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**Datasheet for the decision
of 26 February 2019**

Case Number: T 2474/13 - 3.3.04

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Title of invention:

Method and compositions for treating stroke with fever

Applicant:

NoNO Inc.

Headword:

Stroke/NONO

Relevant legal provisions:

EPC Art. 54(5), 56

Keyword:

Novelty - (yes)
Inventive step - (yes)

Decisions cited:

T 1399/04, T 0734/12, T 1118/12

Catchword:



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Case Number: T 2474/13 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 26 February 2019

Appellant:
(Applicant)

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Decision under appeal:

**Decision of the Examining Division of the
European Patent Office posted on 26 July 2013
refusing European patent application No.
07796769.3 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman G. Alt
Members: D. Luis Alves
P. de Heij

Summary of Facts and Submissions

- I. The applicant (appellant) filed an appeal against the decision of the examining division refusing European patent application No. 07 796 769.3, entitled "*Method and compositions for treating stroke with fever*". The application was filed as an international application which was published as WO 2008/008348 ("application as filed").
- II. The following documents are referred to in this decision:
- D4: US 2005/0059597
- D11: Wang, Yang *et al*, *Stroke*, 2000, 31, 404-409.
- D18: Ginsberg and Busto, *Stroke*, 1998, 29, 529-534.
- D19: Meden, Per *et al*, *Brain Research*, 1994, 647, 131-138.
- D21: Memezawa, Hajime *et al*, *Brain Research*, 1995, 670, 48-52.
- D23: Gerriets, T. *et al*, *Stroke*, 2003, 34, 2234-2239.
- D24: Bråtane, Bernt T. *et al*, *Stroke*, 2011, 42, 3265-3270.
- III. In the decision under appeal the examining division dealt with a main request and five auxiliary requests. The subject-matter of the claims according to the main request and auxiliary requests 2, 3, 4 and 5,

respectively, was held to extend beyond the content of the application as filed (Article 123(2) EPC). The subject-matter of the claims of all auxiliary requests was found to lack inventive step (Article 56 EPC).

As regards lack of inventive step, the examining division reasoned in relation to auxiliary request 1 that document D4 represented the closest prior art. The difference between the subject-matter of claim 1 and the disclosure in document D4 was that the subjects being treated had a fever of at least 38°C on initiating treatment. No particular technical effect was achieved by this difference, other than stroke patients with a fever of 38°C upon initiating treatment were now also being treated. The objective technical problem was "to treat a sub-group of stroke patients who also has a fever of 38°C upon initiating treatment". The skilled person when faced with such a patient would not hesitate to use the peptide known from document D4 for the treatment of stroke. Declaration D17 had been taken into account, but it was considered that also in the light of this document the skilled person had no reason to doubt that the same peptides could likewise be useful to successfully treat a stroke patient having fever.

IV. With the statement of grounds of appeal, the appellant filed a main request and six auxiliary requests.

Furthermore, documents D18 to D25 were filed.

The appellant requested that oral proceedings be held should the main request and auxiliary requests 1 to 3 not be found allowable.

- V. The board appointed oral proceedings and subsequently issued a communication pursuant to Article 15(1) RPBA, to which the appellant replied.
- VI. At the oral proceedings a set of claims was filed to replace the set of claims of the main request. The 14 claims of this new main request are identical to claims 1 to 14 of auxiliary request 1 underlying the decision under appeal.

The two independent claims read as follows:

"1. A peptide having an amino acid sequence comprising [E/D/N/Q]-[S/T]-[D/E/Q/N]-[V/L] for use in the treatment, optionally wherein the treatment is prophylactic, of the damaging effect of stroke exacerbated by fever in a subject having a fever of at least 38 degrees Celsius on initiating treatment.

13. A pharmaceutical composition for use in treating stroke exacerbated by fever in a subject having a fever of at least 38 degrees Celsius on initiating treatment, which comprises in unit dose from 0.05 to 500 mg, optionally 0.1 to 100 mg, for example 0.5 to 50 mg such as 1 to 20 mg of a peptide as set forth in any of claims 1 or 3 to 7."

The board expressed the opinion that the subject-matter of the claims of the main request did not contain added subject-matter, was novel and involved an inventive step.

At the end of the oral proceedings the chair announced the decision of the board.

VII. The appellant's arguments, insofar as relevant to this decision, may be summarised as follows:

At the oral proceedings the appellant identified the objective technical problem as the provision of a treatment of stroke for subjects having a fever of at least 38°C on initiating treatment, the treatment having similar efficacy in reducing infarct size and cognitive deficits in subjects with hyperthermia as in subjects without.

Such problem was credibly solved as shown from the results in the application when compared to those in document D24.

The solution was not obvious for two main reasons.

Firstly, fever was generally known to exacerbate the effects of stroke, as stated in the application as well as in documents D11, D18 and D19. The skilled person would have no reasonable expectation that patients could be effectively treated.

Secondly, fever was generally known to render neuroprotective drugs ineffective, as stated in, *inter alia*, documents D18, D21 and D23.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims of the main request, filed during the oral proceedings, or, alternatively, on the basis

of one of the sets of claims of auxiliary requests 1 to 6 filed with the grounds of appeal.

Reasons for the Decision

Main request

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is therefore admissible.

Amendments - Article 123(2) EPC

2. The board is satisfied that the requirements of Article 123(2) EPC are met.

Novelty - Article 54 EPC

3. Claim 1 is directed to a therapeutic application of the peptides according to the formula in the claim in the treatment of the damaging effect of stroke in a subject having a fever of at least 38°C on initiating treatment.
4. Document D4 discloses methods of reducing the damaging effect of injury to brain cells, specifically that caused by ischaemic or traumatic injuries (see paragraph 3 and claim 3). The methods are based on disrupting the interaction between N-methyl-D-aspartate receptors (NMDARs) and postsynaptic density-95 protein (PSD-95). PSD-95 couples NMDAR to pathways mediating excitotoxicity and ischaemic brain damage. Disruption of said interaction achieved the desired effect of attenuating the NMDAR signalling whilst reducing the

negative consequences associated with blocking NMDAR activity.

Document D4 discloses for this purpose the use of peptides derived from either of the interacting PDZ2 domain of PSD-95 and C-terminus of NMDAR subunit NR2B, including PSD-95 inhibitory peptides as defined in claim 1 at issue. The use of the peptides is expected to have a neuroprotective effect and to provide a practical therapy for stroke (see paragraphs 9, 12 and 14).

The examples concern experiments wherein peptides administered one hour post stroke onset could reduce infarct volume in animal models of ischaemic stroke kept under controlled body temperature between 36.5°C and 37.5°C.

5. According to the established case law of the boards of appeal, for subject-matter of a claim to lack novelty over the prior art it must be directly and unambiguously derivable therefrom, either explicitly or implicitly (see Case Law of the Boards of Appeal of the European Patent Office, 8th edition 2016, I.C.4.3).

6. In the present case, document D4 already discloses the use of the same peptides for treating stroke, so that for the assessment of novelty of claim 1 it should first of all be determined whether the feature "in a subject having a fever of at least 38 degrees Celsius on initiating treatment" is also disclosed in the document.

7. As can be seen from the summary above, document D4 does not disclose individual subjects being treated for stroke that have a fever. This is so because the only disclosure of administration of the peptides is that taking place at controlled body temperature.
8. Additionally, the disclosure of document D4 as summarised above makes no mention of fever being an inclusion or exclusion criterion when treating stroke subjects with the peptides. Therefore, the subject group characterised by having stroke and fever is not addressed in said prior art document.
9. Thus, the feature "in a subject having a fever of at least 38 degrees Celsius on initiating treatment" is not directly and unambiguously derivable from document D4.
10. In the case law of the boards of appeal it has often been considered that the use of the same compound in the treatment of the same disease can constitute a novel therapeutic application, provided that it is carried out on a new group of subjects which is distinguished from the former by its physiological or pathological status (see e.g. decisions T 1399/04, point 35 of the Reasons; T 734/12, point 24 of the Reasons; and T 1118/12, point 13 of the Reasons).
11. The board is satisfied that the feature "in a subject having a fever of at least 38 degrees Celsius on initiating treatment" translates into a group of patients that is distinguishable by its pathological and physiological status from the group disclosed in document D4. This is so because the presence of fever correlates with a worse prognosis in stroke patients (see documents D11, D18 and D19, the contents of which

are further discussed below). Thus, also when the novelty of the claimed subject-matter is assessed in the light of the jurisprudence referred to above, the claimed therapeutic use is considered to be new, since the subject group defined by having fever in claim 1 is a new group in relation to the group disclosed in document D4.

12. The board thus comes to the conclusion that the subject-matter of claim 1 is novel over the disclosure in document D4.

Inventive step - Article 56 EPC

13. The examining division held that the subject-matter of claim 1 lacked an inventive step over document D4 as representing the closest prior art.

The relevant contents of this document are summarised in point 4 above.

14. The subject-matter of claim 1 differs from that disclosed in document D4 in that the subjects to be treated have a fever of at least 38°C on initiating treatment (see point 9 above).

The objective technical problem

15. As concerns the technical effect attained by the distinguishing feature, the application shows in Figure 5 the results of the use of the claimed peptides in terms of infarct volume in relation to hemispheric and cortical infarcts. The studies were carried out in an animal model of permanent ischaemia in which the

animals were subjected to a permanent middle cerebral artery occlusion (pMCAO). The PSD-95 inhibitory peptide was administered, *inter alia*, in an amount of 3 nmol/g at one hour after stroke (see page 26 of the description). The infarct volume was determined by tissue staining at 24 hours. The figure shows that a reduction on average of 35% to 40% in terms of infarct volume was achieved (see the description corresponding to Figure 5 in paragraphs 89 and 90).

16. Document D24 discloses the same experiments in respect of the surgical procedure, volume of infarct caused, peptide administered and its dose, time point of administration, as well as the analytical technique to measure the infarct volume at 24 hours. The only difference is that the experiments according to document D24 were carried out under controlled temperature conditions (page 3266, second full paragraph) whereas in the application the temperature was not controlled.

The results in Figure 1 of document D24 show a reduction in infarct volume of about 30% (see also abstract).

17. Thus, in the light of the results in the application and in document D24, the appellant's argument is accepted that the technical effect of the distinguishing feature is that a treatment is provided for subjects with an increased temperature of at least 38 degrees Celsius that leads to a benefit in terms of reduction in infarct volume comparable to that obtainable under controlled temperature conditions.
18. In the light of this technical effect, the board concludes that the objective technical problem may be

formulated as follows: the provision of a treatment for stroke in subjects having a fever of at least 38°C on initiating treatment which is as effective as one achieved in patients without fever.

19. The board is satisfied that the problem as formulated above is derivable from the application as filed because the application states (see paragraph 30): "*The invention is based in part on results described in the examples in which certain peptides were found to reduce infarction volume in a rat model of permanent ischemia notwithstanding severe hyperthermia (≥ 39 °C) and lack of prior fasting. Surprisingly, subjects with stroke and fever or hyperglycemia can be treated as effectively as subjects not suffering from such comorbid complications." (underline added by the board).*

Obviousness

20. The question to be answered is whether the skilled person starting from document D4 and faced with the problem formulated above would arrive in an obvious way at a treatment based on the administration of the peptides as defined in the claim.
21. It has been argued by the appellant that the skilled person would not because it was generally known that (i) fever exacerbates the effects of stroke, and (ii) neuroprotective drugs were ineffective in stroke patients with fever. In this respect the appellant referred, *inter alia*, to documents D11, D18, D19, D21 and D23, discussed below.

22. Document D19 aims at studying the efficacy of thrombolytic therapy with tissue plasminogen activator (tPA) as a function of body temperature in an animal model of embolic stroke. The abstract states that there was a significant correlation between infarct volume and body temperature and that the mortality rate was also significantly higher in the animals with hyperthermia compared to controls. The authors conclude that "*Hyperthermia had a detrimental effect when combined with thrombolytic therapy and should be avoided in clinical trials of this treatment*" (see abstract) and also state that the "*Extrapolation of data from animal studies to human stroke needs caution, but clinical reports support the view that hyperthermia is deleterious in ischemic stroke ...*" (see last page, last paragraph of the left-hand column).

Document D11 reports the results of a retrospective study on the prognostic role of patients' admission body temperature on short-term and long-term mortality of patients with acute stroke. It is concluded that "*An association between admission body temperature and stroke mortality was noted independent of clinical variables of stroke severity*" (see abstract).

Document D18 reviews studies on the correlation between hyperthermia and stroke. The authors list several mechanisms through which hyperthermia leads to worsening of cerebral ischaemia and consider that the available studies constitute compelling evidence to recommend controlling body temperature for at least several days to avoid fever in acute stroke patients.

23. Taken together these documents show that stroke patients having fever had a worse prognosis and that the thrombolytic treatment with tPA was not expected to

be effective in such patients. The only derivable recommendation is to control the patient's temperature.

24. Documents D18, D21 and D23 additionally support the view that there was the expectation of neuroprotective drugs not being effective in such patients, as follows.
25. Document D18, the contents of which are introduced in point 22 above, states in the context of patient management in acute stroke: "*The action of otherwise neuroprotective drugs in ischemia may be nullified by mild hyperthermia*" (see abstract).
26. Documents D21 and D23 both disclose the results of studies in pMCAO animal models and specifically on the effect of the NMDA antagonist MK-801.

The authors of document D21 conclude: "*The results suggest that amelioration of focal ischemic damage cannot be expected if body and brain temperature is allowed to rise above normal*" (see abstract), and "*The important result is that MK-801 was prevented from exerting ameliorating effect by a rise in temperature to 39.0-39.5 °C. It is probably not unreasonable to assume that hyperthermia also nullifies the effect of other drugs than MK-801*" (see paragraph bridging pages 51 and 52).

The authors of document D23 also generalise their conclusions to other neuroprotective drugs, stating: "*This appears to be the situation for the NMDA antagonist MK-801, but it seems reasonable to assume that other neuroprotective drugs may not work or may appear less effective if artificial hyperthermia is not avoided*" (see page 2238, penultimate paragraph).

27. In view of the observations in points 22 to 26 above, the board thus takes the view that the skilled person would not have arrived in an obvious way at a treatment for stroke patients with fever based on the peptides disclosed in D4.

28. In the decision under appeal, the examining division considered that, among documents D1 to D6, document D4 was the closest prior art document and found that the claimed subject-matter lacked inventive step in the light of this document. The board agrees with this choice; however, it comes to the opposite conclusion when regarding the disclosure in document D4 in the light of the disclosure in documents D11, D18, D19, D21, D23 and D24. Of those documents D18, D19, D21, D23 and D24 were only filed in the appeal proceedings.

29. Having reversed the examining division's finding on inventive step, the board considered whether other documents on file, in particular those which were filed during the appeal proceedings, would constitute a more promising starting point for the assessment of inventive step. Yet, the board has not identified any document that would lead to a different conclusion on inventive step.

30. Thus, the subject-matter of claim 1 is considered to comply with the requirements of Article 56 EPC. The same applies to claims 2 to 14, since they all share the features discussed above.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the examining division for further prosecution on the basis of the main request, filed during the oral proceedings of 26 February 2019.

The Registrar:

The Chair:



S. Lichtenvort

G. Alt

Decision electronically authenticated