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Datasheet for the decision of 10 November 2020

Case Number: T 0966/18 - 3.3.04

Application Number: 03783083.3

Publication Number: 1578253

IPC: A61K38/17, A61K39/00, A61K45/06, A61K51/10

Language of the proceedings: EN

Title of invention:
Prevention and treatment of synucleinopathic disease

Patent Proprietors:
Prothena Biosciences Limited
The Regents of the University of California

Former Opponent:
H. Lundbeck A/S

Headword:
Synucleinopathic disease/PROTHENA BIOSCIENCES

Relevant legal provisions:
EPC Art. 100(b), 83, 111(1)

Keyword:
Sufficiency of disclosure - (yes)
Appeal decision - remittal to the department of first instance (yes)

Decisions cited:
T 0609/02

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

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

Case Number: T 0966/18 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 10 November 2020

Appellant: (Patent Proprietor 1)	Prothena Biosciences Limited 25-28 North Wall Quay Dublin 1 (IE)
Appellant: (Patent Proprietor 2)	The Regents of the University of California 1111 Franklin Street, 12th Floor Oakland, CA 94607 (US)
Representative:	Goodfellow, Hugh Robin Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Former Respondent: (Former Opponent)	H. Lundbeck A/S Ottilavej 9 2500Valby (DK)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 23 March 2018 revoking European patent No. 1578253 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chair	G. Alt
Members:	B. Rutz
	L. Bühler

Summary of Facts and Submissions

I. The appeal of the patent proprietors ("appellants") lies from the opposition division's decision to revoke European patent No. 1 578 253 ("the patent"). The patent is entitled "*Prevention and treatment of synucleinopathic disease*".

II. An opposition was filed against the patent. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), and under Article 100(b) and 100(c) EPC.

III. The opposition division decided that claim 3 of the main request (claims as granted) infringed the requirements of Article 123(2) EPC, and that the invention to which the set of claims of auxiliary request 1 (filed during the oral proceedings) related was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC).

IV. With the statement of grounds of appeal, the appellants filed documents D88 and D89 and a set of claims of a main request (corresponding to auxiliary request 1 on which the decision under appeal was based) and conditionally requested oral proceedings.

Claim 1 of the main request reads:

"1. A pharmaceutical composition comprising an agent that induces an immunogenic response against α-synuclein, for use in prophylaxis or treatment of a disease characterized by Lewy bodies or α-synuclein

aggregation in the brain, wherein the agent is α-synuclein or an immunogenic fragment thereof or an antibody to α-synuclein or an immunogenic fragment thereof, and wherein the disease is Parkinson's disease, dementia with Lewy bodies, diffuse Lewy body disease, pure autonomic failure, Lewy body dysphagia, incidental Lewy body disease, inherited Lewy body disease or multiple system atrophy."

V. The opponent filed a reply to the statement of grounds of appeal and document D90 and subsequently withdrew their opposition with a letter dated 2 May 2019.

VI. The appellants replied to the opponent's reply. With a further submission the appellants filed document D91.

VII. The board summoned the appellants to oral proceedings as requested and informed them of its preliminary opinion in a communication pursuant to Article 15(1) RPBA.

In point 11 of this communication, the board indicated that it considered the claims of the main request to comply with the requirements of Article 123(2) EPC.

In points 12 and 13, the board drew attention to issues relating to sufficiency of disclosure and its intention to hear the appellants on these issues at the oral proceedings.

VIII. Oral proceedings before the board took place on 10 November 2020 in the form of a videoconference as requested by the appellants. At the end of these proceedings, the chair announced the board's decision.

IX. The following documents are cited in the present decision:

D2 US 2002/151464

D3 WO 01/60794

D4 Hashimoto, M. et al., Neuron, 2001, vol. 32(2), 213-223

D5 Windisch, M. et al., Journal of Molecular Neuroscience, 2002, vol. 19(1-2), 63-69

D7 Wanker, E. E., Molecular Medicine Today, 2000, vol. 6, 387-391

D17 Solomon, B., Current Medicinal Chemistry, 2002, vol. 9, 1737-1749

D26 WO 99/27944

D30 Cao, C. et al., Neuroscience, 2002, Abstract with proof of publication (published online on 27 August 2002)

D43 Decision dated 24 July 2013 in the opposition proceedings against EP 1 994 937

D44 Bae, E.-J. et al., The Journal of Neuroscience, 2012, vol. 32(39), 13454-13469

D49 Hashimoto, M. et al., Brain Pathology, 1999, vol. 9, 707-720

D50 Borghi, R. et al., Neuroscience Letters, 2000, vol. 287, 65-67

D51 Forloni, G. et al., Ann. Neurol., 2000, vol. 47, 632-640

D52 Lansbury, P., Proc. Natl. Acad. Sci. USA, 1999, vol. 96(7), 3342-3344

D53 Volles, M. J. et al., Biochemistry, 2001, vol. 40, 7812-7819

D54 Bard, F. et al., Proc. Natl. Acad. Sci. USA, 2003, vol. 100(4), 2023-2028

D55 Bergström, A.-L. et al., Movement Disorders, 2016, vol. 31(2), 203-213

D56 Schneeberger, A. et al., Movement Disorders, 2016, vol. 31(2), 214-224

D58 Masliah et al., Science, 2000, vol. 287(5456), 1266-1269

D61 Games, D. et al., The Journal of Neuroscience, 2014, vol. 34(28), 9441-9454

D62 Declaration of Eliezar Masliah, undated

D70 Decision of Opposition Division on EP 2 305 282

D76 Additional data on antibody seeding assay

D77 Dufty, B. et al., American Journal of Pathology, 2007, vol. 170, 1725-1738

D78 Doucet, M. et al., PLOS ONE, 2017, 1-25

D79 Brody, D. et al., Annual Review of Neuroscience, 2008, vol. 31, 175-193

D80 Kohyama, K. et al., ImmunoTargets and Therapy 2015, vol. 4, 27-34

D82 Declaration of Patrik Brundin, 30 November 2017

D84 Spillantini M., et al., Nature, 1997, vol. 388, 839-840

D85 Polymeropoulos, M. et al., Science, 1997, vol. 276, 2045-2047

D86 Narhi, L. et al., Journal of Biological Chemistry, 1999, vol. 274, 9843-9846

D88 Declaration of Wagner Zago, 2 August 2018

D89 New Alzheimer's and Parkinson's Immunotherapy Data at AAN (4th May 2018) - https://www.alzforum.org/news/conference-coverage/new-alzheimers-and-parkinsons-immunotherapy-data-aan

D90 Declaration by Anne Messer (including CV), 16 December 2018

D91 Prothena press release, September 2020

X. The reasoning in the decision under appeal regarding lack of sufficiency of disclosure is summarised as follows.

Case law

According to the relevant case law, see for example T 609/02, it is not always necessary that results of applying the claimed composition in clinical trials, or at least to animals are reported. Yet, this does not mean that a simple verbal statement in a patent specification is enough to ensure sufficiency of disclosure in relation to a claim to a pharmaceutical.

In that decision the board also stated that the patent has to provide some information, for example in the form of experimental tests, to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent.

Showing a pharmaceutical effect *in vitro* might be sufficient if for the skilled person this effect directly and unambiguously reflects such a therapeutic application, or if there is a clear and accepted relationship between the shown physiological activities and the disease.

Prior art

In the present case, the most important question was whether, for the skilled person, the effect of a reduction of α-synuclein aggregates reflected directly and unambiguously the therapeutic application referred

to in the claim, i.e. a treatment of a Lewy body disease.

In the prior art, reduction of α-synuclein aggregation had been achieved by α-synuclein-binding peptides and antibodies (documents D1 and D2, respectively).

Document D30 disclosed that, by vaccination with α-synuclein, considerable antibody titers were created, but an effect on aggregates was not measured.

It was not contested that α-synuclein aggregation was known to be linked to Lewy body diseases. However, at the filing date, there was a lack of understanding about what the role of these aggregates was in the pathology of Lewy body diseases.

In view of documents D50 to D53, the skilled person would not come to the conclusion that targeting the aggregations was the first choice for a treatment; other mechanisms could be useful targets.

Thus, a clear and accepted relationship between α-synuclein aggregates as the cause of the disease was not known from the prior art.

Disclosure in the patent

Example I described active immunisation with human α-synuclein by injecting peripherally human α-synuclein in a mouse model of Lewy body disease. Injected mice were divided into three groups of four animals according to their antibody titer (low, high, none).

Injected α-synuclein elicited a decrease in α-synuclein inclusion formation in the brain tissue of the mice, as

disclosed on page 27, line 43 and lines 48 to 49, and shown in Figure 2 (and the reproduction of it - document D57).

Table 1 indicated that the number of animals in each group was only four, i.e. very small, and the statistical significance of the results was not disclosed.

Moreover, the number of synuclein-positive inclusions per mm^2 brain tissue as shown in Table 1 largely overlapped in the three groups. A trend towards a dose-dependent reduction of inclusions by vaccination could not be identified from Table 1.

Therefore, and because the skilled person knew about the biological variability of *in vivo* animal models, the data of Table 1 did not credibly demonstrate successful active immunisation, i.e. neither a reduction of aggregations nor that it was linked to anti-α-synuclein titers.

Example II disclosed the use of mouse neuronal GT1-7 cells having mouse α-synuclein-inclusions associated with the cell surface - which includes cell membranes and intracellular membranes (see Figures 3c and 3d and Figure 4) - for screening for α-synuclein antibodies able to clear these inclusions from the membranes. One of the tested antibodies showed clearing activity.

Hence, the experimental set-up of Example II was not representative for passive immunisation as no *in vivo* data were provided, and it thus had not been shown whether injected antibodies would arrive at the brain to exert their effects.

Consequently, in summary, the patent did not plausibly establish the link between reduction of α-synuclein aggregates and treatment of Lewy body disease.

XI. The appellants' arguments submitted in writing and during the oral proceedings, as far as relevant to the decision, may be summarised as follows.

Main request

Sufficiency of disclosure (Article 83 EPC)

Case law

The board explained in decision T 609/02 that:

i) A mere assertion that compound X is suitable for treating disease Y is not sufficient on its own to render the invention plausible (Reasons 9).

ii) The disclosure of the patent specification does not have to be definitely predictive of the efficacy of the invention: *in vitro* tests which may well not be reproducible in humans or animals may suffice (Reasons 10 and 11).

iii) The patent should provide some information to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, an example of adequate support being experimental tests (Reasons 9).

iv) Ultimately the purpose of the requirement of sufficiency is to place the reader in possession of the invention without imposing undue burden on them by way of further investigation or research (Reasons 10).

Prior art

It was widely accepted at the filing date that α-synuclein aggregation was at least one of the causative factors of synucleinopathic diseases.

Reducing α-synuclein aggregates was regarded as a treatment of the disease because it reduced an abnormal, characteristic disease pathology (see for example D49, D84, D85, D58).

Disclosure in the patent

Example I showed *in vivo* - for the first time and using an accepted animal model of synucleinopathies (see document D51) - that immunisation with peripherally administered α-synuclein (active immunisation) could provide a dose-dependent "*marked decrease*" in both the size and intensity of synuclein inclusions, which were, as was known from the prior art, the "hallmark pathology" of synucleinopathic diseases.

Table 1 showed the number of synuclein inclusions per mm^2 in the three different groups of tested mice (no titer, moderate titers and high titers). The highest titers of anti-human α-synuclein antibodies correlated with the lowest levels of synuclein inclusions.

The quantitative results in Table 1 (relating to the number of synuclein inclusions) did not contradict the highly encouraging qualitative results (i.e the dose-dependent marked decrease in both the size and intensity of synuclein inclusions). Thus, the pooled results of Table 1 showed a quantitative trend that was consistent with the trend in qualitative results.

The data in Example I demonstrated that peripherally induced antibodies were involved in the *in vivo* reduction of α-synuclein deposits in the brain, thus providing a mechanistic explanation which supported the plausibility of passive immunotherapy according to the invention.

The patent also provided *in vitro* data showing that antibodies to α-synuclein were effective in clearing or preventing the development of α-synuclein inclusions in neuronal cells (Example II) and provided this neuronal cell model as an example of a method by which the skilled person could screen for further antibodies which might be used in the claimed treatment.

The experimental evidence and teaching in the patent made it plausible that immunotherapy targeting α-synuclein would be a useful therapeutic strategy for the treatment of synucleinopathies.

The experiments disclosed in the patent represented the initial *in vivo* proof-of-concept work, using an accepted animal model of synucleinopathies, which led to the development of α-synuclein-based active and passive immunotherapies for synucleinopathies. The results in the patent prompted the development and publication of various examples of successful α-synuclein-related active and passive immunotherapies for synucleinopathies, some of which were now being pursued in phase 2 clinical trials.

The prior art supported the view that, at the filing date, reduced aggregation would have been considered a credible measure of likely therapeutic effects in treating synucleinopathies.

XII. The appellants request that the decision under appeal regarding auxiliary request 1 (the main request in the appeal proceedings) be set aside and the case be remitted to the opposition division for further prosecution of the remaining grounds of opposition.

Furthermore, the appellants request that documents D88, D89 and D91 be admitted into the proceedings.

Reasons for the Decision

Parties to the appeal proceedings

1. The opponent withdrew their opposition during the appeal proceedings (see section V. above) and thus ceased to be a party to these proceedings. Hence, the appellants/patent proprietors are the sole party.

Issues considered in the present decision

2. The opposition division decided the issue of sufficiency of disclosure in favour of the opponent. Before withdrawing its opposition, the opponent had replied to the statement of grounds of appeal. Thus, the reasoning in the present decision deals with the opponent's arguments reflected in the reasoning of the decision under appeal and reiterated in their reply to the statement of grounds of appeal.

3. In the decision under appeal, the opposition division found all claims of the main request, except for claim 3, to comply with Article 123(2) EPC. Auxiliary request 1 (identical to the present main request) differed from the main request in that the objected term "comprises" in dependent claim 3 had been replaced with "is".

Consequently, the opposition division found auxiliary request 1 to comply with Article 123(2) EPC.

4. In view of the opponent having ceased to be a party to the proceedings, the board only deals with the reasons for revocation in the decision under appeal with regard to auxiliary request 1 (now the main request) and sees no need to consider *ex officio* any further arguments submitted by the opponent with the reply.

Admission of documents (Articles 12(4) and 13(1) RPBA)

5. The board holds that documents D88, D89 (by the appellants) and document D90 (by the former opponent) were filed in relation to issues in the decision under appeal and that they could not have been filed earlier. The filing of document D91 is considered a reaction to an argument in the opponent's reply. Consequently, the board sees no reason to hold documents D88 to D90 inadmissible or to not admit document D91.

Main request

Sufficiency of disclosure

6. In the decision under appeal, claim 1 of the set of claims of auxiliary request 1 - which are the claims of the present main request - was found not 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.

7. Claim 1 is drafted as a second medical use claim pursuant to Article 54(5) EPC and is directed to a pharmaceutical composition comprising either

(i) α-synuclein or an immunogenic fragment thereof or

(ii) an antibody to α-synuclein or an immunogenic fragment thereof

for use in the prophylaxis or treatment of a disease characterized by Lewy bodies or α-synuclein aggregation in the brain.

8. In this decision, solely the embodiment of claim 1 relating to "treatment" is dealt with, absent of any arguments by the opponent regarding the "prophylaxis" aspect of the claim. The treatment with composition (i) above is referred to in the decision under appeal as "active immunisation" and that with composition (ii) above as "passive immunisation", wording which will also be used in the present decision. The feature "treatment of a disease characterized by Lewy bodies or α-synuclein aggregation in the brain" will be referred to here as "treatment of Lewy body disease(s)".

9. It is established case law of the boards of appeal that, in a claim pertaining to a second medical use, the therapeutic effect referred to in the claim - here the treatment of a disease characterized by Lewy bodies or α-synuclein aggregation in the brain - is a functional technical feature of that claim (see decision T 609/02 and Case Law of the Boards of Appeal of the EPO, 9th edition 2019, I.C.7.2.).

10. At the heart of the present case lies the question whether or not the skilled person, having regard to the disclosure of the patent and the common general knowledge at the relevant date of the application, would have considered that the compounds referred to in the claim were suitable to achieve the therapeutical

effect (see decision T 609/02, point 9). Or, in other words, whether it was plausible (or, in yet other words, whether it was credible) that the therapeutic effect could be achieved by the claimed composition.

11. The opposition division found that it was not plausible that the treatment of a Lewy body disease could be achieved by the claimed composition, because:

(i) "[N]*o causative link is demonstrated in the original application or is derivable from the common general knowledge establishing that a reduction of alpha-synuclein aggregation will likely lead to Lewy body disease treatment*";

(ii) Examples I and II, and the tables and figures related to them, did not show that active or passive immunisation led to a reduction of α-synuclein aggregations, and hence the patent did not plausibly establish the link between reduction of α-synuclein aggregates and treatment of Lewy body disease either.

Prior art

12. A number of documents have been cited to illustrate the knowledge of the skilled person working in the field of amyloid diseases at the priority date. The board summarises this body of knowledge as follows.

Referred to by the appellants

13. Document D84 states "*the intracytoplasmic Lewy body is therefore central to the neurodegenerative process, and both Parkinson's disease and DLB may be α-synuclein diseases*".

14. Document D86 finds that "*the formation of α-synuclein aggregates could be a critical step in PD pathogenesis, which is accelerated by the PD-linked mutations*" (see Abstract), and that "[s]*uch inhibitors* [i.e. compounds that block α-synuclein aggregation] *could be useful as PD therapeutics if aggregation of α-synuclein is a critical step in all forms of PD*" (see page 9846, right column).

15. Document D49 states on page 711, right column: "*Interestingly, preliminary observations suggest that transgenic mice overexpressing α-synuclein develop inclusion bodies and dopaminergic deficits (Figure 3), supporting the contention that abnormal aggregation of α-synuclein might play a central role in LBD.*" Based on this finding the authors put forward a model in which "*intracellular NACP/α syn aggregation*" plays a central role for the pathology of the disease (see Figure 4, reproduced below).

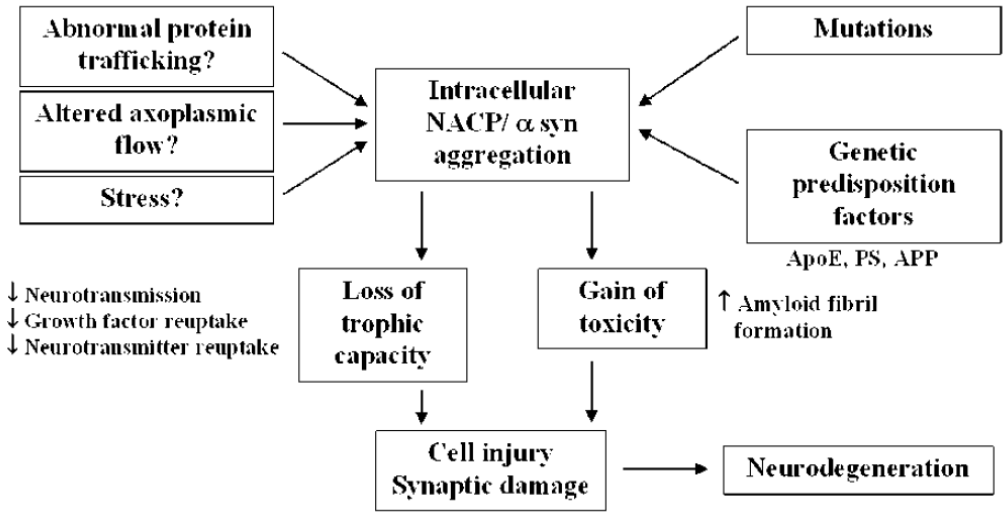

Figure 4. Central role of α-synuclein in the mechanisms of neurodegeneration in LBD.

16. The preliminary results referred to in the review D49 were published in document D58. In its final sentence

the authors state: "*increased expression or intracellular accumulation of wild-type α-synuclein may play a key role in the pathogenesis of these conditions*".

17. Document D2 states in paragraph [0008] that "[r]*ecent studies on transgenic animals* [D58] *also suggest that aggregation of α-synuclein is harmful to neurons*" and in paragraph [0024] that "*decrease in the amount of aggregation indicates that the agent is capable of inhibiting the aggregation of α-synuclein, and thus that the agent would be useful in the treatment of the disease*".

18. Document D3 shows that β-synuclein overexpression in α-synuclein transgenic mice resulted in a reduction of neuronal inclusions, that this was accompanied by a reduction in neuronal loss, and that this was indicative of potential as an anti-Parkinsonian therapeutic.

19. In document D4 it is stated that "*inhibition of α-synuclein aggregation may represent a feasible therapeutic strategy in LBD and related disorders*" (see page 213, final paragraph).

20. In document D5 it is noted with reference to document D4 that "[t]*here is a clear correlation between decrease in α-synuclein inclusion bodies and an improvement in motor function, which has been described elsewhere*" (see page 66, right column).

21. The patent illustrates why α-synuclein was likely to be a causative agent for Lewy body diseases as follows:

"*(1) this protein accumulates in LBs (Spillantini et al., Nature (1997) 388:839-40* [D84]*; Takeda et al., AM. J. Pathol. (1998) 152:367-72; Wakabayashi et al., Neurosci. Lett. (1997) do239:45-8), (2) mutations in the alpha-SN gene co-segregate with rare familial forms of parkinsonism (Kruger et al., Nature Gen. (1998) 18:106-8; Polymeropoulos MH, et al., Science (1997) 276: 2045-7* [D85]*) and, (3) its overexpression in transgenic mice (Masliah et al., Science (2000) 287:1265-9* [D58]*) and Drosophila (Feany et al., Nature (2000) 404:394-8) mimics several pathological aspects of PD*" (see paragraph [0005]).

22. From this collection of scientific and patent literature alone, the board is convinced that, at the priority date, there was agreement that the intracytoplasmic Lewy body potentially caused neurodegeneration. The development of a mouse model in which human α-synuclein was overexpressed, and which not only showed intracellular accumulation of α-synuclein but also some of the pathological symptoms associated with Parkinson's disease, was considered in the field to be a confirmation of this hypothesis. Compounds that block α-synuclein aggregation were already suggested as therapeutics for Parkinson's disease (see document D86).

Referred to in the decision under appeal and by the former opponent

23. The former opponent cited a number of documents (D7, D30 and D50 to D53) which were also relied upon by the opposition division (see point 19.3.6 of the decision). However, in the board's view, these documents rather strengthen the view that α-synuclein is a causative agent for Lewy body diseases.

24. In document D7 it is said that "*the results obtained in both model systems strongly suggest that the accumulation of wild-type and/or mutant α-synuclein in neurons plays a causal role in PD*" (page 388, top of third column).

25. Document D50 summarises that "[a] *series of evidences indicate that abnormal accumulation and aggregation of α-synuclein, a presynaptic protein, play a primary role in PD pathogenesis. Lewy's bodies, the round intracellular inclusions that form in degenerating neurons, are composed by polymers of full-length α-synuclein [13]; point mutations of α-synuclein gene are associated with early-onset familial PD [9,11,12]; mutant α-synuclein proteins show an increased tendency to form detergent insoluble filaments as well as a higher toxicity than wild type peptide in cultured neurons [4]*" (see page 65, left column).

26. The authors of document D51 state that "[t]*he causal role of α-synuclein aggregation in PD is supported by the finding that the mutations (A53T and A30P) associated with familial PD influenced the self-aggregation capacity of the protein. ... Although ... alternative explanations have been proposed for the pathogenic mechanism associated with the protein mutations, our data indicate that α-synuclein aggregation is a pathological event potentially sufficient to cause dopaminergic cell death*" (see page 639, left column, first full paragraph), and finally: "*The results of this study show the potential neurotoxic effects of α-synuclein aggregation*" (see page 639, left column, second full paragraph).

27. Document D52 states on page 3344, right column that both "*extreme models*" might be correct, namely that "*fibrils are an epiphenomenon linked to disease*" and that "*fibril formation causes disease*" (see also Figure 2).

28. Document D53 summarises that "[e]*ither the α-synuclein fibril itself or a protofibrillar species could be responsible for cell death in PD (18). The identification of the toxic species and characterization of its mechanism of action would provide novel therapeutic targets*" (see page 7812, left hand column). It further finds that "[t]*he correlation between fibrillar α-synuclein (Lewy bodies) and cell death in Parkinson's disease appears to reflect a causal link*" (see page 7815, right hand column), and "[c]*ompounds that inhibit the conversion of monomer to protofibril could be novel therapeutics against Parkinson's disease*" (see page 7818, left column).

29. Finally, document D30, published shortly before the priority date, discloses a vaccine strategy against Parkinson's disease which targets α-synuclein. The authors report the administration of recombinant α-synuclein to mice and rats resulting in a considerable antibody titer against the synuclein protein.

30. In summary, in contrast to the opposition division, the board is persuaded that the skilled person was made aware by the body of knowledge evidenced above of a link between the reduction of α-synuclein aggregation and the treatment of Lewy body disease.

31. Thus, the board also endorses the appellants' summarising statement that "[reduction of] *aggregation was an accepted measure of likely therapeutic effects*".

Relevant disclosure of the patent

32. The relevant disclosure in the patent referred to in the decision under appeal is found in Examples I and II.

33. The opposition division held that the results of Example I, active immunisation with α-synuclein, were not appropriate to demonstrate that a reduction in α-synuclein aggregations was linked to the anti-α-synuclein titers, because:

(i) The number of animals in each group was small, i.e. it comprised only four animals.

(ii) The results of Example I displayed in Table 1 did not comprise any statistical assessment of their significance.

(iii) The ranges of antibody titers displayed in Table 1 greatly overlapped so that no trend towards a link between titer and reduction could be derived.

34. It is the board's view that the skilled person would have derived from the prior art that reduction of aggregates was "*an accepted measure of likely therapeutic effects*" on Lewy body diseases (see point 30. above). The experimental set-up of Example I and its results have to be seen against this background.

35. Moreover, the disclosure in paragraph [0157] of the patent and in Figure 2 and Table 1, both relating to Example I, should not be neglected.

36. Paragraph [0157] discloses: "*Neuropathological analysis showed that mice producing high titers had a marked decrease in the size of synuclein inclusions. Mice producing moderate titers showed a smaller decrease. ... Fig. 2 shows synuclein inclusions in panel (b)* [CFA only] *but not panel (a)*[non-transgenic]*. In panel (c), treated mouse, moderate titers, the inclusions are somewhat reduced in intensity. In panel (d) the inclusions are markedly reduced in intensity.*"

37. The immuno-stained brain sections shown in Figure 2, and even better in its reproduction in document D57, show a trend inversely correlating antibody titer and α-synuclein inclusions. This is reflected qualitatively by the size, number and intensity of the inclusion bodies in the figure.

38. As regards point (iii) above, i.e. the issue that the ranges of α-synuclein-positive aggregates per mm^2 brain tissue in Table 1 overlap, the board agrees that there is a certain overlap: no antibody: 18-29, low antibody titer: 15-29, high antibody titer: 10-22. However, like in Figure 2, a clear trend towards lower numbers of Syn(+) inclusions/mm^2 in relation to higher antibody titers is also recognisable here. Thus, the data in Table 1 quantitatively support the data from Figure 2.

39. Hence, in view of the combined qualitative and quantitative data in Figure 2 and Table 1, the skilled person would have concluded that Example I of the patent shows that active immunisation with full-length human α-synuclein results in the production of high titer anti-α-synuclein antibodies that cross the blood-brain barrier and reduce the size, number and intensity of α-synuclein inclusions in or attached to neurons in the brain of vaccinated mice.

40. As regards points (i) and (ii) in point 33. above, the board considers that the lack of statistical information and the small number of animals would not have diminished the credibility of the results of Example I, because they build upon what the skilled person would have expected from the prior art, namely that a link existed between the reduction of α-synuclein aggregation and the treatment of Lewy body disease.

41. As regards the use of antibodies against α-synuclein for the treatment of Lewy body diseases (see point 7. (ii) above), i.e. the so-called passive immunisation, the opposition division held that the experimental set-up of Example II was not representative for such a treatment.

42. Whether this is the case for Example II or not, the board considers that the results of Example I also support the suitability of the claimed compounds for passive immunisation because endogenous antibodies generated in the peripheral system and detectable in the blood were able to cross the blood-brain barrier and act in the brain (see titers in Table 1 and effect on inclusions in Figure 2). The skilled person would therefore have concluded that antibodies administered peripherally (passive immunisation) would achieve a similar effect. This conclusion is further supported by the data obtained *in vitro* in Example II which show an effect of polyclonal antibodies on α-synuclein inclusion bodies attached to membranes by immuno-staining of cells (Figure 3) and by Western blot of cellular fractions (Figure 4).

43. In conclusion, the data in the patent support the hypothesis developed in the patent that active and passive immunisation targeting α-synuclein can reduce synuclein inclusion bodies in the brain. Together with the comprehensive body of knowledge in the prior art (see points 13. to 29. above), the medical use of claim 1 is thus plausible.

Further support by later published evidence

44. The following evidence, published after the relevant date of the application, further supports the appellants' position that the findings in the decision under appeal were not correct.

45. Document D55 summarises a number of clinical trials (see page 205, Table 1) and states: "*Immunotherapy using antibodies targeting alpha-synuclein has proven to be an effective strategy for ameliorating pathological and behavioural deficits induced by excess pathogenic alpha-synuclein in various animal and/or cellular models*" (see Abstract). The authors conclude: "*In summary, these studies provide support for alpha-synuclein antibodies being able to target both extracellular and intracellular alpha-synuclein*" (see page 207, left column, end of first full paragraph).

46. Document D56 discusses the utility of vaccination as a potential treatment for synucleinopathies. It summarises a number of preclinical results using full-length or fragments of α-synuclein (see Table 2), as well as clinical studies involving short peptides that mimic a region of the α-synuclein molecule (see Table 3). Despite stating in the introduction that "[a]*ll* [synucleinopathies] *lack a causal therapy*", this document lists a number of vaccination strategies

targeting α-synuclein and states: "*Evidence is mounting for a causative role of α-Syn, especially in PD and MSA (Table 1)*" (see page 214, right column).

47. Document D91 reports preliminary results of a phase 2 study (clinical trial NCT03100149) using an antibody against an epitope in the C-terminus of α-synuclein (PRX002/prasinezumab). Prasinezumab demonstrated "*signals of efficacy on multiple pre-specified secondary and exploratory clinical endpoints, including measures of motor function and biomarkers, in patients with early Parkinson's disease*" and "[s]*ignificantly reduced decline in motor function by 35% vs. placebo at one year and delayed time to clinically meaningful worsening of motor progression over one year*".

48. The board concludes that the use of compositions comprising α-synuclein or an immunogenic fragment of it, or an antibody to α-synuclein or to an immunogenic fragment of it, for therapy of Lewy body diseases is also supported by later published evidence in which such therapies were and still are developed.

Conclusion

49. In view of the observations above, the board concludes that the reasons given in the decision under appeal, for holding that the invention claimed in claim 1 was not disclosed in a manner sufficiently clear and complete for it to be carried out by the skilled person, do not hold. Hence, the decision under appeal is to be set aside.

Remittal

50. Under Article 111(1) EPC, the board of appeal may either decide on the appeal or remit the case to the department which was responsible for the decision appealed.

51. In the present case, the opposition division decided on added subject-matter (Articles 100(c) and 123(2) EPC) and sufficiency of disclosure (Articles 100(b) and 83 EPC) but not on priority (Article 87 EPC), novelty (Article 54 EPC) and inventive step (Article 56 EPC).

52. It is the primary purpose of the appeal proceedings to review the decision under appeal in a judicial manner (see Article 12(2) RPBA 2020). It would run counter to this purpose of appeal proceedings if the boards were required to examine questions regarding the patentability of the claimed subject-matter which have not yet been decided on by the department of first instance. Also, in view of the fact that appeal proceedings are less investigative than first-instance proceedings, it appears more appropriate to remit the case for consideration of undecided issues of patentability unless there are good reasons to depart from this course. However, there were none in the present case. The board therefore allows the appellants' request for remittal of the case to the opposition division.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division for further prosecution.

The Registrar: The Chair:

A. Chavinier Tomsic G. Alt

Decision electronically authenticated