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**Datasheet for the decision
of 5 April 2019**

Case Number: T 0109/13 - 3.3.01

Application Number: 08827578.9

Publication Number: 2198292

IPC: G01N33/68

Language of the proceedings: EN

Title of invention:
IMPROVED ALZHEIMER'S DIAGNOSIS

Applicant:
Washington University

Headword:
Alzheimer's diagnosis/WASHINGTON UNIVERSITY

Relevant legal provisions:

EPC R. 115(2)
RPBA Art. 15(3)
EPC Art. 56

Keyword:
Oral proceedings - held in absence of appellant
Inventive step - (no)

Decisions cited:

Catchword:



Beschwerdekammern
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Case Number: T 0109/13 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 5 April 2019

Appellant: Washington University
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Representative: V.O.
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Decision under appeal: **Decision of the Examining Division of the
European Patent Office posted on 10 August 2012
refusing European patent application No.
08827578.9 pursuant to Article 97(2) EPC**

Composition of the Board:

Chairman A. Lindner
Members: T. Sommerfeld
L. Bühler

Summary of Facts and Submissions

- I. The appeal lies from the decision of the examining division, in which European patent application No. 08827578.9, based on an international application published as WO 2009/026432, was refused under Article 97(2) EPC.

- II. At oral proceedings the examining division considered the then pending main request and first auxiliary request as not being allowable under Article 56 EPC, while the second auxiliary request, filed during the oral proceedings, was found to comply with the requirements of the EPC. The examining division then issued a communication under Rule 71(3) EPC, informing of the intention to grant a European patent on the basis of the said second auxiliary request. Instead of providing the required translations of the claims proposed for grant, the patent applicant replied to the communication of the examining division by sending translations of the main request and requesting that a patent be granted on the basis of said claims. The examining division then issued the appealed decision.

- III. The applicant (hereinafter "the appellant") lodged an appeal against the decision of the examining division, requesting that the decision be set aside and that a patent be granted according to the main claim request or, alternatively, according to auxiliary requests I to VII, all filed with the statement of grounds of appeal.

- IV. The board issued a communication pursuant to Rule 100(2) EPC and Article 17(1) RPBA providing a detailed preliminary opinion on inventive step as regards all the requests on file.

- V. The appellant replied by letter dated 4 July 2018, replacing all the previous requests with a new main request identical to the request which had been proposed for grant by the examining division.

The **main request** comprises three claims, claim 1 reading as follows:

"1. A method to analyze a cerebrospinal fluid for evidence of Alzheimer's disease in a subject from which the fluid has been derived, which method comprises determining the level of the markers Visinin-like protein 1 (VLP-1) in combination with determining the level [of] amyloid- β peptide 1-42 (A β 1-42) and hyperphosphorylated Tau (pTau) and optionally tTau in a sample of said cerebrospinal fluid; and

comparing the level of said markers with the levels of the same markers in normal controls; and

wherein a higher level of VLP-1 in combination with a lower level of A β 1-42 and a higher level of pTau and optionally tTau in the sample of said cerebrospinal fluid as compared to normal controls is evidence of Alzheimer's disease in said subject; and

wherein said method provides an improvement in accuracy of Alzheimer's disease detection as compared to determinations based on VLP-1 or any of said additional biomarkers alone."

- VI. The board issued summons for oral proceedings, followed by a further communication pursuant to Article 15(1) RPBA providing a negative opinion on inventive step and added subject-matter.

- VII. The appellant submitted a further reply, dated 5 March 2019, maintaining the same request. With a

further letter, dated 29 March 2019, the appellant informed that "the Applicant decided today to let the above mentioned European patent application go abandoned and the Representative will not attend oral proceedings".

- VIII. Oral proceedings took place as scheduled, in the absence of the appellant. At the end of the oral proceedings, the chairman announced the board's decision.
- IX. The appellant's arguments, in so far as relevant to the present decision, may be summarised as follows:

D2 taught that A β 1-42 alone had limited value in distinguishing Alzheimer's disease (AD) from other forms of dementia and hinted at pTau as the most promising cerebrospinal fluid (CSF) marker for the detection of AD. Nevertheless, D2 taught that none of these CSF markers alone or in combination showed sufficient sensitivity or accuracy to clearly differentiate AD from other types of dementia, in particular in early stage, it still being essential to base the clinical diagnosis of AD on cumulative information gained from clinical examination, brain-imaging and biochemical essays. When looking for alternative CSF marker combinations, the skilled person would avoid the claimed combination because D1 taught that all currently used brain damage markers were not sufficiently specific, and it was furthermore silent on which markers allowed differentiating AD from other types of dementia. Moreover, D1 determined VLP-1 only in stroke patients and in a rat stroke model, but not in AD patients.

- X. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed with the letter of 4 July 2018.

Reasons for the Decision

1. The appeal is admissible.
2. The duly summoned appellant did not attend the oral proceedings, as announced by letter dated 29 March 2019. In accordance with Rule 115(2) EPC, the board decided to continue the proceedings in the appellant's absence.

Moreover, pursuant to Article 15(3) RPBA the board is not obliged to delay any step in the proceedings, including its decision, by reason only of the absence at oral proceedings of any party duly summoned. Accordingly, the absent appellant was treated as relying only on its written case.

Main and sole request

3. Inventive step
 - 3.1 The present application relates to methods and kits to diagnose neurodegenerative diseases such as Alzheimer's disease (AD), and more specifically, to methods using biomarkers (paragraph [0002]). According to the application, evaluating the Visinin-like protein 1 (VLP-1) biomarker in combination with another biomarker, selected from amyloid- β peptide (A β), hyperphosphorylated Tau (pTau) and total Tau (tTau),

gives rise to an improved diagnostic method in comparison to relying on the interpretation of any one biomarker alone (paragraph [0009]).

3.2 Document D2, which is explicitly directed at the early diagnosis of Alzheimer's disease and at improving its diagnostic accuracy (abstract, lines 1 to 3), is the closest prior art. It teaches the use of CSF (cerebrospinal fluid) biomarkers, such as "total tau protein (t-tau), amyloid $\beta_{(1-42)}$ protein $A\beta_{42}$, and tau protein phosphorylated at AD-specific epitopes (p-tau)", and concludes that "the combination of the CSF markers and their ratios may significantly increase the specificity and the accuracy of AD diagnosis" (abstract, lines 5 to 9).

3.3 The difference to the subject-matter of claim 1 is that the use of the combination of biomarkers as claimed, namely determining the level of VLP-1 in combination with determining the level of $A\beta_{1-42}$ and pTau (and optionally tTau) in a sample of the cerebrospinal fluid, is not disclosed in D2. There are no data in the application or elsewhere on file comparing the results obtained with the claimed biomarker combination to those obtained with the biomarker combination of D2. Moreover, the application has not provided any data allowing the conclusion that the claimed marker combination is suitable to distinguish AD from other forms of dementia: in the examples, the levels of these biomarkers are assessed in patients with a clinical diagnosis of AD and compared to the levels in healthy individuals and not in patients with other forms of dementia (paragraph [0024]). Hence, the application does not teach more than D2 in this respect. Accordingly, no conclusions can be drawn regarding the accuracy of the claimed method as compared to the

method of D2, and the objective technical problem can be formulated as the provision of an alternative method for diagnosis of AD. The solution is the method as claimed and, in view of the application's data and of the prior art (e.g. D2 discussing A β 1-42 and pTau as markers for AD), the board is satisfied that the technical problem is solved.

3.4 Prompted by D2 to combine biomarkers for Alzheimer's diagnosis, the skilled person would search for further suitable biomarkers. It would thus consider the teaching of document D1, which discloses a number of markers for brain damage (Title), including for such brain damage as caused by AD (paragraph [0015] and claim 20). A list of suitable biomarkers is given in Table 1 starting at the bottom of page 11 of D1. The first of said biomarkers is VLP-1, and this is also the main biomarker that is further investigated in D1's Examples. The skilled person would thus be motivated to test any of D1's biomarkers, in particular VLP-1, as further potential diagnostic markers for AD. However, because D1's biomarkers are not specific to AD but rather to brain damage (which may have other causes not limited to AD), the skilled person would certainly recognise the need to combine these biomarkers with known biomarkers for Alzheimer's disease, such as any of the three CSF markers extensively discussed in D2, and would thus be motivated to test combinations of VLP-1 with any of said three CSF biomarkers; one of these combinations would be the claimed combination, namely VLP-1, A β 1-42 and pTau.

3.5 As to the appellant's arguments that D2 taught that A β 1-42 alone had limited value in distinguishing AD from other forms of dementia (D2, page 41, right column, third paragraph), and hinted at pTau as the

most promising CSF marker for the detection of AD, high CSF concentrations of pTau having only been found in patients with AD (D2, page 43, left column, second paragraph), the application has also not provided any data allowing the conclusion that the claimed marker combination is suitable to distinguish AD from other forms of dementia, since in the examples the levels of these biomarkers are only assessed in AD patients and in healthy individuals (paragraph [0024]). Further, while D2 indeed states that "it is reasonable to assume that the examined CSF markers for AD should not be used as isolated tests and the clinical diagnosis of AD should be based on cumulative information gained from clinical examination, brain-imaging, and biochemical assays" (page 44, right column, last paragraph), it also suggests that "the examined CSF markers have great clinical potential for this diagnostic challenge", namely "to identify and discriminate incipient and early AD from benign MCI, depression, and variants thereof, as well as alcohol-related cognitive dysfunction" (page 44, right column, second paragraph). In this respect, the application itself does not provide any evidence that a diagnosis of AD can be established by assessing solely the biomarkers.

- 3.6 As regards the appellant's arguments concerning D1, the board notes that the claimed subject-matter does not encompass the use of VLP-1 alone as a marker for AD, but rather in combination with the well-known markers for AD, A β 1-42 and pTau. In view of the teachings of D1 (in combination with D2), the skilled person would certainly consider using the combination of these three markers (or any of the markers listed in D1 with any of the three AD markers discussed in D2) in a "method to analyze cerebrospinal fluid for evidence of Alzheimer's disease". It is true that VLP-1 is only one among a

number of markers disclosed in D1; however, D1 discloses all the listed markers as equally suitable for the diagnosis of brain damage, including that caused from AD, and thus the mere selection of one of them cannot be considered inventive. The fact that D1 only tested VLP-1 in stroke patients and stroke rat models would not deter the skilled person from testing it also in AD patients. Again, D1 does not teach VLP-1 as a specific marker for AD but merely as a marker for brain damage, which can have different causes. This is also true, however, for the application, which teaches that "When an elevated level of VLP-1 is detected in bodily fluids, e.g., in cerebrospinal fluid or in serum, it is associated with brain injury such as that caused by Alzheimer's disease (AD)" (paragraph [0008], emphasis added by the board).

- 3.7 Claim 1 of the main request thus lacks inventive step. The main and sole request is not allowable for lack of compliance with Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



M. Schalow

A. Lindner

Decision electronically authenticated