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Datasheet for the decision of 1 August 2024

Case Number: T 0326/22 - 3.3.08

Application Number: 13746964.9

Publication Number: 2812443

IPC: C12P21/08, A61K39/395, C07K16/28

Language of the proceedings: EN

Title of invention:
CD47 antibodies and methods of use thereof

Patent Proprietor:
Inhibrx, Inc.

Opponent:
Forty Seven, Inc.

Headword:
CD47 antibodies/INHIBRX

Relevant legal provisions:
EPC Art. 56, 83, 114(2)
RPBA 2020 Art. 12(1)(a), 12(4)

Keyword:
Requirements of the EPC met - (yes)

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It can be changed at any time and without notic

Decisions cited:
T 0431/96, T 1466/05, T 0657/10, T 1852/11, T 0435/20

Catchword:

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Case Number: T 0326/22 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 1 August 2024

Appellant: (Opponent)	Forty Seven, Inc. 333 Lakeside Drive Foster City, CA 94404 (US)
Representative:	Goodman, Daniel and Chapman, Mark Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Respondent: (Patent Proprietor)	Inhibrx, Inc. 11025 N. Torrey Pines Road, Suite 200 La Jolla, CA 92037 (US)
Representative:	Bezzubova, Olga and An, Xiaojin Jones Day Rechtsanwälte, Attorneys-at-Law, Patentanwälte Prinzregentenstrasse 11 80538 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 21 December 2021 concerning maintenance of the European Patent No. 2812443 in amended form**

Composition of the Board:

Chair	T. Sommerfeld
Members:	M. Montrone
	L. Bühler

Summary of Facts and Submissions

I. An appeal was lodged by the opponent (appellant) against an interlocutory decision of the opposition division according to which the European No. 2 812 443 could be maintained in amended form. This patent is based on European patent application No. 13 746 964.9 filed as International patent application which was published as WO 2013/119714 ("patent application").

II. The opposition proceedings were based on the grounds for opposition in Article 100(a) EPC in relation to inventive step (Article 56 EPC), and Article 100(b) and (c) EPC. The opposition division took the view that the claims as granted (main request) comprised added subject-matter while auxiliary request 1 was held to comply with the requirements of the EPC. Further the opposition division did not admit documents D19 to D24 and D28 to D30 into the proceedings.

III. With their statement of grounds of appeal, the appellant submitted *inter alia* arguments under insufficiency of disclosure (Article 83 EPC) and lack of inventive step (Article 56 EPC) against the subject-matter of auxiliary request 1. In support of their case, written submissions already filed during opposition proceedings were re-submitted.

IV. In reply, the patent proprietor ("respondent") submitted *inter alia* new evidence and re-submitted the written submissions filed during the opposition proceedings.

V. Further submissions were filed by the parties, including new documents.

VI. In a communication pursuant to Article 15(1) RPBA, the parties were informed of the board's preliminary opinion.

VII. In reply, the appellant provided further arguments.

VIII. Oral proceedings by videoconference were held in the presence of both parties.

IX. The documents referred to in this decision include the following:

D1: WO 2011/143624

D2: Pietsch E.C. *et al.*, Blood Cancer Journal, 2017, Vol. 7, e536

D4: Weiskopf K. *et al.*, The Journal of Clinical, Investigation, 2016, Vol. 126(7), 2610-2620

D6: Epitope Mapping Protocols, 2nd edition, 2009, Ed. Reinecke U. and Schutkowski M., 1-456

D7: Gershoni J.M. *et al.*, Biodrugs, 2007, Vol. 21(3), 145-156

D13: US 7,696,325

D25: Leclair P. *et al.*, Cell Death & Disease, 2018, Vol. 9, 544

D26: Petrova P.S. *et al.*, Clin. Cancer Res., 2017, Vol. 23(4), 1068-1079

D27: Liljeroos L. *et al.*, Journal of Immunology

Research, 2015, ID 156241, 1-17

D31: Hatherley D. *et al.*, Molecular Cell, 2008, Vol. 31, 266-277

X. Claims 1, 8 and 9 of auxiliary request 1 read:

"1. An isolated monoclonal antibody or immunologically active fragment thereof that binds to human CD47, wherein the antibody or immunologically active fragment thereof binds to a discontinuous epitope on CD47, wherein the discontinuous epitope comprises amino acids residues Y37, K39, K41, K43, G44, R45, D46, D51, H90, N93, E97, T99, E104, and E106 of CD47 when numbered in accordance with SEQ ID NO: 147, and wherein the antibody or immunologically active fragment thereof prevents CD47 from interacting with signal-regulatory-protein a (SIRPα) and does not cause a significant level of agglutination of cells after administration."

"8. A pharmaceutical composition comprising the antibody or immunologically active fragment thereof of any one of claims 1 to 7 and a carrier."

"9. An antibody or an immunologically active fragment thereof as defined in any one of claims 1 to 7 for use in a method of alleviating a symptom of a cancer or other neoplastic condition in a subject".

Claims 2 to 7 are directed to further embodiments of the antibody of claim 1, while claims 10 to 12 further define the subject-matter of claim 9.

XI. The appellant's submissions, insofar as relevant to the present decision, may be summarised as follows:

Admittance/consideration of documents D19 to D27

Documents D19 to D27 were timely filed within the deadline of Rule 116 EPC in direct response to comments made in the opposition division's preliminary opinion annexed to the summons.

Documents D19 to D24 were relevant for the assessment of inventive step and the decision of the opposition division not to admit them suffered from an error in its use of discretion. Therefore, the opposition division's decision not to admit these documents should be overturned. Furthermore, the circumstances of the appeal justified the admittance of D19 to D24 in appeal.

Documents D25 to D27 were admitted into the proceedings and formed part of the evidence on which the decision under appeal was based. These documents thus formed necessarily part of the appeal proceedings.

Claim construction - claim 1

The claimed antibodies encompassed a pool of CD47 antibodies that were functionally defined only.
In the absence of a qualifier in claim 1, for example, a threshold or an assay, the feature "*does not cause a significant level of agglutination*" in claim 1 had to be read broadly. This was also in line with the description of the patent (paragraph [0018]). A non-significant agglutination encompassed therefore a detectable but low cell agglutination.

Sufficiency of disclosure - claim 1

Claim 1 was not limited to antibody 2A1 or its derivatives. The patent application provided the sequence information for the antibody 2A1 and its humanised derivatives only, while other antibodies having the claimed properties were not disclosed. In line with T 1466/05, the provision of the structural information of 2A1 and its derivates alone was not sufficient for preparing substantially all antibodies that fell within the scope of claim 1.
Consequently obtaining substantially all CD47 antibodies encompassed by claim 1 required their *de novo* generation by repeating the immunisation process disclosed in the patent application using CD47-IgV as antigen. Since this was a random process, the requirements of Article 83 EPC were not fulfilled for this reason alone (T 657/10).

Furthermore, the patent application did also not provide sufficient guidance for arriving at the claimed antibodies generated by a *de novo* immunisation. An antigen was not provided that generated reliably and specifically further antibodies that shared their binding specificity with antibody 2A1; moreover appropriate screening assays that led necessarily and directly towards the selection of the claimed antibodies were lacking; instead many screenings had to be carried out: for CD47 binding, for SIRPα blocking and for a lacking cell agglutination.

Since these assays did not provide antibodies that necessarily bound to the epitope defined in claim, the epitope structure recognised by the antibody had to be determined by X-ray crystallography ("XRC") as well. However, the patent application was silent on instructions how the protein crystallisation of the antibody / CD47 complex mentioned in Example 11 was

carried out. Although document D31 was mentioned in Example 11, it was not cited as reference for crystallising the complex. Furthermore document D31 disclosed solely the crystallisation of a CD47 / SIRPα complex. SIRPα was not an antibody and had a lower molecular weight. The molecules were thus unrelated.

Independent thereof, XRC was commonly known as a complex and burdensome technique (e.g. document D7) and did not necessarily provide structural data (e.g. document D4, page 2612, right column, second paragraph and document D27, page 5, right column, penultimate paragraph and page 6, left column, second paragraph). Moreover, evidence was available that CD47 required modifications before protein crystals were obtained (document D2, Supplementary information, page 4, last sentence and page 5, penultimate paragraph). None of these modifications were taught in the patent application or in document D31. Also the disclosure of a single antibody only in the patent application having the claimed functional properties was an indication that the finding of this antibody was based on chance. This was comparable to the finding of an elite event (T 657/10). Thus the evidence provided demonstrated that the finding of substantially all antibodies having the claimed properties involved an unreasonable amount of trial and error.

The use of a competitive cross-blocking assay for narrowing down the number of antibodies that bound to the same or similar epitope as 2A1 did not replace the need for XRC as a screening tool. Document D2, for example, disclosed three non-haemagglutinating and SIRPα-blocking antibodies (B6H12, C47B161 and C47B222, sentence bridging pages 2 and 3 and sentence bridging pages 3 and 4) which, however, bound to different but

partially overlapping epitopes compared to 2A1. These antibodies competed thus with 2A1 for its binding to CD47. Accordingly there existed still a need for XRC as high-throughput screening method for finding further antibodies that bound to the claimed epitope, rather than using XRC for confirmation purposes only. Therefore many protein crystals had to be generated which required individual crystallisation conditions. Also this amounted to undue burden.

The fact situation in this case closely resembled that of decision T 435/20 which concerned an antibody that bound to a discontinuous epitope too. In that case, sufficiency of disclosure was denied.

Inventive step - claim 1

Documents D1 and D13 represented the closest prior art.

Document D1 disclosed that *inter alia* the B6H12 and 5F9 antibodies blocked the CD47-SIRPα interaction. Moreover, full-length B6H12 antibody (document D2, Supplementary Table 3, document D25, Figure 2C and document D26, Figure 5C) as well as Fab fragments of B6H12 and 5F9 did not agglutinate cells. Fab fragments were incapable of cross-linking (agglutinating) CD47 cells because they contained a single antigen binding site only. In addition, document D1 disclosed bispecific B6H12 and 5F9 antibodies which had a single antigen binding site for CD47 too and a further binding specificity for a cancer antigen. These antibodies bound minimally to red blood cells and showed a non-significant haemagglutination only.

Document D13 disclosed non-haemagglutinating MABL scFv antibodies that blocked the CD47-SIRPα interaction.

The claimed CD47 antibodies differed from the antibodies in documents D1 and D13 only by their binding to the epitope structure as defined in claim 1. Thus the claimed antibodies and those of documents D1 and D13 bound to different CD47 epitopes.

No advantageous effect was associated with this distinguishing feature. The objective technical problem to be solved resided thus in the provision of alternative CD47 antibodies. However, the provision of alternative CD47 antibodies that did not possess any unexpected properties lacked an inventive step.

XII. The respondent's submissions, insofar as relevant to the present decision, may be summarised as follows:

Admittance/consideration of documents D19 to D27

Documents D25 to D27 should not be admitted into the proceedings. The experimental data disclosed in documents D25 and D26 lacked the level of scrutiny, detail and consistency compared to the patent application. Document D27 did not add anything to the the disclosure of the other documents on file.

Sufficiency of disclosure - claim 1

The claimed anti-CD47 antibodies bound to a particular epitope that comprised 14 amino acids. It was demonstrated in the patent application that the antibody's binding to this epitope was responsible for blocking the CD47-SIRPα interaction without causing cell agglutination. The patent application disclosed all steps for arriving at antibodies (Examples 1 to 10) that bound to the claimed epitope including sequence

information of antibody 2A1 that was used for the determination of the claimed epitope as well as sequences of other antibodies with identical or similar CDRs (Table 1, paragraphs [0111] and [0112]). Moreover, the antigen used for immunisation (Example 1) and the epitope structure on CD47 was disclosed (Example 11 and Figure 11C) including assays that allowed the assessment of the antibodies' SIRPα-blocking activity (Example 3) and cell agglutination (Examples 4 and 5). Furthermore the use of a cross-competitive binding assay was mentioned for testing whether the antibodies bound to the epitope of 2A1 (paragraphs [00116] and [00117]).

The assertion that the use of a cross-competitive binding assay would not relieve the undue burden of the skilled person was not supported by verifiable facts. The skilled person screening for antibodies binding to the same epitope as 2A1 would have chosen appropriate conditions to ensure that only antibodies were selected that bound to identical or very similar epitopes on CD47.

XRC represented the gold standard at the relevant date for epitope mapping (e.g. document D6, page 78, first paragraph). XRC was not needed for high-throughput screening but for confirming the bound epitope structure since only preselected antibodies were crystallised, i.e. antibodies that showed SIRPα-blocking and non-cell agglutinating activities and moreover competed with 2A1 for their binding to the claimed epitope.

Contrary to the appellant's submission, the epitope determination by XRC of CD47 complexed with various binding partners including antibodies was successful in

all documents on file, i.e. the patent application, and documents D2, D4 and D31. These documents provided evidence that potential crystallisation issues were easily resolved by routine measures.

The fact situation in decisions T 435/20, T 1466/05 and T 657/10 differed fundamentally from the present case so that these decisions lacked relevance.

The claimed subject-matter was thus sufficiently disclosed in the patent application.

Inventive step - claim 1

At the relevant filing date of the patent there were no (full-length) antibodies available that blocked SIRPα's binding to CD47 and did not agglutinate cells.

Documents D1 and D13 represented the closest prior art. The CD47 antibodies of claim 1 were at least distinguished therefrom by the claimed epitope. This epitope conferred unique properties to the antibodies bound thereto irrespective of the antibodies' format. Any antibody (i.e. full-length or fragment) that bound to the claimed epitope blocked SIRPα's binding to CD47 and had non-cell agglutinating activities. The skilled person had thus any freedom in selecting the most appropriate antibody format for the desired application. Since none of the available prior art documents suggested or pointed at the epitope indicated in claim 1, the antibodies of claim 1 were inventive.

XIII. The relevant requests of the parties for this decision are (for the complete set of requests, see the minutes of the oral proceedings):

(a) The appellant requests that:
- the decision under appeal be set aside and that the patent be revoked *in toto*, and that
- documents D19 to D24 be admitted/considered in the appeal proceedings

(b) The respondent requests that:
- the appeal be dismissed and that the patent be maintained on the basis of auxiliary request 1;
- documents D19 to D27 not be admitted/considered in the proceedings, and
- that new lines of argument under sufficiency of disclosure and inventive step not be admitted/ considered.

Reasons for the Decision

Admittance/consideration of documents D19 to D30

1. Documents D19 to D30 were filed by the appellant during the opposition proceedings on the final date for making written submissions fixed by the opposition division pursuant to Rule 116(1) EPC. The opposition division admitted documents D27 to D27 into the proceedings, but decided not admit documents D19 to D24 and D28 to D30.

1.1 As regards documents D19 to D24 and D28 to D30, the opposition division held in the decision under appeal (point 11.5 of the Reasons) that these documents were late filed and either not more relevant (D19 to D24) than the documents already on file, or were irrelevant since they related to communications issued by an examining division (D29 and D30) in the context of a later unrelated patent application (D28). Thus these documents were not admitted.

1.2 It is established case law that an opposition division has a certain degree of freedom in taking discretionary decisions and that the board should overrule the way in which the opposition division exercised its discretion only if it concludes that this was done according to the wrong principles or without taking into account the right principles, or that the opposition division exercised its discretion in an unreasonable way and thus exceeded the proper limit of its discretion (Case Law of the Boards of Appeal of the EPO, 10th edition 2022, ("Case Law"), V.A.3.4.1 b)).

1.3 Relevance is one of the criteria to be applied for discretionary decisions on the admittance of late filed documents. The board has no reasons to doubt that the opposition division heard the parties on the relevance of these documents and considered this criterion in detail and in a reasoned manner in the decision under appeal. Nor in fact does the appellant contest this but rather the issue of how the facts were assessed in substance. As set out above, the Boards of Appeal normally review a first instance's discretionary decision insofar only as to establish whether the discretion was exercised fairly and properly, and not to determine whether it would have decided differently on the facts.

1.4 In view of the evidence on file, the board is convinced that the opposition division has not exercised its discretion in an unreasonable way or according to the wrong principles. The opposition division's decision not to admit D19 to D24 into the proceedings is thus confirmed (Article 12(6) RPBA).

1.5 Since the appellant did not rely on documents D28 to D30 in their argumentation during the oral proceedings,

the admittance of these documents was not discussed with the parties. There was thus no need for the board to decide on their admittance into the proceedings.

2. The respondent requested not to admit documents D25 to D27 into the appeal proceedings.

2.1 The opposition division admitted/considered documents D25 to D27 in the opposition proceedings and based its reasoning on them (decision under appeal, points 11.2 to 11.4.2, 14.4, 14.5, 15.2 and 15.3 of the Reasons).

2.2 The opposition division considered that documents D25 to D27 were filed in direct reply to its preliminary opinion annexed to the summons and were highly relevant under sufficiency of disclosure and inventive step. Arguments that the opposition division did not hear the parties on the relevance of these documents are not on file. Furthermore, the decision under appeal considers the relevance of these documents in detail and in a reasoned manner. In view thereof, the board concludes that the discretion was exercised fairly and properly and that documents D25 to D27 were correctly admitted into the opposition proceedings.

2.3 The EPC does not provide a legal basis for the exclusion in appeal proceedings of documents which were correctly admitted in the opposition proceedings. This is all the more true, if the contested decision was based on them (e.g. T 1852/11, Reasons 1.3 and Case Law, V.A.3.4.4). Documents D25 to D27 are thus part of the appeal proceedings (Article 12(1)(a) RPBA).

Auxiliary request 1

Claim construction - claim 1

3. Claim 1 is directed to a monoclonal antibody or an immunologically active fragment thereof characterised by the following functional features:

- it binds to an epitope comprising amino acids "*Y37, K39, K41, K43, G44, R45, D46, D51, H90, N93, E97, T99, E104, and E106 of CD47*" of the amino acid sequence of mature human CD47 encoded by SEQ ID NO: 147,
- it prevents "*CD47 from interacting with signal-regulatory-protein α (SIRPα)*" (i.e. it is a SIRPα-blocking CD47 antibody) and
- it does "*not cause a significant level of agglutination of cells after administration*".

3.1 Thus claim 1 is directed to a pool of functionally defined human CD47 monoclonal antibodies/fragments.

3.2 CD47 is a cancer antigen expressed on cell surfaces with a monomeric immunoglobulin-like structure (patent, paragraph [0002]).

3.3 The residues making up the epitope in claim 1 are not contiguous along the primary amino acid sequence of human CD47 but reside in different regions (positions 37 to 51 and 90 to 106: patent, paragraph [0284]). The epitope is thus indicated as "*discontinuous*".

3.4 While the epitope as defined in claim 1 must include all of the amino acid residues at the indicated positions, the epitope is not limited thereto. This follows from the use of the term "*comprises*" as regards a "*discontinuous epitope*" in conjunction with the normal rules of claim construction, in which terms in a claim are given their broadest technically sensible

meaning in the context in which they appear (Case Law, II.A.6.1). This construction of "*epitope*" in claim 1 is also in line with paragraph [0284] of the patent which states that: "*The 2A1 epitope on CD47 is discontinuous, and includes residues Y37, K39, K41, the KGRD (SEQ ID NO: 56) loop (residues 43-46), D51, H90, N93, E97, T99, E104, and F106 of CD47 when numbered in accordance with SEQ ID NO: 147*" (emphasis added).

3.5 The meaning of the terms "*isolated monoclonal antibody*" and "*immunologically active fragment thereof*" in claim 1 was contested between the parties. These terms have a clear meaning in the art and encompass all kinds of monoclonal antibodies/fragments thereof, for example, chimeric and bispecific antibodies ("BsAbs"), Fab fragments, Fv and scFvs. This is also in line with the patent's teaching (paragraphs [0085] and [0163]). Moreover, the term "*immunologically active fragment thereof*" in claim 1 refers to a fragment that contains a site that binds to the epitope defined in claim 1.

3.6 The functional requirements "*prevents CD47 from interacting with...(SIRPα)*" and "*not cause a significant level of agglutination of cells*" in claim 1 are not further defined, for example, by reference to a certain level/degree, an antibody concentration, or a reference CD47 antibody. The meanings of "*prevents CD47 from interacting*" and "*not cause a significant level*" are relative and differ depending on the context in which they are used. According to the normal rules of claim interpretation features in a claim should typically be given their broadest technical sensible meaning (Case Law, II.A.6.3.1).

3.7 The two functional requirements indicated in point 3.6 above result from the antibodies' binding to the

epitope on CD47 as defined in claim 1 and not from their constant IgG regions (patent, paragraphs [0261], [0271], [0272] and decision under appeal, point 15.7). In other words, the binding of an antibody to the claimed epitope must be such as to fulfil the two other properties mentioned. This is uncontested and depends on the antibody's orientation on CD47 when bound to the claimed epitope (patent, paragraph [00284] and Figure 11C). Antibody 2A1 or its chimeric variant 2A1-xi are exemplary antibodies that bind to this epitope in the required orientation (patent, page 23, Table 1, paragraph [0255] and page 49, lines 14 to 16).

3.8 As regards the claimed property of the antibodies of not causing a significant level of cell agglutination, the patent discloses in Examples 4 and 5 (e.g. paragraphs [0248] to [0250], [0255] and [0257] and Figures 4A to 4E) that antibodies 2A1 and 2A1-xi do not agglutinate CD47-expressing cells at all concentrations tested, contrary to various prior art SIRPα-blocking CD47 antibodies including document D1's antibody B6H12.

3.9 The non-cell agglutinating property of the 2A1 antibody and its derivatives is thus absolute under the conditions tested. However, as indicated in points 3.1, 3.3 and 3.4 above, claim 1 is neither limited to 2A1 (and its derivatives) nor to the specific epitope, but comprises a pool of antibodies binding to discontinuous epitopes that include the residues as claimed at the specified positions. The expression "*not cause a significant level*" in claim 1 has no defined boundaries.

3.9.1 The appellant submitted that due to this expression, claim 1 encompassed antibodies that agglutinated cell at a low but detectable level.

3.9.2 The board agrees with the appellant only insofar as the feature "*not cause a significant level*" in claim 1 does not exclude cell agglutination in an absolute manner. The skilled person in the art, however, would construe said expression in the context of the claimed invention that cell agglutination mediated by the antibodies is such that it is biologically not relevant.

3.10 As regards the claimed antibodies' property in preventing *"CD47 from interacting*" with SIRPα, the patent discloses in Example 3 in conjunction with Figures 3A and 3B that the exemplary antibody 2A1 prevents the interaction between CD47 and SIRPα in a concentration-dependent manner. Paragraph [0073] of the patent discloses further that the CD47 antibodies of the invention block CD47/SIRPα interaction in a range from "*at least 40%*" to "*at least 99%*". Thus in the absence of further limitations in claim 1, all CD47 antibodies preventing at least to some degree SIRPα/ CD47 interactions comply with this functional property.

3.11 SIRPα is the ligand of CD47 (patent, paragraph [0017]). Antibodies blocking SIRPα's binding to CD47 promote phagocytosis of CD47-expressing cells mediated by macrophages which has a beneficial anti-tumour effect (patent, paragraphs [0057], [0059], [0073] and [0276]).

3.12 Lastly, since the cells indicated in claim 1 are not further specified, all cells expressing human CD47 on their surfaces fall within the claimed scope.

Sufficiency of disclosure

Admittance of a new line of argument under sufficiency of disclosure

4. The respondent requested not to admit/consider in the appeal proceedings an alleged new line of argument of the appellant related "*to a lack of information on a suitable immunogen*".

5. The board admitted this line of argument into in the appeal proceedings (Article 12(4) RPBA). In view of the proceeding's outcome, there is no need for the board to provide reasons for arriving at its decision.

Substantive matters

6. Article 83 EPC requires the patent application to disclose the claimed invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. With respect to the invention as defined in claim 1, this means that the skilled person must be able to prepare substantially all monoclonal antibodies/fragments falling within the claimed scope without undue burden.

7. As set out above (see points 3 and 3.7 to 3.9), an antibody/fragment of claim 1 is defined by three functional features, namely its binding to a defined discontinuous epitope on human CD47, its prevention of SIRPα/CD47 interaction and in that it does not cause a significant level of cell agglutination.

8. In a first line of argument, the appellant in essence argued that the antibody as defined in claim 1 was insufficiently disclosed in the patent application as a matter of principle because this required a *de novo* generation of further CD47 antibodies by a process that was based on chance (T 657/10, Reasons 12.2).

8.1 The relevant issue is whether or not the skilled person based on the teaching of the patent application taking common general knowledge into account is able to find further antibodies with the claimed functional properties across substantially the whole breadth of the claim in a reliable manner with a reasonable amount of trial and error.

8.2 However, as long as the generation of these further CD47 antibodies requires nothing but routine work that may be tedious and time consuming, the method of generating these antibodies cannot be regarded *per se* as being based on undue burden (T 431/96, Reasons 6).

9. In a further line of argument, the appellant submitted that neither the antigen nor the assays disclosed in the patent application allowed the skilled person to reliably obtain further antibodies falling within the scope of claim 1 without undue burden.

9.1 The board does not agree either. The patent application describes a complete process for generating the CD47 antibody 2A1 including its functional characterisation. It is uncontested that antibody 2A1 and its derivatives have the functional properties set out in claim 1. The processes in Examples 1 to 5 of the patent application describe the antigen used for immunisation ("*CD47-IgV*", i.e. the immunoglobulin-like variable-type domain being the extracellular domain (ECD) of CD47 (patent application, paragraphs [00231] and [00270])), as well as the assays relied on for screening and selecting SIRPα-blocking and non-cell agglutinating CD47 antibodies. In addition, Example 11 of the patent application mentions that X-ray crystallography ("XRC") was used for determining the epitope structure on CD47 bound by the chimeric antibody 2A1-xi and discloses the

epitope's structural information (see also Figure 11C). In addition, the patent application teaches that a cross-competitive binding assay may be used to test the candidate antibodies for their binding to 2A1's epitope on CD47 (paragraphs [00116] and [00117]).

9.2 Furthermore, the patent application provides the skilled person with the sequence information of the six CDRs of the 2A1 antibody and of various derivatives thereof including their full variable light and heavy chain sequences (Table 1 on pages 32 and 33, paragraphs [00111] and [00112]). Antibodies with these sequences fulfil the functional properties indicated in claim 1. It is also uncontested that varying these sequences and obtaining further antibodies are routine and hence impose no undue burden on the person skilled in the art. Thus, in agreement with the appealed decision (point 14.1 of the Reasons), the board considers that the skilled person in following this route routinely arrives at further antibodies with the functional properties of claim 1.

9.3 In summary, the patent application provides the skilled person with the antigen, the epitope, the assays needed for selecting antibodies with the claimed properties and for assessing the antibodies' binding to the claimed epitope. Moreover, structural information of several exemplary antibodies is provided.

9.4 The appellant nevertheless contested that this information in the patent application sufficed for obtaining without undue burden substantially all antibodies encompassed by claim 1. Instead the skilled person was left with a *de novo* generation of antibodies based on a random immunisation process using CD47-IgV

as antigen which elicited many antibodies, not only those with the claimed properties.

9.5 The board agrees with the appellant insofar as the process of immunising an animal with the CD47-IgV antigen disclosed in Example 1 of the patent application for generating further CD47 antibodies is based on chance. As a result of this immunisation the skilled person obtains an antibody pool which binds to epitopes (linear and discontinuous) anywhere on the surface of the CD47 antigen.

9.6 There are, however, no indications available to the board that the CD47-IgV antigen or the discontinuous epitope on CD47 as defined in claim 1 are uncommon in the sense that the generation of further antibodies against them requires specific conditions or circumstances. This has also not been argued. In the absence of evidence to the contrary, the claimed epitope thus represents a standard epitope on a standard antigen. The disclosure in the patent application of solely one antibody (2A1) and its derivatives as such is no evidence that the generation of 2A1 was based on chance. The appellant's submission in this regard is not based on verifiable facts and hence not persuasive. No reasons are apparent why the skilled person by merely repeating the immunisation protocol of Example 1 as described in the patent application would not reliably arrive at further antibodies that bind to the claimed epitope.

9.7 In these circumstances the issue to be assessed is whether the skilled person based on the patent application's teaching taking common general knowledge into account can reliably and without inventive skill find those antibodies in the pool of generated CD47

antibodies that show the functional properties indicated in claim 1.

9.8 Examples 3 to 5 of the patent application disclose two independent screening assays. In a first assay (Example 3) antibody candidates of the generated pool are selected for their SIRPα-blocking activity. This selection reduces the number of originally generated antibodies to a first sub-pool wherein all antibodies have SIRPα-blocking activity. These antibodies are then screened in a second assay (Examples 4 and 5) for eliminating those antibodies that induce cell agglutination. The finally obtained second sub-pool consists of antibodies which show SIRPα-blocking and non-cell agglutination properties. Since the 2A1 antibody is available, the skilled person would use 2A1 as control in both assays and, in applying standard conditions, would select those candidate antibodies that have comparable properties with 2A1.

9.9 It is credible that the skilled person thereby arrives at a relatively low number of candidate antibodies. Reasons for that are the statement in the patent application that 2A1's observed lack of cell agglutination is "*rare amongst the CD47 antibodies examined*" and that 2A1 "*was the only antibody in Figure 4B with absent or reduced hemagglutinating activities*" (paragraph [00242]).

9.10 As indicated above, the patent application (paragraphs [00116] and [00117]) further teaches the use of a cross-blocking assay for testing the previously selected candidate antibodies (i.e. that block SIRPα-binding and do not agglutinate cells) for their binding to the same or similar epitope as that of 2A1. This

provides an indication whether or not the candidates bind to the epitope defined in claim 1.

9.10.1 The appellant submitted that such a cross-blocking assay was of no help since it sufficed for cross-blocking that the candidate antibody bound to a few of the CD47 residues identified in claim 1 but not necessarily to all of them.

9.10.2 The board agrees with the appellant insofar only as that indeed a few overlapping residues between the epitope recognised by a candidate antibody and the claimed epitope may suffice that this antibody competes with 2A1 for binding to CD47, i.e. shows a cross-blocking behaviour. However, as indicated above (point 9.10), the cross-blocking studies are carried out with pre-selected antibodies and not with all antibodies obtained after immunisation. As set out above too (points 3.7 and 9.9), SIRPα-blocking and lack of cell agglutination are rare among CD47 antibodies and caused by their binding to the claimed epitope. This rareness has the effect that candidate antibodies competing with 2A1 for the binding to the claimed epitope have a high "*likelihood*" (patent application, paragraph [00117]) that they bind to the claimed epitope as well. It belongs further to the skilled person's common general knowledge to select conditions in the cross-competitive assay that are sufficiently stringent for ensuring that an antibody binds to the same or very similar epitope of 2A1.

10. In a further line of argument the appellant submitted that the necessary generation of protein crystals of CD47 complexed with an antibody for confirming the epitope structure as defined in claim 1 imposed an additional undue burden on the skilled person. This was

so because the patent application was silent on how these protein crystals were generated, the general unpredictability associated with protein crystallisation, the high number of protein crystals needed and the observed repeated failure of obtaining these crystals in post-published documents (D2, D4 and D27).

11. The board does not agree.

11.1 As regards the lack of information in the patent application about crystallising CD47-antibody complexes, the following is relevant.

11.1.1 While indeed Example 11 of the patent application is silent on the conditions used for crystallising CD47-IgV complexed with the Fv parts of antibodies B6H12 and 2A1, Example 11 mentions "*Hatherley et al. [...]*" (paragraph [00270]), i.e. document D31 in these proceedings.

11.1.2 Document D31 discloses the crystallisation of CD47 complexed with its ligand SIRPα. This ligand contains immunoglobulin superfamily (IgSF) domains which are likewise present in antibodies (abstract and Figure 1 including its legend).

11.1.3 In the absence of further information in the patent application about the conditions used for crystallising the CD47-IgV / antibody complex, the skilled person would have consulted document D31 mentioned in Example 11 to study the experimental conditions disclosed therein.

11.1.4 Firstly, it belongs to the skilled person's common general knowledge that protein crystals of receptor/

antibody complexes have been generated before the filing date of the patent application (document D7, page 149, left column, second paragraph), i.e. conditions for successfully crystallising complexes of receptor / antibodies were generally known in the art irrespective of the size of the complex. Secondly, SIRPα contains IgSF domains (see point 11.1.2 above) and, hence, is structurally related to antibodies.

11.1.5 Thirdly document D31 is cited in post-published documents D2 and D4 too which report on the successful crystallisation of various CD47 / antibody complexes (document D2, abstract and page 3, right column, first paragraph: "*(PDB code 2JJS;[25])*"; document D4, abstract and page 2612, right column, last paragraph: "*Notably, the Hu5F9-G4 diabody/CD47-ECD complex bears a striking resemblance to that of SIRPα in complex with CD47 (21)*". References "*25*" and "*21*" in documents D2 and D4, respectively refer to document D31 in these proceedings. This is a further indication that the skilled person would have consulted document D31 when reading Example 11 of the patent application.

11.1.6 Thus and contrary to the appellant's assertion, the skilled person would not have been deterred from consulting document D31 because the patent application did not indicate this document as reference for crystallisation, or because document D31 disclosed conditions for crystallising CD47 complexed with its ligand SIRPα only. Also it is irrelevant that SIRPα has a lower molecular weight than a Fv part of an antibody.

11.2 As regards the unpredictability of generating protein crystals, the appellant pointed, for example, to the statement in document D7 that in the context of epitope characterisation in a "*antigen:antibody complex*" XRC is

a "*sophisticated, tedious, demanding and rather capricious*" method (see paragraph bridging pages 148 and 149). However, this passage of document D7 likewise mentions that XRC is the "*gold standard*" for characterising an epitope (also confirmed in document D6, page 78, first paragraph), i.e. XRC is the standard tool for characterising epitopes and belongs to the skilled person's common general knowledge. In the year 2007, i.e. about 5 years before the priority date of the patent application, document D7 mentions that "*only some 70 unique co-crystals*" of antigen-antibody complexes had been generated and their structure resolved. In this context document D7 states that this number (i.e. 70) is an indication of the "*exceptionally low over-all efficiency of this technique*" (page 149, left column, second paragraph). However this statement is no proof that the skilled person faces an undue burden in preparing protein crystals but instead demonstrates that the method works, albeit with low efficiency. If at all this statement in document D7 indicates to the skilled person that crystallisation of proteins is less suitable for applications requiring high numbers of protein crystals as, for example, in high-throughput screening assays.

11.3 As regards the asserted need for high numbers of protein crystals, as indicated above, the screening of antibody candidates is primarily done by the assays described in Examples 3 to 5 of the patent application in conjunction with a standard cross-blocking assay. There is thus no need in the present case for high crystals numbers to run high-throughput screening assays but for a low number only to confirm the epitope structure on CD47.

12. As regards the appellant's further argument that documents D2, D4 and D27 provide evidence that protein crystals of CD47-antibody complexes could not be generated under all conditions, the board considers that these documents do not show a failure in producing protein crystals. On the contrary, documents D2 and D4 disclose the successful preparation of protein crystals of CD47 / antibody complexes and respective structural data (document D2, Figure 1, supplementary information, page 4, last paragraph to page 5, third paragraph; document D4, page 2612, right column, second paragraph). Nor do documents D2 and D4 provide evidence that the solving of certain technical issues required more than common general knowledge of the skilled person. Document D31, for example, already discloses the recombinant expression of non-glycosylated proteins for facilitating protein crystallisation (e.g. page 267, left column, last paragraph). Document D27 is irrelevant for the present case since it discloses a failure in crystallising an unrelated antigen-antibody complex (PD-L1 and its antibody, page 5, right column, fourth paragraph).

13. The fact situation underlying the present case differs thus fundamentally from that in decision T 435/20 where the patent in suit neither disclosed a suitable antigen for raising antibodies nor appropriate screening assays for selecting antibodies that specifically bound to the claimed epitope. Such screening assays were also not known from the prior art (Reasons 30, 31, 34, 43 to 49). This decision cannot therefore support the appellant's case.

14. The same applies to decision T 1466/05 where the patent application did not provide a clear and complete teaching of a screening process that led necessarily

and directly with a reasonable amount of trial and error toward the specific selection of the antibodies claimed (Reasons 19 and 25). Nor did the patent application provide any details on how the claimed antibody was prepared or gave any guidance concerning the preparation of further antibodies. For the reasons indicated above, this does not apply to the present case. These reasons apply also to decision T 657/10. These decisions cannot therefore support the appellant's case either.

15. In view of the considerations above, it is credible that the skilled person by applying the teaching of the patent application and taking common general knowledge into account would arrive without undue burden at further antibodies falling within the scope of claim 1. These considerations apply likewise to the subject-matter of claims 8 and 9 which refer back to the antibody of claim 1 and for which no specific objections have been raised by the appellant.

16. Auxiliary request 1 complies therefore with the requirements of Article 83 EPC.

Inventive step

Admittance of a new line of argument under inventive step

17. The respondent requested not to admit/consider in the appeal proceedings an allegedly new line of argument of the appellant relying on the MABL antibodies disclosed in document D13 as closest prior art. The board admitted this line of argument in the present appeal proceedings (Article 12(4) RPBA). In view of the proceeding's outcome, there is no need for the board to provide reasons for arriving at its decision.

Substantive issues - claim 1

18. The parties agreed that either document D1 or D13 represented the closest prior art for the antibody defined in claim 1.

19. It is uncontested that the claimed antibody differs from the antibodies in documents D1 and D13 at least in that it binds the specific discontinuous epitope of CD47 comprising the indicated 14 amino acid residues.

20. It is contested, however, whether or not this difference is associated with a technical effect which exceeds the mere provision of antibodies against a further (arbitrary) epitope on a known antigen (CD47).

21. Claim 1 encompasses as embodiments full-length CD47 antibodies or immunological fragments thereof, for example, Fab or scFv (see point 3.5 above).

Document D1 as closest prior art

22. Document D1 discloses *inter alia* the CD47 antibodies B6H12 and 5F9 (paragraphs [0017] and [0022]) including functional fragments thereof (paragraph [0043]). The B6H12 antibody is "*known to block the interaction between CD47 and SIRPα*" (paragraph [0097]). The same property can be implied for antibody 5F9, since the consequence of antibodies blocking the interaction between CD47 and SIRPα is that they "*induce phagocytosis*" (paragraph [0108]).

22.1 Document D1 is silent on the epitope structure recognised by antibodies B6H12 and 5F9 on CD47 including any information about the cell agglutinating

properties of these two antibodies. The appellant argued that B6H12 had either no cell agglutination activity (as shown in post-published documents, see below) or if the antibody had this property than this required the presence of both epitope / antigen binding sites. The appellant has never argued that the full-length antibody 5F9 lacked a hemagglutinating activity. This property was only asserted for the 5F9 Fab fragment or a BsAb containing one antigen binding site of 5F9. It is thus uncontested that the full-length 5F9 antibody has hemagglutinating activity.

22.2 Document D1 mentions BsAbs either in general (paragraph [0031]), or in the context of B6H12 (paragraph [00102]). The appellant argued that, since BsAbs contained only one of B6H12 or 5F9's two antigen binding sites and a second site with a further undefined antigen binding specificity, BsAbs of B6H12 and 5F9 were incapable of agglutinating cells. The board does not agree. Evidence that B6H12 or 5F9 BsAbs do not agglutinate cells is neither disclosed in document D1 nor in any of the other available prior art documents. Nor is it credible that B6H12 or 5F9 BsAbs in general do not agglutinate cells. On the contrary, BsAbs contain two different antigen binding sites and thereby cross-link, i.e. agglutinate cells that carry these two antigens on their surface either on the same or on different cells.

Full-length antibody embodiment of claim 1

22.3 The patent (Figures 4A to 4E) discloses for the isolated 2A1 and B6H12 antibodies experimental data which compare the antibodies' hemagglutination activities under identical conditions. In this context paragraph [0248] of the patent states that "*the 2A1*

antibody of the present invention was the only SIRPα blocking antibody that did not promote homotypic interactions of CD47 expressing cells" (emphasis added). Although the antibodies falling within the scope of claim 1 are not limited to 2A1, it is uncontested that any antibody binding to the claimed epitope has a non-significant cell agglutinating and a SIRPα-blocking activity (see point 3.7 above).

22.4 The appellant submitted that the post-published documents D2, D25 and D26 showed that antibody B6H12 had no hemagglutinating activity. The board does not agree. While it is true that the pictures taken from serial dilutions disclosed in Supplementary Figure 1 of document D2 and Figure 2C of document D25 do not show hemagglutination under the conditions applied, this is no proof for a non-(significant) hemagglutinating activity of B6H12. The dilution assay disclosed in these documents, for example, may simply not be sensitive enough. That sensitivity of the dilution assay in documents D2 and D25 might be an issue is, for example, evident from assays based on fluorescence labelled antibodies (Figure 2D of document D25 and Figure 5C of document D26). These latter assays disclose that B6H12 has a detectable and significant hemagglutinating activity which is consistent with the data disclosed in Figures 4A to 4E of the patent.

22.5 In light of these considerations, the board is convinced that all antibody embodiments falling within the scope of claim 1 show less cell agglutination compared to the full-length monospecific and bispecific B6H12 and 5F9 antibodies of document D1.

22.6 Compared to the full-length B6H12 and 5F9 antibodies of document D1, the objective technical problem to be

solved resides thus in the provision of an improved CD47 antibody.

22.7 In view of the experimental data disclosed in Figures 4A to 4E of the patent, the board is satisfied that this problem has been solved by all embodiments encompassed by claim 1.

Obviousness

22.8 Document D1 provides no pointers for the skilled person to select the epitope on CD47 as defined in claim 1 for solving the technical problem formulated above. Thus the claimed antibodies are based on an inventive step over the disclosure of the full-length monospecific and bispecific B6H12 and 5F9 antibodies of document D1.

Document D13 as closest prior art

23. In a second line of argument, the appellant selected the MABL anti-CD47 scFv monomers and dimers in document D13 as closest prior art. ScFv monomers and dimers are embodiments of claim 1 (see point 21 above).

23.1 Document D13 discloses that full-length MABL antibodies have a hemagglutinating activity (e.g. column 23, Table 2), i.e. the same activity as the full-length B6H12 and 5F9 antibodies of document D1 (see above). It is uncontested that the scFv monomers and dimers of these MABL antibodies lack hemagglutinating activity.

23.2 The board agrees with the appellant that since the MABL scFvs of document D13 show no hemagglutinating activity, the epitope as defined in claim 1 as sole distinguishing feature is not associated with an advantageous technical effect. Consequently, the

technical problem to be solved resides in the provision of an alternative CD47 antibody or immunologically active fragment thereof.

23.3 The board is satisfied that the antibodies as defined in claim 1 solve this technical problem.

Obviousness

24. The appellant submitted that since CD47 as antigen was known, the selection of the claimed epitope was arbitrary since this epitope was not associated with any technical effect except for being recognised by a CD47 antibody. Consequently, the claimed epitope was the sole distinguishing feature and, hence, the antibodies of claim 1 were obvious over any other prior art CD47 antibody being directed against any other CD47 epitope, for example, the MABL scFvs. The claimed antibodies lacked thus an inventive step.

24.1 Since the argument of the appellant is solely based on the asserted arbitrariness of the claimed epitope, it has to be assessed whether or not this is correct.

24.2 As set out above (see point 22.3), the epitope defined in claim 1 imposes on the antibodies binding thereto certain functional properties, namely SIRPα-blocking and non-significant cell agglutination. This is absolute in the sense that this applies for all CD47 antibodies encompassed by claim 1, i.e. full-length or fragment, for example, Fab and scFv and thus irrespective of the antibodies' format. Contrary thereto, document D13 discloses that the epitope bound by the MABL antibodies imposes different functional properties on these antibodies depending on their

format: full-length MABL antibodies agglutinate cells, while scFvs do not (see point 23.1 above).

24.3 Consequently, the epitope on CD47 bound by the MABL antibodies in document D13 (the same applies for the epitope recognised by the B6H12 and 5F9 antibodies of document D1) restricts their non-hemagglutinating properties to a scFv format. No such restrictions apply to the claimed CD47 antibodies. This is uncontested. Since the epitope of claim 1 allows the skilled person thus a free choice as regards the CD47 antibody format for any intended application, the claimed epitope is associated with a technical effect in addition to being merely recognised by a CD47 antibody. Contrary to the appellant's view, the selection of the claimed epitope is therefore not arbitrary.

25. Moreover, since document D13 does not point the skilled person to the claimed epitope for removing any potential restrictions as regards the format of the antibody, the skilled person would not arrive in an obvious manner at this epitope in light of the teaching of document D13 either.

26. The same arguments set out above for the MABL scFvs apply for the scFv and Fab fragments of B6H12 and 5F9 mentioned in document D1 (paragraph [0037]).

27. The antibodies as defined in claim 1 are thus inventive over the teaching of documents D1 and D13. The same applies to the subject-matter of claims 8 and 9 which refer back to the antibody of claim 1.

28. Auxiliary request 1 complies with the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

C. Rodríguez Rodríguez T. Sommerfeld

Decision electronically authenticated