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Datasheet for the decision of 27 June 2024

Case Number: T 1731/22 - 3.3.04

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Title of invention:
Antibodies and vaccines for use in therapeutic and diagnostic methods for alpha-synuclein-related disorders

Patent Proprietor:
BioArctic AB

Opponents:
James Poole Limited
UCB Biopharma SRL
CARPMAELS & RANSFORD (SPECIALITIES) LLP

Headword:
Alpha-synuclein oligomer antibodies/BIOARCTIC

Relevant legal provisions:
EPC Art. 54, 56, 84

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Keyword:
Novelty - main request, auxiliary request 2 (no)
Claims - clarity - auxiliary requests 4 to 7, 12 to 15, 20 to 23 (no)
Inventive step - auxiliary requests 1, 3, 8 to 11, 16 to 19 (no)

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Case Number: T 1731/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 27 June 2024

Appellant: (Patent Proprietor)	BioArctic AB Warfvinges väg 35 112 51 Stockholm (SE)
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Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 3 May 2022 revoking European patent No. 2 282 758 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	B. Rutz
	A. Bacchin

Summary of Facts and Submissions

I. The appeal by the patent proprietor (appellant) lies from the decision of the opposition division to revoke European patent No. EP 2 282 758, which is based upon European patent application No. 09 738 534.8, published under the PCT as international application WO 2009/133521.

II. The patent had been opposed on the grounds of Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and of Article 100(b) and (c) EPC.

III. With regard to the main request (filed on 8 October 2020), the opposition division decided that the subject-matter of its claim 9 was not novel over the disclosure of document D66 (Article 54 EPC).

With regard to auxiliary request 1, the opposition division decided that the subject-matter of independent claims 1 (medicament for use), 8 (antibody), 10 (method of detecting) and 11 (method of producing) lacked inventive step over the disclosure of documents D39 or D66 combined with the disclosure of documents D19 or D47 (Article 56 EPC).

The same reasoning applied to auxiliary requests 2, 3 and 8 to 23. Claim 1 of auxiliary requests 4 to 7 was found to be unclear (Article 84 EPC).

IV. With its statement of grounds of appeal, the appellant refiled the main request and auxiliary requests 1 to 23 dealt with in the decision under appeal.

V. Opponent 1 (respondent I) replied to the appeal and filed documents D76 to D78: these correspond to its notice of opposition and further written submissions made during the opposition proceedings. Opponents 2 and 3 (respondents II and III) did not make any written submissions in appeal.

VI. The appellant replied to the submission by respondent I and filed document D79.

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

VIII. In that communication, the board indicated, *inter alia,* that it preliminarily found the subject-matter of claim 9 of the main request and claim 8 of auxiliary requests 1 and 2 to lack novelty over the disclosure of document D66. The question of inventive step of the antibody claimed in claim 8 of auxiliary request 1 starting from document D66 in combination with either document D19 or document D47 might also have to be considered at the oral proceedings. The antibodies claimed in auxiliary requests 3 and 8 to 23 lacked either novelty or inventive step over document D66 alone or in combination with documents D19 or D47. The board preliminarily agreed with the decision under appeal that the claims of auxiliary requests 4 to 7 lacked clarity.

IX. Claim 9 of the main request and claim 8 of auxiliary request 2 read as follows (underlining by the board):

"9. A monoclonal antibody, capable of binding a stabilized soluble α-synuclein oligomer, the stabilized

soluble α-synuclein oligomer having a lower formation rate to a non-soluble aggregated form than a non-stabilized soluble oligomer of the α-synuclein, wherein the antibody is produced from the stabilized soluble α-synuclein oligomer, wherein the stabilized soluble α-synuclein oligomer comprises α-synuclein of a sequence selected from SEQ ID NOs: 1-8, wherein the stabilized soluble α-synuclein oligomer is stabilized by cross-linking with a protein cross-linking agent or by binding to a stabilizing agent, and wherein the antibody has higher binding strength to soluble α-synuclein oligomers as compared with binding strength to α-synuclein monomers and insoluble fibrils."

Claim 8 of auxiliary request 1 and claim 7 of auxiliary request 3 differ from claim 9 of the main request in that the underlined text above is replaced by the following text:
"4-hydroxy-2-nonenal and/or 4-oxo-2-nonenal," (HNE and/or ONE)

The corresponding claims of auxiliary requests 4 to 7, 11 to 15 and 20 to 23 contain the following amendment compared with the main request:
"and wherein the antibody has binding strength (IC_{50}) for α-synuclein protofibrils compared to α-synuclein monomers in the range of 1:50-2000"

Compared with the claim set of the main request, in the claim set of auxiliary requests 8 to 23 the claims directed to "a monoclonal antibody" and to "a method of detecting soluble α-synuclein oligomers in vitro" have been deleted. These requests therefore contain only claims limited to "a medicament for use in the treatment of an α-synuclein-related disorder" and to "a

method of producing a monoclonal antibody" (for exact wording, see electronic file).

Auxiliary requests 16 to 23 contain only a single claim directed to a "method of producing a monoclonal antibody".

Claim 1 of auxiliary request 16 reads:

"1. A method of producing a monoclonal antibody for treatment of an α-synuclein-related disorder in an individual, wherein the α-synuclein-related disorder is selected from the group consisting of Parkinson's disease, dementia with Lewy bodies and/or Lewy neurites, Multiple Systemic Atrophy (MSA), and other diseases with Lewy body pathology, and wherein the antibody or fragment thereof binds a stabilized soluble α-synuclein oligomer, the stabilized soluble α-synuclein oligomer having a lower formation rate to a non-soluble aggregated form than a non-stabilized soluble oligomer of the α-synuclein, the method comprising administering an antigen to a non-human animal; and collecting antibody formed against the antigen, the antigen comprising a stabilized soluble α-synuclein oligomer having a lower formation rate to a non-soluble aggregated form than a non-stabilized soluble oligomer of the α-synuclein, wherein the α-synuclein oligomer comprises α-synuclein of a sequence selected from SEQ ID NOs: 1-8, wherein the stabilized soluble α-synuclein oligomer is stabilized by cross-linking with a protein cross-linking agent or by binding to a stabilizing agent, and wherein the antibody has higher binding strength to soluble α-synuclein oligomers as compared with binding strength to α-synuclein monomers and insoluble fibrils."

X. At the end of the oral proceedings in the presence of the appellant and respondents I and III, the chairwoman announced the board's decision.

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

D19 T. Näsström et al., "*The lipid peroxidation metabolite 4-oxo-2-nonenal cross-links α-synuclein causing rapid formation of stable oligomers*", Biochemical and Biophysical Research Communications 378, 2009, 872-6

D47 Z. Qin et al., "*Effect of 4-Hydroxy-2-nonenal Modification on α-Synuclein Aggregation*", Journal of Biological Chemistry 282(8), 2007, 5862-70

D66 S. Emadi et al., "*Isolation of a human single chain antibody fragment against oligomeric α-synuclein that inhibits aggregation and prevents α-synuclein induced toxicity*", Journal of Molecular Biology, 368(4), 2007, 1132-44

D69 T. Wahlberg et al., "*DEVELOPMENT OF OLIGOMER-SPECIFIC ALPHA-SYNUCLEIN ANTIBODIES*", Alzheimer’s & Dementia 4(4), 2008, Supplement, T481-T482, P2-372

XII. The appellant's submissions are summarised as follows:

Main request - claim 9, auxiliary request 2 - claim 8
Novelty (Article 54 EPC)

Following the teaching of document D66, the skilled person would not inevitably end up obtaining a single chain variable fragment (scFv) named "*D5*" or an

antibody which specifically bound to oligomeric α-synuclein. The mere possibility that the skilled person could produce an antibody that bound oligomeric α-synuclein following the teaching of document D66 was not detrimental to novelty of the claimed antibody. There was also no evidence that D5 scFv, or any scFv obtained with the method disclosed in D66, would have all the properties of the antibody claimed. In particular, there was no evidence of binding to a stabilised α-synuclein that was stabilised by a cross-linking or stabilising agent, and that had a lower formation rate to an aggregated form. In particular, the skilled person would not consider the deposit of phage scFvs that were already bound to the α-synuclein antigen onto a mica surface for imaging to be a test of whether the scFv was capable of binding to a stabilised antigen. In addition, the skilled person would not consider the mica surface to be a stabilising agent or a protein cross-linking agent.

Auxiliary requests 1, 3, 8 to 11
Inventive step (Article 56 EPC)

Document D66 described the selection of an scFv from a library using α-synuclein oligomers and monomers, whereas the currently claimed invention related to antibodies produced from and which bound to α-synuclein oligomers which were stabilised by cross-linking with HNE or ONE and which had a lower formation rate to a non-soluble aggregated form than a non-stabilised soluble oligomer of the α-synuclein. The technical effect associated with the difference was that the antibodies bound to an antigen different from the antigens reported in document D66.

The use of a stabilised soluble oligomeric α-synuclein facilitated the production of antibodies specifically against this stabilised form. Antibodies produced from the stabilised form might recognise epitopes on that stabilised oligomeric form. The objective technical problem could therefore be formulated as the provision of antibodies which bind to oligomeric α-synuclein and their uses. The solution was not obvious over document D66. The authors in document D66 used both α-synuclein oligomers and monomers to pan for antibodies in the antibody library. It was only after enrichment of scFvs that bound to the monomeric/oligomeric mixture of α-synuclein that the binding of the clones identified to monomeric, oligomeric and fibrillar forms of α-synuclein using an ELISA was tested. The oligomeric form was not stabilised.

There was no suggestion in document D66 to stabilise the oligomeric forms of α-synuclein and then to use these as antigens to produce antibodies. Documents D19 and D47 disclosed soluble, stabilised α-synuclein oligomers. D19 investigated the effects of ONE on α-synuclein, examining the structural implications of ONE modification in particular. D47 examined the effects of HNE on α-synuclein. These documents did not, however, suggest using the stabilised oligomers as a target for therapy, let alone using them as an antigen to produce antibodies. Because there was nothing in document D66 to suggest stabilising the antigen, the skilled person would have no prompt or reason to look at these documents. Nor did D19 or D47 themselves suggest using the stabilised oligomers as an antigen to produce antibodies, or as a target for antibodies. The fact that methods of stabilising α-synuclein oligomers were known did not provide the skilled person with any

motivation to apply those methods in the context of the panning in document D66.

Auxiliary requests 4 to 7, 12 to 15, 20 to 23
Clarity (Article 84 EPC)

The claim did not recite a specific IC_{50} value, but specified a ratio of IC_{50} values. The fact that a different specific IC_{50} value might be determined using different assays did not result in a lack of clarity because it was the ratio of IC_{50} values that was defined in the claim. The skilled person would use the same measurement method to determine the IC_{50} value of both protofibrils and monomers. The exact measurement method was not important, as a consistent ratio of IC_{50} values would be obtained. There was no ambiguity arising in the subject-matter for which protection was sought. The requirements of Article 84 EPC were met.

Auxiliary requests 16 to 19
Inventive step (Article 56 EPC)

The claim was directed to a method of producing a monoclonal antibody for treating an α-synuclein-related disorder. In document D69, the authors set out to make antibodies that were specific to oligomeric α-synuclein as study tools (see Background, lines 6 to 7). The poster reported immunising mice with "*preparations of oligomeric recombinant α-syn*" (see Methods, first line), without giving further details of those preparations. In the results section, the authors reported that "[o]*ngoing subcloning aims at further isolating IgG-positive clones with a high degree of α-syn oligomer specificity*" (see Results, last sentence).

Document D69 discussed a programme to develop oligomer-specific antibodies as tools for studies by immunising mice with preparations of recombinant α-synuclein, while the claim was directed to a method of producing antibodies for treatment of α-synuclein-related disorders, involving administering a soluble α-synuclein oligomer that was stabilised by cross-linking with HNE or ONE. The technical effect associated with this difference was the generation of antibodies that bound to the stabilised soluble α-synuclein and that reliably exhibited preferential binding to an oligomeric form of α-synuclein.

The technical problem could be formulated as the provision of a method for producing antibodies which had a higher binding strength to the soluble oligomeric form of α-synuclein. The solution, involving immunisation with soluble oligomeric α-synuclein stabilised by cross-linking or by binding to a stabilising agent, was not obvious.

There was no suggestion in document D69 to modify or stabilise the antigen as required by the claim. The skilled person would be wary of modifying the antigen in an immunisation protocol, for example by stabilisation, in case the antibodies raised against the stabilised antigen were not able to bind to α-synuclein oligomers that were not modified or stabilised.

There was therefore nothing to motivate the skilled person to look at documents that related to the effects of ONE/HNE on α-synuclein (D47 or D19) when seeking to provide a method of producing antibodies which had a higher binding strength to the soluble oligomeric form of α-synuclein.

XIII. Respondent I and III's submissions are summarised as follows:

Main request - claim 9, auxiliary request 2 - claim 8
Novelty (Article 54 EPC)

Document D66 disclosed how to obtain the D5 scFv from publicly available phage libraries. The Tomlinson I and J antibody libraries that were panned to identify the D5 scFv were readily available from the MRC Center for Protein Engineering (see page 6, penultimate paragraph, of document D66). Document D66 also provided detailed guidance on the biopanning protocol that was used to obtain the D5 scFv, as well as the assays that were used to confirm the oligomer selectivity of the D5 scFv. In view of these teachings, the skilled person would have been able to obtain the library that contained the D5 scFv and identify it (or an antibody with the same oligomer selectivity) within the library by repeating the same screening steps disclosed in document D66. Therefore document D66 provided an enabling disclosure of the D5 scFv or, at the very least, an antibody with the same oligomer selectivity as the D5 scFv.

Document D66 was entirely focused on antibodies having α-synuclein oligomer selectivity and the advantages presented by such antibodies. Therefore implementing the technical teaching of document D66 would indeed result in the identification of the D5 scFv (or an antibody with the same oligomer selectivity). This was because document D66 effectively instructed the skilled person to use its protocol specifically to identify an antibody that had oligomer selectivity.

The claim did not specify that stabilisation must be achieved through chemical modification. Furthermore, paragraph [0033] of the patent explained that the purpose of binding the oligomers to a "stabilizing agent" was to stabilise "*the soluble oligomeric form such that further aggregation to non-soluble fibril conformation is prevented*". This goal was achieved by the immobilisation of oligomers on mica in document D66. Accordingly, "stabilized … by binding to a stabilizing agent" encompassed the mica immobilisation used in document D66.

The claimed antibody lacked novelty over the disclosure of document D66.

Auxiliary requests 1, 3, 8 to 11
Inventive step (Article 56 EPC)

Document D66 disclosed that α-synuclein antibodies ideally bound selectively to the oligomeric form of α-synuclein. Document D66 provided an example of such an antibody, the D5 scFv, as well as a protocol for obtaining it (or a similarly oligomer-selective antibody) from publicly available phage display libraries. The skilled person would have been able to reproduce the experiments in document D66 without inventive skill. The alleged difference between the subject-matter of claim 8 of auxiliary request 1 (or the respective claims of auxiliary requests 3 and 8 to 11) and the D5 scFv was that the claimed antibody bound to an α-synuclein oligomer that had been stabilised in a different way (i.e. "by cross-linking with HNE or ONE", instead of by immobilisation on mica). There was nothing in the patent that showed that this alleged difference gave rise to any technical effect. The

absence of an affinity limitation in the claims meant that the antibodies were permitted to bind minimally to such oligomers. In the absence of a technical effect, specifying minimal binding to an oligomer that had been stabilised by cross-linking with HNE or ONE was arbitrary.

The objective technical problem could be formulated as the provision of alternative anti-α-synuclein antibodies. Inventive step could not be acknowledged for arbitrary alternative antibodies.

Auxiliary requests 4 to 7, 12 to 15, 20 to 23
Clarity (Article 84 EPC)

The opposition division correctly noted that "*IC50 values are absolutely dependent on the assay by which they are measured, and thus, they can only be compared with values obtained for other antibodies with the exact same assay*". Third parties would not be able to determine whether they were working within or outside the range specified in the claim. The patent provided no guidance on how this parameter was to be measured, leaving the skilled person to guess whether or not they were in possession of something falling within the claim scope. Further ambiguity and undue burden came from the fact that the form of α-synuclein protofibril and monomer used to determine binding strength was not specified either (e.g. wild-type and modified forms were contemplated in the patent in e.g. paragraphs [0027] to [0029]). In addition, it was not clear from the parentheses whether the reference to IC_{50} was supposed to be limiting or not.

There was no technical reason for the ratio to remain constant for all measurement methods under all

conditions, all of which were encompassed by the claims. In any event, an IC_{50} value was a half-maximal inhibitory concentration, which was not a conventional measure of "binding strength". Post-filed document D58 provided some insight with respect to how an IC_{50} could be measured in this context. However, none of that information was in the patent. In addition, this parameter had not been measured in the prior art. Therefore it would have been unclear to the skilled person reading the patent how to determine the IC_{50} ratio mentioned in the claims.

Auxiliary requests 16 to 19
Inventive step (Article 56 EPC)

Document D69 was an appropriate choice for the closest prior art because it related to a similar purpose or effect. The authors of D69 stated that: "*Our aim is to develop oligomer specific monoclonal antibodies as tools for studies on cell cultures and transgenic mice with α-syn pathology. Such antibodies might be useful for diagnostic purposes and for immunotherapy of DLB and PD*". D69 described administering α-synuclein oligomers to a non-human animal and collecting the oligomer-specific antibodies. D69 did not disclose that the oligomers had been stabilised. However, there was nothing in the patent that showed that this difference gave rise to any technical effect. Nor was there any evidence that the claimed antibodies were produced more frequently when the oligomer immunogen had been stabilised by cross-linking. Thus there was no evidence of any improvement relative to the method disclosed in document D69 for generating oligomer-specific antibodies.

Accordingly, the objective technical problem might be formulated as the provision of an alternative method for producing α-synuclein oligomer-specific antibodies. The skilled person seeking alternative methods for producing α-synuclein oligomer-specific antibodies would have looked for documents relating to oligomers of α-synuclein. In doing so, they would have come across D19 and D47. Combining D69 with D19 or with D47 would have prompted them to arrive at an antibody in accordance with the claims.

XIV. The appellant requested that the decision under appeal be set aside and the patent be maintained based on the claims of the main request or, alternatively, on the set of claims of one of auxiliary requests 1 to 23 (all dealt with in the decision under appeal).

Respondents I and III requested that the appeal be dismissed and the decision to revoke the patent be upheld. They further requested that document D79 not be admitted into the proceedings.

Reasons for the Decision

Absence of a duly summoned party (Rule 115(2) EPC)

1. Respondent II had been duly summoned to the oral proceedings, but had indicated by letter dated 6 June 2024 that it would not be attending.

Admission of document D79 (Article 12(4)(6) RPBA)

2. Document D79 provides evidence of comparisons of the binding strengths of an antibody to different conformations of a target in a similar field to that of

the invention. The question of whether such comparisons were "unusual" at the filing date of the patent was, however, not relevant to the decision. It was therefore not necessary to decide on admission of document D79 into the proceedings.

Main request (filed on 8 October 2020) - claim 9
Novelty (Article 54 EPC)

3. Document D66 discloses a method for generating human single-chain antibody fragments against oligomeric α-synuclein that inhibits aggregation and prevents α-synuclein-induced toxicity. The patent in this regard specifies that an "*antibody may be Fab fragment* [...] *or a single chain antibody*" (see paragraph [0049]). The method of document D66 involves the use of two phage display antibody libraries with a diversity of greater than 10^8 scFvs each, the production of different α-synuclein morphologies (monomer/oligomer mixture, oligomer and fibrillar) and the panning of the phage display libraries against a mixture of monomeric/ oligomeric morphologies of α-synuclein followed by deposition of the incubated solution on freshly cleaved mica, fixation and atomic force microscopy (AFM) (see page 6, last paragraph to page 7, third paragraph). From the second and third rounds of panning, 26 and 13 clones respectively showed positive binding to monomeric/oligomeric α-synuclein in an ELISA. PCR analyses showed the presence of full-length scFvs in 11 out of the 21 clones from round 2, and 3 out of the 13 clones from round 3. Two full-length scFvs showed preferential binding for the oligomeric form of α-synuclein (see page 3, first full paragraph). An amber stop codon with a glutamine codon (CAG) in the stronger binder clone (D5 scFv) was replaced using site-directed mutagenesis. The D5 scFv specifically

recognised the oligomeric form of α-synuclein as indicated by soluble ELISA against three different α-synuclein morphologies, while no binding was observed with a non-specific control scFv (anti-phosphorylase B) (see Figure 3). This was confirmed by Western blot and Biacore X biosensor.

4. It was undisputed that document D66 discloses a method which can lead to an antibody (scFv) which meets at least the criteria of "higher binding strength to soluble α-synuclein oligomers as compared with binding strength to α-synuclein monomers and insoluble fibrils" (see Figure 3).

5. Two main questions arise:
   (a) Is the antibody produced by the method disclosed in document D66 "*capable of binding a stabilized soluble α-synuclein oligomer, the stabilized soluble α-synuclein oligomer having a lower formation rate to a non-soluble aggregated form than a non-stabilized soluble oligomer of the α-synuclein [...] wherein the stabilized soluble α-synuclein oligomer is stabilized by cross-linking with a protein cross-linking agent or by binding to a stabilizing agent*"?
   (b) Does the method disclosed in document D66 "inevitably" lead to an antibody as claimed?

6. With regard to question (a), the appellant argued that the binding of the phage α-synuclein oligomer in document D66 was performed in solution, i.e. before the complex was immobilised on the mica surface. Moreover, binding to mica was only performed for imaging purposes and not for stabilisation as required by the claim. Finally, paragraph [0033] of the patent required that the stabilisation result in a "structural modification"

of the α-synuclein oligomer, which the skilled person would understand as a chemical modification.

7. The board does not agree. The fact that the initial binding of phage and α-synuclein oligomer was performed in solution is irrelevant because document D66 also shows that the phage maintains binding to the α-synuclein oligomer after fixation on the mica surface (see AFM images in Figure 1 and Figure 5). This means that the binding is maintained when the α-synuclein oligomer is stabilised as well, i.e. the selected fragment is capable of binding to a stabilised α-synuclein oligomer.

8. The definition in paragraph [0033] of the patent is not limited to chemical modifications which are not mentioned either, but includes other structural modifications, e.g. non-chemical interactions. Moreover, paragraph [0033] requires that "[t]*he stabilizing agent stabilizes the soluble oligomeric form such that further aggregation to non-soluble fibril conformation is prevented*". This is precisely the case in document D66, where the fixation of oligomer-phage complexes prevents the interaction of the complexes with each other or with monomeric α-synuclein, thus preventing "*further aggregation to non-soluble fibril conformation*".

9. Document D66 therefore discloses binding of the antibody fragment (scFv) obtained to a stabilised α-synuclein oligomer.

10. With regard to question (b), namely whether the method disclosed in document D66 would inevitably result in an antibody as claimed, the appellant argued that for novelty it was not sufficient that a disclosed method

potentially yields a product, but that this was inevitable. Starting from a high number of phage particles in the libraries used in document D66, it was not certain that the skilled person would obtain an antibody having the features as claimed. Each of the steps required to obtain this result was fraught with uncertainties, so the end result was equally unpredictable. The possibility that the skilled person could produce an antibody that bound oligomeric α-synuclein following the teaching of document D66 was therefore not detrimental to novelty of claim 9. For example, not all the clones obtained were full-length (11 out of 21 from round 2 and 3 out of 13 from round 3). The two clones selected contained an amber stop codon which had to be removed. All this indicated that there was no direct and unambiguous disclosure of the antibody claimed.

11. The board does not agree with the appellant's arguments. Document D66 discloses all the necessary steps to arrive at an antibody (scFv) which preferentially binds α-synuclein oligomers stabilised on a mica surface (see points 6. to 8. above). The fact that there are several steps in order to arrive at the final result or that these steps select clones from a large number of initial phages in the library does not change the completeness and enablement of the disclosure. Document D66 also provides a successful result of the method, D5 scFv, which was tested and found to bind preferentially to α-synuclein oligomers. The number of panning rounds to arrive at this was low: two or three. The skilled person, even in the event of an isolated failure, would repeat the method to arrive at an antibody having the claimed features, which are the very features that document D66 aims at. The fact that not all clones were full-length or that some

clones contained stop codons cannot be seen as raising doubts as to the enablement of the disclosed method either, because it is within the routine tasks of the skilled person to check these parameters and if necessary adapt the clone accordingly by the methods also taught in document D66.

12. The subject-matter of claim 9 lacks novelty over the disclosure of document D66.

Auxiliary request 1 (filed on 8 October 2020) - claim 8
Inventive step (Article 56 EPC)

13. The parties agree on document D66 as closest prior art for the subject-matter of claim 8.

Difference, effect and objective technical problem

14. Given the inherent difficulty in deciding whether an antibody raised against an α-synuclein oligomer stabilised by HNE or ONE is different from an antibody raised according to the method of document D66, the following assumption is made, in favour of the appellant.

15. In the claim, the α-synuclein oligomer is stabilised by HNE or ONE, while in document D66 it is stabilised on a mica surface. HNE or ONE can change the three-dimensional organisation of the oligomer and/or introduce new epitopes by chemical modification of amino-acid side chains (see e.g. document D19, page 875, left-hand column, last two paragraphs, and document D47, Abstract). This leads to a different structure of the stabilised α-synuclein oligomer, which in turn can lead to the selection of different antibodies, so the method disclosed in document D66

does not inevitably lead to an antibody having all the characteristics as claimed, in particular "*binding to a stabilized soluble α-synuclein oligomer* [...] *wherein the stabilized soluble α-synuclein oligomer is stabilized by cross-linking with 4-hydroxy-2-nonenal and/or 4-oxo-2-nonenal*".

16. Therefore document D66 discloses a method which is capable of generating an scFv which "*reacts specifically with an oligomeric form and does not react with either monomeric or the fibrillar forms of α-synuclein*", but does not disclose whether this antibody is obtainable, i.e. "producible", from a stabilised soluble α-synuclein oligomer having one of the required sequences and wherein the "stabilisation" is achieved by cross-linking with HNE and/or ONE.

17. The appellant argued that the effect associated with this difference was the binding to a different antigen. The appellant, however, has not shown any evidence that antibodies against HNE- or ONE-stabilised oligomeric α-synuclein showed any particular effect, such as improved specificity, affinity, differential binding etc. Nor has the appellant argued that the antibodies claimed showed different effects when used in therapy.

18. In the absence of any evidence for an effect achieved by the above assumed difference, the objective technical problem is the provision of an antibody binding to an alternative form of a soluble oligomeric α-synuclein.

Obviousness

19. The skilled person, when starting from the method disclosed in document D66 and aiming at identifying

alternative soluble oligomeric α-synuclein targets, would consider documents D19 and D47, which disclose α-synuclein oligomers stabilised with HNE or ONE, as already apparent from their titles and abstracts.

20. Document D19 discloses that "[o]*ne of the most commonly formed aldehydes in the brain is 4-hydroxy-2-nonenal (HNE) [16], which has been demonstrated to induce oligomerization of aggregating proteins such as α-synuclein, the amyloid-β peptide, and the lambda and kappa light chains of immunoglobulins [20-22]. Recently, a similarly structured aldehyde, 4-oxo-2-nonenal (ONE) (Fig. 1) was identified and suggested to be a more potent crosslinker than HNE*" (page 872, right-hand column, first full paragraph). The "*generated α-synuclein oligomers were covalently cross-linked and not sensitive to the denaturing conditions of the SDS-PAGE analysis*" (page 875, left-hand column, last paragraph). Finally, the authors hypothesise that "*ONE may cause cytoxicity* [sic] *in the brain by cross-linking α-synuclein into the formation of stable oligomers*" (page 876, left-hand column, third full paragraph).

21. Document D47 discloses that the "*HNE modification of α-synuclein resulted in a major conformational change involving increased β-sheet*" and that "*HNE-induced oligomers were very stable with an extremely slow rate of dissociation*" (see Abstract). The authors conclude "*that HNE-modified oligomers are potentially toxic and could therefore contribute to the demise of neurons subjected to oxidative damage. In addition, it is important to note that HNE-modified α-synuclein oligomers may have different pathological effects compared with oligomers formed from unmodified α-synuclein because it is clear that both types of*

oligomers have significantly different structures and stabilities" (see page 5870, left-hand column).

22. Both documents therefore teach the skilled person how to obtain α-synuclein oligomers stabilised with HNE or ONE, that these structures are very stable and that they are likely to play a role in the pathology of Lewy body diseases. When the objective technical problem seeks an "alternative" solution, no pointer or motivation to use a particular option provided in the prior art is required. In any case, the skilled person would find such motivation in the disclosures of documents D19 and D47, which both indicate the physiological relevance of the stabilised α-synuclein oligomers and note their enhanced stability. It is part of the skilled person's common general knowledge that stable structures are advantageous for raising antibodies.

23. The skilled person would therefore have used the stabilised α-synuclein oligomers disclosed in documents D19 or D47 in the method disclosed in document D66, and would have obtained antibodies binding to these oligomers.

24. The appellant has not argued that this would pose any particular problems for the skilled person or that the HNE- or ONE-stabilised oligomers would not be suitable for the method of document D66.

25. The skilled person would therefore have arrived at the claimed antibodies in an obvious manner. The subject-matter of claim 8 lacks inventive step.

Auxiliary request 2 - claim 8
Novelty (Article 54 EPC)

26. Since claim 8 is identical to claim 9 of the main request, the same considerations with regard to novelty apply, so its subject-matter lacks novelty over the disclosure of document D66.

Auxiliary request 3 - claim 7
Inventive step (Article 56 EPC)

27. Since claim 7 is identical to claim 8 of auxiliary request 1, the same considerations with regard to inventive step apply, so its subject-matter lacks inventive step starting from document D66 as closest prior art.

Auxiliary requests 4 to 7, 12 to 15, 20 to 23
Clarity (Article 84 EPC)

28. The board agrees with the decision under appeal that the definition of the binding strength IC_{50} ratio 1:50-2000 lacks clarity. As the opposition division correctly reasoned, IC_{50} values are dependent on the assay by which they are measured, and can thus only be compared with values obtained for other antibodies with exactly the same assay. Furthermore, as argued by the respondent, there is no information in the patent on how to measure an IC_{50}, i.e. the half-maximal inhibitory concentration, to determine binding strength. The board also cannot agree with the argument by the appellant that this lack of clarity would be resolved by relying on a relative "ratio of IC_{50} values", because different measurement methods could also yield different IC_{50} ratios, leaving the skilled

person in doubt whether a given antibody fell within the terms of the claim or not.

Auxiliary requests 8 to 11
Inventive step (Article 56 EPC)

29. The same considerations with regard to inventive step as for auxiliary request 1 apply because document D66 discloses the link between Lewy body diseases and α-synuclein oligomers:

> "*Aggregates of α-synuclein are major components of the Lewy bodies and Lewy neurites associated with Parkinson's Disease (PD). A natively unfolded protein, α-synuclein can adopt different aggregated morphologies, including oligomers, protofibrils and fibrils. The small oligomeric aggregates have been shown to be particularly toxic. Antibodies that neutralize the neurotoxic aggregates without interfering with beneficial functions of monomeric α-synuclein can be useful therapeutics.*" (see page 1, "*SUMMARY*").

30. With regard to the potential medical use of the α-synuclein oligomer-binding antibodies produced with the disclosed method, document D66 states: "*This scFv can have potential therapeutic value in controlling misfolding and aggregation of α-synuclein in vivo when expressed intracellularly in dopaminergic neurons as an intrabody.*") (see page 1, "*SUMMARY*").

31. No data going beyond the finding in document D66 with regard to a potential medical use of antibodies binding to α-synuclein oligomers has been provided in the patent. The subject-matter of claim 1 of these requests thus lacks inventive step.

Auxiliary requests 16 to 19
Inventive step (Article 56 EPC)

32. The (single) claim of these requests is directed to a method of producing a monoclonal antibody which binds to a stabilised soluble α-synuclein oligomer (see point IX. above). Both parties agreed on document D69 as the closest prior art for the subject-matter claimed. It discloses a method for producing antibodies which bind to α-synuclein oligomer, but does not disclose the use of stabilised oligomers. The patent or the application as filed does not disclose any effect of this difference, but only shows binding of the generated antibodies to oligomers without a comparison with monomers or fibrils (see Figures 8 and 9). The objective technical problem is thus to provide an alternative method for generating antibodies against α-synuclein oligomers. The solution to this problem is obvious, having regard to the disclosure of documents D19 or D47 (see discussion in points 19. to 24. above).

33. The subject-matter of claim 1 lacks inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated