysed whether the skilled person would have been able to identify the location of the active site in the light chain region of FXI at the relevant date. The parties differ in particular in their definition of the active site. The appellant considers it necessary that the active site be precisely defined in structural terms, while the respondent insists that the active site should not be defined narrowly, e.g. limited to the substrate-binding cleft, and that a functional definition in any case would suffice, "*i.e. requiring inhibition of FXIa in the chromogenic assay*" (reply to the appeal, point 64.). The respondent also, referring to Figure C of document D8, maintains that *"conformational changes of active site upon activation of FXI to FXIa do not raise doubt whether it would be possible to generate an antibody that binds both conformations of the active*

site and inhibits FXIa in the chromogenic assay" (reply to the appeal, point 65.).

18. As detailed above (see points 7. to 14.), the feature "binds at the active site" cannot be determined with a chromogenic activity assay in the case at hand. The application does not provide any other assay to identify the claimed antibodies either. The active site thus needs to be defined structurally in order to obtain an antibody as defined in the claims.

19. This, however, confronts the skilled person with several problems. Firstly, by definition only the enzyme FXIa, but not the inactive zymogen FXI, contains an active site. Upon activation by proteolytic cleavage of FXI, a conformational change occurs in the molecule which results in the catalytic domain having a different structure in the resulting FXIa (see Figure C in document D8 and points 8 to 12 therein). The "pre-active" site of FXI therefore cannot be equated with the active site of the enzyme FXIa.

20. Secondly, even if one were to assume that the active site of FXIa was largely identical to the "pre-active" site of the zymogen FXI, the skilled person, in the absence of concrete information about the composition, i.e. amino acids involved, and structure of the active site, would not know against which region or epitope of the molecule an antibody had to be raised.

21. Thirdly, it is common general knowledge that antibodies against some epitopes (in particular non-linear ones) are not routine to make and can require considerable inventive skill (see e.g. T 435/20, point 60. of the Reasons).

22. Finally, the skilled person, from the application as filed, had no starting point of an actual antibody to generate and compare further antibodies meeting the requirements of the claim.

23. The appellant referred to post-published document D5 as evidence that even eight years after the priority date of the present patent generating an antibody as claimed was not considered routine: "*A mAb that binds to the active site of FXI/FXIa and blocks the conversion of protein and peptide substrates by FXIa, would be a preferred option for therapeutic applications. However, until now such an inhibitory mAb against the active site of Factor XIa has not been described*" (see page 3, lines 19 to 22).

24. The respondent referred to the same document as evidence that an antibody as claimed could be made (antibody 34.2). The respondent further referred to post-published document D41, which disclosed the antibody NOV1401 that bound to both FXI and FXIa and showed the structure of the antibody bound to the active site of FXI (see Example 5 and Figures 4 and 5). The antibody also inhibited FXIa activity in a chromogenic assay.

25. It is established case law that insufficient disclosure cannot be remedied by post-published evidence, i.e. information which the skilled person did not have available at the relevant date (see Case Law of the Boards of Appeal of the EPO, 10th edition, 2022, II.C.2 and II.C.6.8). The disclosure of documents D5 and D41 is therefore not taken into account.

26. In conclusion, the invention is not disclosed in a manner sufficiently clear and complete for it to be

carried out by a person skilled in the art (Article 83 EPC).

Auxiliary requests 1 to 7
Sufficiency of disclosure (Article 83 EPC)

27. The respondent has not provided arguments as to how the additional features in the claims of these requests could overcome the objections.

28. The same reasoning as for the main request applies because the monoclonal antibody or binding fragment thereof is defined by essentially the same functional features.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated